Understanding skew deviation and a new clinical test to differentiate it from trochlear nerve palsy

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SUMMARY

Skew deviation is a vertical strabismus caused by a supranuclear lesion in the posterior fossa. Because skew deviation may clinically mimic trochlear nerve palsy, it is sometimes difficult to differentiate the 2 conditions. In this review we compare the clinical presentations of skew deviation and trochlear nerve palsy and examine the pathophysiology that underlies skew deviation. We then describe a novel clinical test—the upright–supine test—to differentiate skew deviation from trochlear nerve palsy: a vertical deviation that decreases by $\geq 50\%$ from the upright to supine position suggests skew deviation and warrants investigation for a lesion in the posterior fossa as the cause of vertical diplopia. (J AAPOS 2010;14:61-67)

Skew deviation is a vertical strabismus caused by supranuclear lesions. It is often associated with ocular torsion and head tilt, which together constitute the ocular tilt reaction. Skew deviation is often the initial manifestation of diseases that affect the brainstem, cerebellum, or peripheral vestibular system. Because both skew deviation and trochlear nerve palsy may result from intracranial lesions or trauma, and because some skew deviations may clinically mimic trochlear nerve palsy, differentiating these 2 conditions can be challenging. Understanding skew deviation remains difficult, partly because it requires knowledge of the underlying anatomy and pathophysiology. In this review, we first compare the clinical presentation of skew deviation versus trochlear nerve palsy. We then focus on the pathophysiologic mechanism of skew deviation and examine some current evidence that shows that skew deviation results from an imbalance of the utriculo-ocular pathway. We then present a novel upright–supine test that can be used clinically to differentiate skew deviation from trochlear nerve palsy at the bedside.

Clinical Presentation

Skew deviation was first induced experimentally in animals by Magendie\(^{11}\) and later Hertwig,\(^{12}\) who produced skew deviation in cats by sectioning the middle cerebellar peduncle. It was first observed in humans with cerebellar tumors by Stewart and Holmes in 1904.\(^{13}\) Skew deviation is a vertical misalignment of the visual axes caused by a disturbance of supranuclear inputs as a result of lesions in the brainstem, cerebellum, or peripheral vestibular system (ie, the inner ear and its afferent projections). The vertical misalignment may be comitant or incomitant. Rarely, it alternates with eye position (eg, right hypertropia on right gaze and left hypertropia on left gaze).\(^{14,15}\) Skew deviation often is associated with other neurologic signs and may be part of the ocular tilt reaction, which consists of a triad of skew deviation, ocular torsion, and head tilt.\(^{1,3,10}\) In ocular tilt reaction, the pathologic head tilt is ipsilateral to the hypertropic eye, and the ocular torsion is such that the upper poles of both eyes rotate in the same direction as that of the head tilt (ie, the hypertropic eye is excyclotorted and the hypertropic eye incyclotorted).\(^{9}\) This is in contrast to physiologic counterroll (see below), during which the upper poles of both eyes rotate in the opposite direction to that of the head tilt.

In skew deviation, the ocular torsion may be conjugate or dissociated between the 2 eyes, or it may be present in one eye only. Acutely, torsional nystagmus is commonly present. Patients with ocular tilt reaction also show a deviation of the subjective visual vertical—when presented with an earth-vertical line in a dark room in the absence of other visual cues, patients perceive the line as tilted toward the same side as the head tilt.\(^{9}\) Skew deviation and ocular tilt reaction are most commonly caused by ischemia, infarction, multiple sclerosis, tumor, trauma, abscess, hemorrhage, syringobulbia, and neurosurgical procedures.\(^{4,6}\) They can also be a finding in the setting of raised intracranial pressure.\(^{16}\)

Distinguishing From Trochlear Nerve Palsy

Trochlear nerve palsy is commonly diagnosed clinically with the “Park’s three-step test.”\(^{17}\) In contrast, the vertical misalignment in skew deviation does not follow any set
The utriculo-ocular pathway has usually been assumed to be disynaptic—primary afferents from otolithic receptors of the utricle in the inner ear project to second-order neurons in the vestibular nuclei, the axons of which then project to the oculomotor and trochlear nuclei via the medial longitudinal fasciculus. The midbrain syndrome,27 pons,28 medial longitudinal fasciculus (eg, lateral medullary syndrome),11,12 but adjacent tegmental structures in the brainstem may have been damaged also. Others5-7 have attributed skew deviation to cerebellar damage from surgery,6 or cerebellar diseases on the basis of clinical findings.6,7,13 In most cases,5-7,13,14,18,37 however, brainstem involvement had not been excluded by either

