The Nerve of That Muscle!
New Understanding of Innervation of the Extraocular Muscles
In Ocular Motility and Strabismus

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Relevance: Ophthalmologists commonly evaluate and treat incomitant strabismus attributed to lesions of motor nerves innervating extraocular muscles (EOMs). Recent developments in understanding of peripheral EOM innervation impact diagnosis and treatment of strabismus.

Delivery Format(s): Didactic lecture with open Q/A forum.

Content: The workshop will review recent genetic, histological, and functional magnetic resonance imaging (MRI) studies of congenital forms of strabismus that are primary cranial neuropathies: Duane syndrome, congenital fibrosis of the extraocular muscles, congenital oculomotor palsy, and Möbius syndrome. These findings will be contrasted with behavioral, histological, and MRI studies of acquired superior oblique (SO) palsy in a primate model. Evidence for non-aneurysmal neurovascular compression as a cause of paralytic strabismus also will be reviewed. The newly-discovered anatomic basis of compartmental innervation of rectus EOMs will be correlated with functional MRI during head tilt testing in SO palsy, as well as with clinical evidence for regional atrophy of individual EOMs. Practical recommendations for strabismus diagnosis and surgery will be discussed.

Learning Objective(s): At the conclusion of this presentation, attendees will be able to: understand most forms of special congenital strabismus as specific disorders of motor cranial nerve development and targeting; incorporate clinical imaging into their practices for diagnosis of neuropathic strabismus; expand the differential diagnosis of cyclovertical strabismus beyond SO palsy; and appreciate the potential contribution of selective compartmental control of rectus EOMs to management of strabismus.

Peripheral innervation to EOMs is much more complex than you learned in medical school, and neural control of EOM function is more nuanced. Progress in understanding EOM innervation is making it easier to diagnose and treat strabismus.

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Pre-Test

1. What happened to a denervated extraocular muscle, and how long does this take?

2. How many layers does each extraocular muscle have?

3. How many functional compartments does each horizontal rectus muscle have?

4. Does the lateral rectus muscle have torsional and vertical actions?

5. Does binocular visual experience reduce or increase strabismus due to acute superior oblique palsy?

6. Does Listing’s Law depend upon function of the superior oblique muscle?

7. What do hereditary Duane syndrome and congenital fibrosis of the extraocular muscles have in common?

8. True or false? Congenital fibrosis of the extraocular muscles is a primary myopathy of the eye muscles.
The Old and New in Ocular Motor Neuroanatomy

Joseph L. Demer, M.D., Ph.D.

I. Bilaminar extraocular muscles (EOMs)
   a. Orbital layer – translates pulleys
      i. Singly-innervated fibers
      ii. Multiply-innervated fibers
   b. Global layer – rotates the globe via tendon insertion on the sclera
      i. Multiply-innervated fibers – small, non-twitch
      ii. Singly-innervated fibers – three types of twitch fibers

II. Oculomotor Nerve
   a. Cell bodies near the aqueduct in the midbrain.
      i. Peripheral motor neurons innervate multiply-innervated muscle fibers
      ii. Central motor neurons innervate singly-innervated muscle fibers.
   b. Nerve divides into two divisions deep to the orbit.
      i. Superior division – superior rectus and levator
      ii. Inferior division – medial rectus, inferior rectus, inferior oblique, ciliary body, and
         sphincter of pupil.
   c. Inferior rectus – multiple bifurcations and reanastamososes on global surface of muscle
      before entering and arborizing anteriorly. Significant mixing of territories innervated by
      principle motor nerve trunks.
   d. Inferior oblique – compact nerve parallels lateral surface of inferior rectus, then turns
      sharply to enter inferior oblique muscle’s inferolateral surface at the pulley. Cell bodies
      of ciliary ganglion may be scattered along the motor nerve.
e. Medial rectus – large, relatively anterior motor branch crosses orbit from temporal to nasal, bifurcates into non-overlapping superior and inferior divisions that enter the global surface of the muscle and bifurcate further as they course anteriorly. The two divisions innervate separate functional compartments.

f. Superior rectus – multiple bifurcations before entering the global surface of the muscle in the deep orbit. Bifurcations are highly mixed, without compartmentalization.

