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Eye Movement Disorders in MS. Focus on Internuclear Ophthalmoparesis.

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Identify most common eye movements disorders encountered in MS
2. Describe clinical presentation and anatomical substrate of Internuclear Ophthalmoparesis (INO) in MS
3. Identify clinical syndromes due to lesion of the medial longitudinal fasciculus (MLF)
A Roadmap to this Talk

• Brief overview of common eye movement disorders encountered in Multiple Sclerosis (MS)
• Internuclear Ophthalmoparesis (INO) in MS
  - Anatomical substrate and pathogenesis
  - Clinical presentation of INO and syndromes associated with lesions of the medial longitudinal fasciculus (MLF)
  - The MLF as a disease model in MS
• A case of INO treated with dalfampridine in a patient with MS
Eye Movement Disorders in MS

- Virtually all disorders of eye movements can be encountered in multiple sclerosis (MS)
- Eye movement disorders are common in MS and mostly arise from lesions of the **posterior fossa (brainstem and cerebellum)**
- The presence of EM abnormalities correlate with **greater level of disability** in affected patients and a worse prognosis *(Derwenskus et al, 2005)*
Common EM disorders in MS

**Brainstem syndromes**

* Syndromes associated with lesion of the MLF
  - internuclear ophthalmoplegia (INO), can be bilateral
  - skew deviation and ocular tilt reaction (OTR)
  - wall-eyed bilateral INO (WEBINO)

* Ocular motor cranial nerves and nuclear syndromes
  - Paresis of CN III-IV-VI
  - horizontal gaze palsy

* Midbrain syndromes
  - upward or downward gaze palsy
Common EM disorders in MS

**Cerebellar syndromes**

- impaired smooth pursuit
- gaze-evoked nystagmus and rebound nystagmus
- downbeat nystagmus
- positional nystagmus
- saccadic dysmetria
- Saccadic intrusions and oscillations
**Cerebellar syndromes**

- impaired smooth pursuit
- **gaze-evoked nystagmus and rebound nystagmus**
- downbeat nystagmus
- positional nystagmus
- saccadic dysmetria
- Saccadic intrusions and oscillations

**Flocculus and paraflocculus (tonsil)**

*Courtesy of Leigh and Zee*
Cerebellar syndromes

- impaired smooth pursuit
- gaze-evoked nystagmus and rebound nystagmus
- **downbeat nystagmus**
- positional nystagmus
- saccadic dysmetria
- Saccadic intrusions and oscillations

Flocculus and paraflocculus (tonsil)

Common EM disorders in MS

Courtesy of Leigh and Zee
Common EM disorders in MS

Cerebellar syndromes

- impaired smooth pursuit
- gaze-evoked nystagmus and rebound nystagmus
- downbeat nystagmus
- **positional nystagmus**
- saccadic dysmetria
- Saccadic intrusions and oscillations

nodulus & ventral uvula
Common EM disorders in MS

**Cerebellar syndromes**
- impaired smooth pursuit
- gaze-evoked nystagmus and rebound nystagmus
- downbeat nystagmus
- **positional nystagmus**
- **saccadic dysmetria**
- Saccadic intrusions and oscillations

Dorsal vermis (OMV) & posterior fastigial nucleus (FOR)

Courtesy of Leigh and Zee
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medial rectus muscle
lateral rectus muscle
lateral rectus motoneuron
abducens nerve
abducens nucleus
MLF
Abducens Nucleus
oculomotor nerve
medial rectus muscle
oculomotor nerve
 Midnight
Vergence
Oculomotor Nucleus
Abducens Nucleus
medial rectus motoneuron
inter nuclear neuron
lateral rectus motoneuron
Pons
BRAINSTEM
lateral rectus muscle
medial rectus muscle
lateral rectus motoneuron
oculomotor nerve
Abducens Nucleus
lateral rectus motoneuron
internuclear neuron
Abducens Nucleus
MLF
Pons
Midbrain
Oculomotor Nucleus
right eye
demyelination
MLF
BRAINSTEM
Courtesy of Frohman T.
Clinical Presentation of INO

Bilateral INO convergence may be preserved
Clinical Presentation of INO

The weak eye might eventually get on target but it gets there slowly.

Ask the patient to look between 2 targets and not to just follow your finger.
Internuclear Ophthalmoparesis

• INO is the most common saccadic eye movement disorder observed in MS
• The *dissociated nystagmus* of the abducted eye consists, in fact, of saccadic oscillations and represents an adaptive response (*Zee et al, 1987*)
• Some patients will describe symptoms only during head or head-on-body turns (walking or driving!) because of a transient *break in binocular fusion* (*Mills et al, 2008*)
• INO is therefore a serious cause of *visual disability* for patients affected
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The MLF also carries information from the otololiths and vertical canals of the inner ear.
MLF lesion - associated syndromes