### Table 1. Clinical characteristics of trochlear nerve palsy versus skew deviation

<table>
<thead>
<tr>
<th>Trochlear nerve palsy</th>
<th>Skew deviation</th>
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<tr>
<td>1. Hypertropia in primary position</td>
<td>1. Hypertropia in primary position</td>
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<tr>
<td>2. Incomitant: hypertropia worse on gaze to opposite side acutely; may become comitant with time</td>
<td>2. Incomitant, comitant, or alternating</td>
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<tr>
<td>3. Hypertropia worse on ipsilateral head tilt</td>
<td>3. Hypertropia may or may not change with head tilt</td>
</tr>
<tr>
<td>4. Compensatory head tilt contralateral to the hypertropic eye</td>
<td>4. Pathologic head tilt contralateral to the hypertropic eye</td>
</tr>
<tr>
<td>5. Excyclotorsion of the hypertropic eye</td>
<td>5. Incyclotorsion of the hypertropic eye if present (and excyclotorsion of the hypotropic eye)</td>
</tr>
<tr>
<td>6. Usually no other neurologic signs (unless caused by brain trauma or lesions in brainstem)</td>
<td>6. Usually has other neurologic signs (eg, gaze-evoked nystagmus, gaze palsy, dysarthria, ataxia, hemiplegia)</td>
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neuroimaging or pathological correlation. To document that a discrete lesion in the cerebellum alone can cause skew deviation, we described in detail the clinical course of 5 patients with skew deviation caused by focal cerebellar lesions. Their lesions were identified by magnetic resonance imaging (MRI) with or without pathological correlation. These patients either had a vascular tumor or infarction in the cerebellar hemisphere or vermis or both.

Pathophysiology

In normal humans, when the head is tilted about the naso-occipital axis, the utricles are activated primarily to generate compensatory torsional eye movements in a direction opposite the head tilt. This torsional vestibulo-ocular reflex, termed ocular counterroll, however, compensates for only about 10% to 20% of the head tilt (eg, a 20° head tilt toward the right shoulder will result in the upper pole of both eyes to rotate 2° to 4° toward the left shoulder). Static ocular counterroll is important from a clinical standpoint because this otolith-driven reflex forms the basis of the Bielschowsky head-tilt test and it explains the compensatory head tilt in patients with trochlear nerve palsy. In normal humans, for example, during right head tilt, the static ocular counterroll activates the right superior oblique and superior rectus muscles, causing the right eye to incyclotort and elevate slightly. Simultaneously, the static ocular counterroll activates the left inferior oblique and inferior rectus muscles, causing the left eye to excyclotort and depress slightly. This reflexive vertical movement of the eyes is partly compensatory to downward translation of the right eye and upward translation of the left eye relative to the earth-horizontal plane due to the head tilt.

In a patient with right trochlear nerve palsy, however, during right head tilt, the elevating action of the superior rectus is unopposed by the palsied superior oblique in the right eye; thus, the right hypertropia increases during right (ipsilateral) head tilt, constituting a positive Bielschowsky head-tilt test (see also Jampolsky). Conversely, these patients often adopt a compensatory left (contralateral) head tilt to minimize their vertical strabismus and diplopia. Recently, however, there is some controversy about the existence of ocular counterroll. We provided further evidence to confirm its existence by demonstrating that the magnitude of ocular counterroll responses is dependent on the age of subjects, viewing distance, target characteristics, and whether or not the target moves simultaneously with the head.

The ocular tilt reaction is a pathological synkinetic triad of skew deviation, ocular torsion, and head tilt. It has been attributed to lesions in the vestibular organ and its nerve, and central connections within the brainstem or cerebellum that asymmetrically disrupt the utriculo-ocular pathway. The utriculo-ocular reflex originates in the maculae of the otolith organ, the utricle, which act as linear accelerometers. The hair cells on the maculae of the utricles have a wide range of polarization vectors that are sensitive to head motion in different directions, and they are oriented roughly in the horizontal plane. Thus the utricles normally mediate the linear or translational vestibulo-ocular reflex during translational motion of the head (ie, right-and-left and fore-and-aft head movements), as well as ocular counterroll during static head tilt (ie, head position with respect to gravity). Normally, balanced signals from the utriculo-ocular pathway are used to align the head’s vertical axis and the eye’s vertical meridian with absolute earth-vertical (gravity) when stationary. Damages to the utriculo-ocular pathway lead to an erroneous internal estimate of absolute earth-vertical (gravity); that is, the brain erroneously computes that the head is tilted despite that fact that the head is in an upright position and that the utricles lie in the horizontal plane. The triad of head tilt, skew deviation, and abnormal torsion seen in ocular tilt reaction represents a righting response, the goal of which is to realign the vertical axes of both the head and the eyes to the internal estimate of, albeit erroneous, absolute earth-vertical.