III. Trochlear nerve

a. Cell bodies near the aqueduct in the midbrain, just caudal to oculomotor nucleus.

b. Mostly, but not totally, decussated. At least 3% ipsilateral projection.

c. Motor nerve enters the superior surface of the superior oblique muscle and bifurcates within the muscle as branches course anteriorly.

IV. Abducens nerve

a. Cell bodies in the ipsilateral pons

b. Motor nerve divides into two approximately-equal, distinct trunks somewhere between the brainstem and the lateral rectus muscle.

c. Inferior trunk enters the muscle 0.4 – 2.4 mm more posteriorly than the anterior trunk, with each trunk bifurcating repeatedly before entering the muscle, and further bifurcating within the muscle as progeny course anteriorly.

d. The two divisions innervate separate functional compartments, comprised of separate sets of muscle fibers.

V. Non-classical Nerves

a. Small nerves enter the rectus muscles from the orbital surface near the orbital apex

b. Some small nerves run among adjacent rectus muscles.

c. Some of these nerves form a network interconnecting 5 – 10 muscle spindles in the orbital layer of each muscle, which are believed to be proprioceptive organs.
VI. Autonomic Nerves

a. Smooth muscle targets
   i. Muscular blood vessels
   ii. Muller’s smooth muscle
   iii. Pulley smooth muscle
   iv. Scleral myofibroblasts
   v. Choroidal smooth muscle

b. Source ganglia
   i. Pterygopalatine ganglion (and scattered elsewhere in the orbit) – nitric oxide neurotransmitter
   ii. Ciliary ganglion – acetylcholine neurotransmitter. Irregular structure between optic nerve and lateral rectus muscle in deep orbit, with scattered ganglion cells on the sclera, along the inferior oblique nerve, and elsewhere in the orbit.
   iii. Superior cervical ganglion – norepinephrine neurotransmitter, fibers travel in a plexus along the carotid artery and then along smaller arteries into the orbit.

VII. Proprioceptive Nerves

a. Palisade endings
   i. Innervated myotendonous cylinders at termination of each multiply-innervated global layer fiber in rectus EOMs.
   ii. Formerly believed to be proprioceptive…
   iii. But, axons use motor neurotransmitter acetylcholine and have other motor features.
   iv. Axons run anteriorly before turning posteriorly to run into the deep EOM.
   v. Nearby cholinergic axons terminate directly on tendon fibers. Function of these strange structures is mysterious.
vi. It is unclear if there are any proprioceptive nerves or organs in the rectus muscle tendons.

b. Spindles

i. Comprised of several orbital layer myofibers and nerve terminal(s) within a thin capsule. Very similar to proprioceptive spindles in skeletal muscles.

ii. Only a handful of spindles per muscle.

iii. Innervated by a separate network of myelinated nerves originating in the orbital apex and interconnecting all the spindles in the same muscle.

References


Functional Evidence for Compartmentalization

In Horizontal Rectus Extraocular Muscles

Robert A. Clark, M.D.

I. Bifid Abducens Innervation
   A. Potential to improve control of eye movement
      1. Offset imbalances during gaze changes
      2. Induce torsion during head tilts
   B. Measurement of Compartmental Contractility
      1. Direct measurement invasive and technically difficult
      2. MRI provides imaging markers for contractility
         a. Change in maximum EOM cross-sectional area
         b. Shift of EOM volume posteriorly

II. Lateral Rectus in Ocular Counter-Rolling
   A. Eight normal subjects
   B. Nine subjects with chronic unilateral SO palsies
   C. Imaged in 90° left and right head tilt
      1. Verified control of horizontal gaze position
      2. Fixated with “up” (extorted) eye in both gaze positions
   D. Image Analysis
      1. Rotate each image plane to bring the LR to scanner vertical
      2. Cropped each image to include only the LR belly
      3. Split the LR belly in half vertically in scanner coordinates
      4. Measure the cross-sectional area of the superior and inferior halves
5. Multiply cross-sectional areas by slice thickness to calculate volume

E. Results

1. LR Superior Compartment – Up (Extorted) versus Down (Intorted)
   a. No significant change in max cross-sectional areas for any group
   b. No significant changes in volumes for any group