SKEW DEVIATION AND OTR

- Skew deviation is a vertical misalignment of the visual axes due to a lesion involving the vestibulo-ocular pathways (Cogan, 1956)
- Skew deviation is due to a lesion involving the otolithic pathways, which can be injured at any site as they ascend within the brainstem, including the MLF
- **Skew deviation may accompany INO**, in which case the higher eye is usually on the side of the lesion
- Skew deviation can be a part of **ocular tilt reaction (OTR)**

OTR is a triad of lateral head tilt, skew deviation and ocular torsion caused by damage of utricular and vertical semicircular canal input

Brodsky, 1999
MLF lesion - associated syndromes

SKEW DEVIATION AND OTR - GRAVICEPTIVE PATHWAYS

Brandt and Dieterich, 1994
MLF lesion - associated syndromes

SKEW DEVIATION AND OTR

Skew deviation in a patient with Left INO

contraversive OTR

hypertropia on the side of the lesion
MLF lesion - associated syndromes

INO AND SKEW DEVIATION

CLINICAL CONSIDERATIONS

- Patients with unilateral INO should also be examined for ocular torsion and a head tilt to the contralateral side
- INO-associated diplopia (vertical) might derive from non evident skew deviation that is sufficient to prevent fusion
- Placement of a small vertical prism may be all that is necessary to relieve the diplopia and restore binocular vision
MLF lesion - associated syndromes

**wall-eyed bilateral INO - WEBINO**

- When the MLF lesion is far rostral within the midbrain, then *vergence can be affected*
- Intact bilateral abduction but nearly absent adduction in either direction of gaze: wall-eyed bilateral INO (WEBINO) syndrome

*Courtesy of Frohman T. et al*
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Raising core body temperature by 0.8°C worsens INO in patients with MS, because of deterioration of conduction along the demyelinated MLF (Davis et al. Neurology 2008)
Fatigue in MS is a poorly understood entity and is usually classified in primary (cognitive and motor) or secondary to other symptoms (bladder incontinence, sleep problems, etc).

Motor Fatigue is defined as an exercise-induced reduction in the force-generating capacity, and it can interfere with exercise-based rehabilitation.

However, no reliable neurophysiologic model is available for primary motor fatigue in MS.

Motor fatigue in MS is unrelated to energy costs (Kempen et al, 2012), therefore fatigue in MS must be mainly central in origin.

Eye movements are suitable for studying components of central fatigue: No peripheral fatigue exists for eye movements (Fuchs, Thier) Extraocular muscles show no motor deconditioning (atrophy from diminished use)

One probable component of primary motor fatigue in MS is due to faulty conduction of neural signals along demyelinated pathways…
Could INO be a model for fatigue in MS?

Matta et al., 2009
A Fatigue Test for Horizontal Eye Movements

Make large (20°) saccades every second for 10 minutes

With this fatigue test –

- Controls: No change in conjugacy
- MS patients: Mild INO became worse

Representative Responses
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Representative Responses

![Graph showing eye velocity over time with labels for Late Abduction and Early Abduction.](image)
A Fatigue Test for Horizontal Eye Movements

Make large ($20^\circ$) saccades every second for 10 minutes

With this fatigue test –

Controls: No change in conjugacy
MS patients: Mild INO became worse

Representative Responses

Abduction/Adduction Peak Velocity Ratio = Measure of INO Severity
A Fatigue Test for Horizontal Eye Movements

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Representative Responses

![Eye Movement Graph]

- Adduction
- Fatigue

Eye Velocity (degrees/second) vs Time (seconds)
The MLF as a disease model in MS

• INO has proven a useful *model for Uhthoff’s phenomenon in MS*, as neural conduction deteriorates along demyelinated pathways.

• INO could provide a *reductionist model for primary motor fatigue* to study how decreased neural transmission determines fatigue in MS, and to test efficacy of appropriate therapies.

• MLF imaging with modern techniques could be used as a *model for defining state of disease* and response to treatment.
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INO treatment with Dalfampridine

• Dalfampridine (Ampyra®) is a potassium channel blocker that enhances conduction along demyelinated axons
• Dalfampridine is FDA-approved for gait imbalance in MS
• On a follow up visit, one of our VA patients with chronic bilateral INO said: “That Ampyra improved my vision, Doc.”

Before Ampyra

3h after Ampyra
Dalfampridine should be considered to treat INO in patients with MS as this can dramatically decrease their visual disability.

Preliminary data suggest that Dalfampridine also improves INO fatigue.
Conclusions

• **Eye movements examination** in MS can provide useful information on localization of lesions, progression of disease and level of disability

• Internuclear ophthalmoparesis (INO) may be used to *model Uhthoff sign and fatigue* in MS

• The medial longitudinal fasciculus (MLF) could be a privileged site to determine state of the disease by correlating eye movement recording findings to advanced neuroimaging results

• Modeling such changes may help identify *new treatments* to mitigate the disabling effects of increased temperature, infection, prolonged exercise, and stress in patients with MS

• **Dalfampridine** may be a useful option to reduce visual disability in MS patients with INO
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