Abnormal static ocular torsion has been demonstrated in patients with skew deviation when they look straight ahead; however, it is unknown whether, or how, torsion is altered during dynamic eye movements or during different gaze directions and whether the relationship of ocular torsion with horizontal and vertical eye position (ie, Listing’s law) is intact in skew deviation. We found that in skew deviation, torsion was abnormal during fixation and dynamic eye movements (saccades) to different gaze directions. Interestingly, we also found that the relationship of ocular torsion with horizontal and vertical eye position was disrupted acutely, but not when the skew deviation is chronic (ie, ≥4 weeks’ duration), suggesting that the neural circuitry underlying Listing’s law is adaptive and is capable of restoring the law with time. What is the functional advantage of restoring Listing’s law? It enhances motor efficiency by minimizing the rotational eccentricity of the eye, thereby reducing the work load on the eye muscles against their elastic recoiling force. In addition, by keeping the eye near the center of its torsional range, Listing’s law allows the eye to respond quickly to targets that may appear unpredictably from any direction.

New Pathophysiologic Evidence

Almost 3 decades have passed since imbalance of the utriculo-ocular reflex was first proposed as responsible for skew deviation and ocular tilt reaction. However, surprisingly few studies have quantitatively documented abnormal otolith function in these patients. As discussed, the utricles normally mediate the linear vestibulo-ocular reflex during translational motion of the head as well as ocular counterroll during static head tilt in response to a change in head position with respect to gravity. We postulate that if skew deviation is indeed caused by imbalance of otolithic projections to ocular motor neurons, then in patients with skew deviation, the
ocular counterroll would be abnormal, the linear vestibular ocular reflex would be abnormal, and the abnormal torsion and vertical strabismus might be head position dependent.

In our first study, we investigated whether static ocular counterroll responses are abnormal in patients with skew deviation.10 Three patients with skew deviation caused by cerebellar lesions and 10 normal subjects were tested. We measured their ocular responses to static, passive head tilts of 30° toward each shoulder during monocular viewing. We found that static ocular counterroll gains were asymmetrical in each patient. This gain asymmetry between the eyes (right vs left) or between directions of head tilt (toward right vs left shoulder) or both provides evidence that imbalance of the utriculo-ocular reflex leads to cerebellar skew deviation.

In a second study, we investigated whether linear vestibulo-ocular reflex responses are abnormal in patients with skew deviation.53 Six patients with skew deviation caused by brainstem or cerebellar lesions and 10 normal subjects were studied. All subjects underwent brief, sudden, interaural translations of the head (ie, head heaves)54 while subjects were studied. All subjects underwent brief, sudden, interaural translations of the head (ie, head heaves)54 while continuously fixating an earth-fixed target monocularly. We found that linear vestibulo-ocular reflex sensitivities (the ratio of peak rotational eye velocity to peak linear head velocity) and velocity gains (the ratio of peak actual to geometrically ideal rotational eye velocities) in patients were decreased by 56% to 62% in both eyes as compared to normal subjects. This binocular reduction in linear vestibulo-ocular reflex responses was asymmetric—the magnitude of reduction differed between eyes by 37% to 143% for sensitivities, and by 36% to 94% for velocity gains. We concluded that the binocular but asymmetric reduction in linear vestibulo-ocular reflex sensitivity and velocity gain provides additional evidence that imbalance in the utriculo-ocular pathway is a mechanism of skew deviation.