2. LR Inferior Compartment – Up (Extorted) versus Down (Intorted)
   a. Highly significant change in normal and SO palsy contralesional max cross-sectional areas
   b. Highly significant change in normal and SO palsy contralesional volumes
   c. No significant change in either value for SO palsy ipsilesional orbits

F. Conclusions

1. MRI detects statistically significant increased contractility of the inferior LR compartment during excyclotorsion

2. The difference in LR compartmental contractility is blunted in the orbit with SO palsy

3. The LR superior and inferior compartments appear to have independent control of innervation

III. Theoretical Implications

A. Orbit® predicts compartmental LR contraction can create about 6 degrees of excyclotorsion

B. Force Vector Analysis

1. Equal Compartmental Contractility – No net torsion (only abducting force)

2. Unequal Compartmental Contractility – Approximately 20% of the inferior LR compartmental force is vertical and/or torsional

C. Diminished LR Compartmental Contractility in SO Palsy

1. Paretic orbit has excess excyclotorsion

2. Reduced LR inferior compartment contractility should reduce excyclotorsion
3. Change in behavior implies active neurological control

D. Modified Surgical Approaches to Torsion

1. Split LR surgery might be used to correct torsion

2. Surgery to restore a displaced LR path should reduce abnormal torsion

E. Future Investigation

1. Differential LR contractility in other positions of gaze?

2. Effect of LR surgery on torsion?

3. Differential innervation and contractility for other extraocular muscles?

Reference

Primate Model of Experimental Superior Oblique Palsy

Howard Ying, M.D., Ph.D.

I. Problems with human studies:
   A. Etiology of vertical misalignment may not be clear (possible assignment error)
   B. Repeated measurements and perturbations are limited
   C. Histology is rarely possible

II. Intracranial trochlear nerve transection in the cavernous sinus (Lewis et al., 1994)
   A. Protocol: Acute IV nerve transection, normal eye viewing for 4 weeks, binocular viewing through neutralizing base-down prism for 2 weeks, monocular viewing for 1 week, ipsilateral intracranial V1 section, repeat data collection
   B. Eye Movement Methods: single implanted scleral search coil in the frontal plane.
   C. Results:
      1. Vertical strabismus was worse in down gaze,
      2. Comitancy but not average deviation improved with binocular viewing, and
      3. After deafferentation, comitancy worsened and pulse-pulse ratio increased due to increase in paretic eye pulse.
   D. Conclusions: Error signal to regulate long-term ocular alignment may be derived from a mismatch between efference copy and proprioceptive afference.

III. Intracranial trochlear nerve transection in the cavernous sinus (Lewis et al., 1999)
   A. Protocol: Acute IV nerve transection, normal eye viewing for 4 weeks, binocular viewing for 2 weeks, binocular viewing through disparity-reducing base-down prism for 2 weeks, paretic eye viewing for 2 weeks, ipsilateral intracranial V1 section, repeat data collection.
B. Eye Movement Methods: single implanted scleral search coil in the frontal plane.

C. Results:

1. Post-saccadic drift in the paretic eye was suppressed during binocular viewing even when there was no fusion,

2. During paretic eye viewing, post-saccadic drift was suppressed in the paretic eye and induced in the normal eye,

3. After deafferentation, change in paretic eye post-saccadic drift was variable without changing post-saccadic drift in the normal eye

D. Conclusions: Post-saccadic drift appeared to occur disconjugately, did not require binocularity, did not minimize retinal slip, and did not require proprioceptive afference in the paretic eye.

IV. Intracranial trochlear nerve transection in the middle cranial fossa – changes in static eye alignment (Shan et al., 2007a)

A. Protocol: Acute IV nerve transection, normal eye viewing for 6-9 days, binocular viewing for 4 weeks,

B. Eye Movement Methods: dual implanted scleral search coil in the frontal and superotemporal planes, measurement in 9 positions of gaze at ± 20° eccentricity.

C. Results:

1. Vertical strabismus was worst in down gaze and adduction, while torsion strabismus was worst in down gaze and abduction

2. During the first 5-6 days, comitancy and average deviation improved, then during the next 3-4 weeks, comitancy was variable while average strabismus worsened with the head straight or tilted

3. Changes in vertical and torsion gradients were nearly constant, with mild horizontal dependence across the visual field, and
4. Vertical and torsional deviations from experimental SOP in monkeys correlates well with clinical SOP in humans.

D. Conclusions: Improvement in alignment during the first 5-6 days after lesion while viewing monocularly suggests a role for proprioception.

V. Intracranial trochlear nerve transection in the middle cranial fossa – changes in dynamic properties during vertical saccades (Shan et al., 2007b)

A. Protocol: Acute IV nerve transection, normal eye viewing for 6-9 days, binocular viewing for 4 weeks,

B. Eye Movement Methods: dual implanted scleral search coil in the frontal and superotemporal planes, measurement of vertical saccade pulse, velocity, drift, and intrasaccadic blips from each of the 9 positions of gaze at ± 20º eccentricity.

C. Results:

1. Vertical saccade amplitude was smaller for the paretic eye (PE), especially downward saccades

2. Vertical drift reduced retinal image disparity except for downward saccades with the PE in abduction

3. Peak dynamic blip (intrasaccadic torsion) increased more for upward saccades (relative extorsion) with the PE in abduction

4. postsaccadic torsional drift increased more for downward saccades (relative intorsion) with the PE in adduction

5. Peak velocity-amplitude relationship in vertical saccades was little affected, but the ratio between the peak velocity of the two eyes was a consistent indicator of the palsy

D. Conclusions: Rhesus monkeys with acute acquired SOP show characteristic changes in vertical and torsional movements during and immediately after vertical saccades that
help define the ocular motor signature of denervation of the SO muscle. These dynamic changes were largely unrelated to the changes in static alignment over time, suggesting that static and dynamic disturbances in SOP are influenced by separate central mechanisms.

VI. Intracranial trochlear nerve transection in the middle cranial fossa – relationship to Listing’s Law (Tian et al., 2007)

A. Protocol: Acute IV nerve transection, normal eye viewing for 6-9 days, binocular viewing for 4 weeks,

B. Eye Movement Methods: dual implanted scleral search coil in the frontal and superotemporal planes, measurement during fixation in a 40º x 40º grid.

C. Results:

1. In the paretic eye, Listing’s plane (LP) rotated 25° temporally,
2. LP thickness (torsional standard deviation) increased only by 0.08° to 0.13° after SOP, and
3. LP thickness during saccades did not change after SOP.

D. Conclusions: Acute SOP in rhesus monkeys leads to a temporal rotation of LP. This is consistent with a relatively increased extorsion in down gaze due to a loss of normal intorsion by the superior oblique muscle. The SD of torsion increased by only a small amount, implying that the validity of Listing’s Law is not affected much by complete SOP, despite the large change in the orientation of LP.

VII. Intracranial trochlear nerve transection in the middle cranial fossa – changes in torsional optokinetic nystagmus (Shan et al., 2008)

A. Protocol: Acute IV nerve transection, normal eye viewing for 6-9 days, binocular viewing for 4-8 months, denervation of ipsilateral inferior oblique muscle, binocular
viewing for 4 months, contralateral inferior rectus recession, binocular viewing for 4 months,

B. Eye Movement Methods: dual implanted scleral search coil in the frontal and superotemporal planes, measurement during viewing a 60º rotating wheel with 20 radial segments, rotating 40 °/s clockwise (CW) or counterclockwise (CCW).

C. Results:

1. After SOP, torsional quick and slow phases were smaller and slower but vertical motion was increased for the paretic eye for both CW and CCW rotations,

2. After corrective inferior oblique surgery, both of these effects were even greater

D. Conclusions: Torsion OKN reflects alterations in the dynamic properties of the extraocular muscles involved in eye torsion, provides information complementary to that provided by alignment (Bielschowsky head-tilt test), and potentially can help distinguish among different causes of vertical ocular misalignment.

VIII. Intracranial trochlear nerve transection in the middle cranial fossa – effects of viewing conditions on ocular alignment and modeling of the ocular motor plant (Quaia et al., 2008)

A. Protocol: Acute IV nerve transection, normal eye viewing for 6-9 days, binocular viewing for 4 weeks,

B. Eye Movement Methods: dual implanted scleral search coil in the frontal and superotemporal planes, measurement in 9 positions of gaze at ± 20º eccentricity, a SQUINT-based model was adapted to monkey geometry.