A New Clinical Test

In a third study, we investigated whether the abnormal ocular torsion and vertical misalignment in skew deviation differed in the upright vs supine positions.55 We tested 10 patients with skew deviation, 14 with unilateral peripheral trochlear nerve palsy, and 12 normal participants. Skew deviation was defined as: (1) a vertical misalignment (with or without head tilt or fundus torsion), the pattern of which was inconsistent with that found in palsy of one or more cyclovertical muscles; (2) presence of lesions in the posterior fossa on MRI; and (3) presence of neurologic symptoms and signs. Unilateral peripheral trochlear nerve palsy was defined as: (1) deficient depression of the hypertropic eye in adduction; (2) incomitant hypertropia which increased with adduction of the hypertropic eye, and with head tilt toward the hypertropic eye; (3) presence of objective or subjective exyclodeviation, ie, torsional diplopia; (4) absence of any neurologic symptoms and signs suggestive of lesions in the trochlear nucleus or fascicle; and (5) negative MRI. Ocular torsion was measured by double Maddox rods while the subject fixated on a small white penlight located at a distance of 1 m in the midsagittal plane at eye level. Vertical misalignment was measured by the prism and alternate cover test while the subject fixated on a single letter e of optotype size 3/32 inch (12-point font size) at a distance of 1 m away.

We found that in skew deviation abnormal torsion and vertical misalignment are head position-dependent—they decreased substantially or disappeared completely when the head changed from an upright position to a supine position. In contrast, in unilateral peripheral trochlear nerve palsy, there were little or no changes in the torsional or vertical deviation between the 2 head positions. Torsion was decreased by 83% in skew deviation, by 2% in trochlear nerve palsy, and by 6% in normal subjects (p < 0.001). Similarly, vertical misalignment was decreased by 74% in skew deviation, increased by 5% in trochlear nerve palsy, and increased by 6% in normal subjects (p < 0.001).55

The head position-dependent changes in torsion and vertical misalignment we55 demonstrated provide the basis of additional tests that could be used clinically to differentiate skew deviation from trochlear nerve palsy. On the basis of the results from our previous study,55 we sought to investigate further the sensitivity and specificity of this new upright–supine test by defining a positive test as one in which the vertical misalignment decreased by ≥50% from the upright to supine position. By using the same definitions for skew deviation and trochlear nerve palsy as in our previous study,55 to date we have recruited 17 patients with skew deviation, 40 patients with trochlear nerve palsy, and 25 patients with other causes of vertical strabismus (eg, dysthyroidism, orbital trauma, Brown syndrome, childhood strabismus, peripheral oculomotor or abducens nerve palsy).56,57

Our preliminary (unpublished) results indicated that 13 of 17 patients with skew deviation had a positive upright–supine test, giving the test a sensitivity of 76%. No patients with trochlear nerve palsy or other causes of vertical strabismus had a positive upright–supine test, giving the test a specificity of 100%. Interestingly, all 4 patients with skew deviation who had a negative upright–supine test had a lesion in the midbrain on MRI, which may have caused a vertical strabismus as a result of a combination of skew deviation and trochlear nerve palsy (with or without concurrent oculomotor nerve palsy). Furthermore, they all had additional neurologic signs (eg, vertical gaze palsies, facial nerve palsy, bilateral ptosis).

What is the physiological basis of this new upright–supine test? We postulate that when changing from an upright to supine position, the orientation of the utricles changes from earth-horizontal to earth-vertical. This new orientation of the utricle with respect to absolute earth-vertical (gravity) leads to a saturation or reduction in the overall afferent activities of the utriculo-ocular reflex, such that any asymmetry of the reflex (as in skew deviation) is minimized. This saturation or reduction in activities and
asymmetry of the reflex in the supine position in turn leads to the reduction of torsion and vertical misalignment in skew deviation. Although the exact mechanism remains to be elucidated, our findings that torsion and vertical misalignment decrease when changing from an upright to supine position in skew deviation are consistent with the currently accepted role of the utricles in detecting changes in head orientation, and provide support that skew deviation is caused by disruption of the utriculo-ocular reflex.

It should be noted that in isolated unilateral peripheral trochlear nerve palsy, the utriculo-ocular pathway remains intact. Thus the magnitude of vertical deviation and exyclotorsion in the hypertropic eye remains the same in upright and supine positions. The contralateral head tilt commonly seen in unilateral trochlear nerve palsy is a compensatory mechanism that exploits the normal intact utriculo-ocular reflex to minimize the magnitude of vertical deviation and diplopia. Sydnor et al58 found that the head tilt in unilateral trochlear nerve palsy disappears in supine position. Because there is no change in utricular input or stimulation with head tilts when supine, the utriculo-ocular reflex is no longer effective in reducing the vertical deviation in unilateral trochlear nerve palsy in the supine position and thus the head tilt disappears.58 This is also the reason why the Bielschowsky head tilt test is not applicable in a supine position and should not be used in a bedridden patient who cannot sit in an upright position.