C. Results:

1. The model reproduced the observed acute deficit induced by SOP only after abandoning Robinson's symmetric simplification of the reciprocal innervation relationship within pairs of agonist-antagonist muscles (Sherrington's Law).
Physiologic variability in orbital geometry has a large impact on model predictions for SOP deficits.

D. Conclusions: The validity of Sherrington’s Law after SOP should be examined.

IX. Intracranial trochlear nerve transection in the middle cranial fossa – effect on vertical pursuit (Tian et al., 2008)

A. Protocol: Acute IV nerve transection, normal eye viewing for 6-9 days, binocular viewing for 4 weeks,

B. Eye Movement Methods: dual implanted scleral search coil in the frontal and superotemporal planes, measurement of vertical pursuit movements along the midline using triangular-wave (20°/s, ±20°) or step-ramp (20°/s) stimuli at a distance of 66 cm.

C. Results:

1. During the early post-lesion period, before binocular viewing was allowed,
   a. pursuit velocity of the paretic eye during upward or downward triangular-wave tracking was lower than that of the normal eye
   b. When the viewing eye crossed straight ahead, the changes in pursuit velocity conjugacy were similar for upward and downward tracking.

2. After habitual binocular viewing was allowed, downward pursuit velocity trended lower than upward pursuit velocity that was less dramatic during the open-loop period of step-ramp tracking than during triangular-wave tracking.

D. Conclusions: After acute acquired SOP, there were deficits for both upward and downward tracking that appeared to be influenced by the habitual viewing condition (monocular versus binocular).

X. Overall conclusions
A. Rhesus monkeys with acute acquired SOP show characteristic changes in alignment, smooth pursuit, saccades, and torsion OKN response that help define the ocular motor signature of denervation of the SO muscle.

B. Changes in dynamic characteristics: pulse-pulse ratios, post-saccadic drift, dynamic torsion, etc. were largely unrelated to the changes in static alignment over time, suggesting that static and dynamic disturbances in SOP are influenced by separate central mechanisms.

C. Early improvement in alignment during the first 5-6 days after the lesion while viewing monocularly suggests a role for proprioception rather than retinal image disparity or efference copy.

D. Error signal to regulate long-term ocular alignment is still mysterious.

References:


Microanatomy of Superior Oblique Palsy in Primate

Joseph L. Demer, M.D., Ph.D.

I. MRI confirms of neurogenic atrophy of superior oblique (SO) muscle
   a. Cross section of deep muscle belly is markedly reduced
   b. Muscle mass shifts anteriorly so anterior cross sections may be increased.
   c. Although maximum cross section is reduced, overall SO muscle volume is preserved.
      This implies that the denervated SO becomes elongated, correlating with the “floppy tendon” phenomenon.

II. Histology
   a. No evidence of trochlear nerve regeneration up to 15 months post-neurectomy
   b. Trochlear nerve fibrosis
   c. Residual muscle mass shifts anteriorly, supporting elongation.
   d. Neurogenic atrophy complete within five weeks post-neurectomy.
      1. Severe atrophy of global layer fibers
      2. Little atrophy of orbital layer fibers
      3. A few nerves run from orbital layer into global layer
      4. Occasional giant fibers in global layer might reflect re-innervation (autonomic, sensory, or non-classical?). These fibers run nearly the entire length of the SO.
      5. Variable fiber atrophy along length of each fiber.

Reference

Congenital Cranial Dysinnervation Disorders

Joseph L. Demer, M.D., Ph.D.

I. Dysinnervation as a common theme
   a. Oculomotor nerve
      1. Hypoplasia
      2. Misdirection
   b. Trochlear nerve is often small or absent.
   c. Abducens nerve
      1. Often small or absent
      2. Often replaced or supplemented by oculomotor nerve branch
   d. Numerous specific mutations affecting cranial motor neural development and axon targeting.

II. Duane syndrome
   a. Superior lateral rectus (LR) zone is either innervated by the abducens nerve, or is non-innervated and severely hypoplastic
   b. Inferior lateral rectus (LR) zone is either innervated by: 1) the abducens nerve; 2) a medial or inferior rectus motor branch of the oculomotor nerve; or 3) both the abducens and oculomotor nerves.
   c. DURS2 – dominant Duane syndrome due to gain of function α2-chimaerin that stabilizes microtubules involved in axonal transport.
      1. Bilateral but not necessarily symmetrical type I and/or III
2. A- of V-pattern: lateral rectus inferior zone contracts or relaxes in infraduction, relaxes or contracts in supraduction.

3. Occasional structural abnormalities of extraocular muscles
   a. Superior oblique muscle hypoplasia - occasional
   b. Superior rectus hypoplasia - occasional

4. Subclinical optic nerve hypoplasia.

5. Oculomotor nerve hypoplasia – occasional

6. Abducens nerve hypoplasia - always

III. Congenital fibrosis of the extraocular muscles (CFEOM)

   a. Three types
   
   1. CFEOM1 – typical. Dominant, with bilateral blepharoptosis, limited supraduction, other strabismus.
   2. CFEOM2 – recessive, congenitally bilateral exotropic ophthalmoplegia and blepharoptosis, may have fixed infra- or supraduction.
   3. CFEOM3 – atypical dominant or recessive form; includes individuals from pedigrees with CFEOM that can be clinically indistinguishable from CFEOM1 or CFEOM2. Other pedigree members, however, have absent or unilateral ptosis, unilateral ophthalmoplegia, non-infraducted resting eye position, and/or the ability to supraduct one or both eyes above central position.

   b. CFEOM1

   1. Maps to chromosome 12
   2. Due to a small number of recurrent heterozygous missense mutations in developmental kinesin motor protein encoded by KIF21A
   3. Clinical findings
      ii. Mostly A-exotropia
iii. Occasionally esotropia

iv. Frequent amblyopia

v. Frequent exposure keratopathy after surgery for blepharoptosis

vi. Forced duction testing – restrictive

vii. Bell’s phenomenon absent

4. Extraocular muscle hypoplasia

   i. Severe levator hypoplasia

   ii. Severe superior rectus hypoplasia

   iii. Inferior oblique hypoplasia

   iv. Superior oblique occasionally hypoplastic

   v. Longitudinal fissure separating superior and inferior LR zones, with

      inferior zone sometimes innervated by oculomotor nerve

      similarly to Duane syndrome

   vi. Hypo-innervated muscles – severely hypoplastic

   vii. Unopposed, innervated antagonists – stiff, but **not** fibrotic

   viii. Pulleys normal

5. Cranial nerve hypoplasia

   i. Optic nerve – usually subclinical

   ii. Oculomotor nerve – consistently severe

   iii. Occasionally abducens nerve – similar to Duane syndrome

6. Clinical suggestion – aggressive surgical ablation (extirpation) is appropriate for

   muscles that lack innervated antagonists. MRI can confirm this pre-op.

c. CFEOM3

   1. Multiple mutations
2. Commonly due to missense mutations in \textit{TUBB3}, encoding neuron-specific $\beta$-tubulin isotype III
   
i. Also involved in axonal transport, similar to KIF21A.
   
ii. Other mutations

3. Clinical findings
   
i. asymmetrical blepharoptosis
   
ii. limited vertical duction
   
iii. variable ophthalmoplegia
   
iv. exotropia
   
   v. paradoxical abduction in infrawduction with A-pattern

4. MRI findings
   
i. Muscle hypoplasia correlates with clinical weakness
   
ii. Oculomotor nerve hypoplasia - ophthalmoplegia only when subarachnoid CN3 width <1.9 mm
   
iii. A-pattern exotropia with innervation of inferior LR zone by oculomotor nerve branch
   
   iii. Subclinical optic nerve hypoplasia

d. Congenital oculomotor palsy
   
1. Incomplete features of pupillary abnormality, ophthalmoplegia, ptosis
   
2. Frequently bilaterally asymmetrical

3. MRI findings
   
i. Hypoplastic subarachnoid oculomotor nerve
   
ii. Hypoplastic orbital motor nerves
   
   iii. Hypoplasia of extraocular muscles innervated by oculomotor nerve

4. Consider similarities to CFEOM
e. Möebius syndrome variant
   i. Congenital facial palsy and ophthalmoplegia
   ii. Severe hypoplasia of all extraocular muscles
   iii. Severe orbital hypoplasia
   iv. Normal cranial nerves

References