The double Maddox rods (ie, subjective torsion) and the prism and alternate cover test we used are simple and quick to perform. They can be performed with a near target as long as its distance from the patient is kept constant in both upright and supine positions. They also have the advantage of not requiring pupillary dilation or indirect ophthalmoscopy, which may not be readily available or feasible for nonophthalmologists, including neurologists and orthoptists. Fundus photography could also be used to document the change in objective torsion in skew deviation, but it requires special equipment (eg, Retcam; Clarity Medical Systems, Inc, Pleasanton, CA) that has the flexibility of taking fundus pictures in the supine position. Whatever method one chooses to measure torsion and vertical strabismus, the head position-dependent changes in torsion and vertical misalignment suggest skew deviation, and warrant investigation for a lesion in the posterior fossa as the cause of the vertical deviation and diplopia.

Summary

On the basis of our findings, we recommend the following (see Figure 1): when a patient presents with a vertical strabismus, a dissociated vertical deviation and pseudostrabismus (eg, ptosis, orbital or facial dysmorphism) should be ruled out. A mechanical restrictive cause also should be sought from the patient's history and clinical examination. If there is any sign of mechanical restriction, an orbital computed tomography or MRI should be ordered. If no sign of mechanical restriction is present, the 3-step test should then be performed. If the 3-step test is negative for trochlear nerve palsy and is suggestive of weakness of other cyclovertical muscles, a brain MRI with gadolinium enhancement should be performed because skew deviation can mimic palsy of any of the cyclovertical muscles. In addition, it is very unlikely for an oculomotor nerve palsy to present with isolated weakness of the superior rectus, inferior rectus, or inferior oblique muscle without ptosis or pupillary dilation. One should also suspect myasthenia gravis if other signs are present (eg, fatigability and variability of ptosis or diplopia). If the 3-step test is positive for trochlear nerve palsy, the upright–supine test should then be performed with a near target at 1/3 meter in both the upright and supine position. If this test is positive, that is, the vertical deviation decreases by $\geq 50\%$ from the upright to supine position, a brain MRI with gadolinium enhancement should be performed to rule out a lesion in the posterior fossa because skew deviation can mimic a trochlear nerve palsy during the 3-step test.

If, on the other hand, the upright–supine test is negative, that is, the vertical deviation decreases by $<50\%$ from the upright to supine position, then one should look for any additional neurologic signs (eg, gaze-evoked nystagmus, gaze palsy, facial nerve palsy, dysarthria, ataxia, hemiplegia). If other neurologic signs are present, a brain MRI with
gadolinium enhancement should be performed; if they are absent, the vertical strabismus is likely caused by a peripheral trochlear nerve palsy. In this situation, signs that are suggestive of a congenital cause should be looked for (eg, presence of a head tilt in old photographs, facial asymmetry, or increased vertical fusional amplitude). If these signs for a congenital cause are absent, the clinician should use his/her clinical judgment to decide whether neuroimaging is warranted.

The aforementioned algorithm is particularly useful when abnormal torsion is absent or not noticeable because although abnormal torsion is found in approximately 80% of patients with skew deviation, it is found only in approximately 40% of patients with trochlear nerve palsy. If abnormal torsion is present, dilated fundus examination or double Maddox rods are helpful in differentiating skew deviation from trochlear nerve palsy. In unilateral trochlear nerve palsy, the torsion is monocular (ie, excyclotorsion of the paretic hypertropic eye only, or a small excyclotorsion of the nonparetic hypotropic eye only), whereas in bilateral trochlear nerve palsy, the torsion is binocular but dissociative (ie, excyclotorsion of both eyes). In most skew deviations except for those caused by a lesion in the lateral medulla, the torsion is binocular and conjugate (ie, excyclotorsion of the hypertropic eye and incyclotorsion of the hypotropic eye). In patients with lateral medullary syndrome, the ocular torsion is monocular (ie, the hypertropic eye is excyclotorted, but the hypertropic eye has normal torsion or is slightly incyclotorted), and more importantly, these patients typically present with characteristic neurologic signs.

In conclusion, there is increasing evidence that skew deviation is caused by an imbalance in the utriculo-ocular pathway. Understanding the underlying pathophysiology of skew deviation has led to the discovery of a new bedside test to supplement the classic Park’s 3-step test in differentiating skew deviation from trochlear nerve palsy. Research is currently underway to determine more precisely the sensitivity and specificity of the upright-supine test we de-

References