CHAPTER **e11** Video Library of Neuro-Ophthalmology

Shirley H. Wray

The proper control of eye movements requires the coordinated activity of many different anatomic structures in the peripheral and central nervous system, and in turn manifestations of a diverse array of neurological and medical disorders are revealed as disorders of eye movement. In this remarkable video collection, an introduction to distinctive eye movement disorders encountered in the context of neuromuscular, paraneoplastic, demyelinating, neurovascular and neurodegenerative disorders is presented.

Cases with Multiple Sclerosis

Video e11-1 (Play video) Fisher's One and a Half Syndrome (ID164-2)

Video e11-2 (Play video) A Case of Ocular Flutter (ID166-2)

Video e11-3 (Play video) Downbeat Nystagmus and Periodic Alternating Nystagmus (ID168-6)

Video e11-4 (Play video) Bilateral Internuclear Ophthalmoplegia (ID933-1) Cases with Myasthenia Gravis or Mitochondrial Myopathy

Video e11-5 (Play video) Unilateral Ptosis: Myasthenia Gravis (Thymic Tumor) (ID163-1)

Video e11-6 (Play video) Progressive External Ophthalmoplegia (PEO: Mitochondrial Cytopathy) (ID906-2) Cases with Paraneoplastic Disease

Video e11-7 (**Play video**) Paraneoplastic Upbeat Nystagmus. Ca Pancreas. Positive Anti-Hu Antibody (ID212-3)

Video e11-8 (Play video) Paraneoplastic Ocular Flutter, Small Cell Adenocarcinoma of the Lung, Negative Marker (ID936-7)

Video e11-9 (Play video) Opsoclonus/Flutter. Bilateral Sixth Nerve Palsy, Adenocarcinoma of the Breast, Negative Marker (ID939-8)

Cases with Fisher Syndrome

Video e11-10 (Play video) Bilateral Ptosis: Facial Diplegia, Total External Ophthalmoplegia, Positive Anti-GQ1b Antibody (ID944-1) Cases with Vascular Disease

Video e11-11 (Play video) Retinal Emboli (Film or Fundus) (ID16-1)

Video e11-12 (Play video) Third Nerve Palsy (Microinfarct) (ID939-2) Case with Neurodegenerative Disease

Video e11-13 (Play video) Apraxia of Eyelid Opening (Progressive Supranuclear Palsy) (ID932-3)

Case of Thyroid Associated Ophthalmopathy

Video e11-14 (Play video) Restrictive Orbitopathy of Graves Disease, Bilateral Exophthalmos (ID925-4)

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| VIII | | P I I | |

| Metadata Element Field | Metadata |
|------------------------|---|
| Identifier | 164-2 |
| Title | Fisher's One-and-a-Half Syndrome |
| Ocular Movements | Unilateral Internuclear Ophthalmoplegia; |
| | Unilateral Horizontal Gaze Palsy; |
| | Upbeat Nystagmus on Upgaze; |
| | Primary Position Upbeat Nystagmus; |
| | Convergence Normal; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Unilateral Internuclear Ophthalmoplegia; |
| | Unilateral Horizontal Gaze Palsy; |
| | Upbeat Nystagmus on Upgaze; |
| | Primary Position Upbeat Nystagmus; |
| | Convergence Normal; |
| | Fisher's One-and-a-Half Syndrome; |
| | Multiple Sclerosis; |
| Presenting Symptom | Diplopia |
| History | This young patient presented with double vision and was found to have on examination the classic findings of Fisher's one-and-a-half syndrome, which are: |
| | Right internuclear ophthalmoplegia on gaze left with adduction weakness OD |
| | Right horizontal gaze paresis with gaze-evoked nystagmus |
| | Full vertical gaze |

| Metadata Element Field | Metadata | |
|------------------------|--|--|
| | In primary position, vertical upbeat nystagmus | |
| | Large-amplitude upbeat nystagmus on upgaze | |
| | Convergence normal Nourclogic Examination: | |
| | Normal | |
| | Diagnosis: | |
| | Multiple Sclerosis | |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah | |
| Date Digital | 2008 | |
| Date Original | 1973 | |
| Resource.Type | Video | |
| Format.Creation | | |
| Source | 16-mm Film | |
| Language | En | |
| Relation-Is Part Of | 166-14, 166-20, 937-8, 941-4, 941-6 | |
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| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 | |
| Annotation | No | |
| Collection | Neurology/Neuro-ophthalmology | |
| Catalogue | http://library.med.utah.edu/NOVEL/Wray | |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP | |
| Contributor Secondary | Ray Balhorn, Video Compressionist | |
| Reviewer | David Zee, MD, Johns Hopkins Hospital, 2006 | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ | |
| Clinical | This MS patient had Fisher's One-and-a-Half Syndrome characterized by: | |
| | A left horizontal gaze palsy with gaze-evoked nystagmus | |
| | A left internuclear ophthalmoplegia on gaze right with adduction weakness OS | |
| | Abducting nystagmus OD | |
| | Full Vertical gaze Inheat pystamus on upgaze (ill sustained) | |
| | Convergence normal | |
| | The "One-and-a-Half" syndrome was first described by Fisher in 1967 . The disorder is characterized by a lateral gaze palsy in one direction with an internuclear ophthalmoplegia (INO) in the other direction. In the complete form of the syndrome, the ipsilateral eye lies fixed at the midline for all lateral movements; the other eye can only abduct and exhibits horizontal jerk nystagmus in abduction. | |
| | The syndrome is usually due to a unilateral lesion in the lower part of the dorsal pontine tegmentum affecting the ipsi- lateral paramedian pontine reticular formation (PPRF), the abducens nucleus, and internuclear fibers of the ipsilateral medial longitudinal fasciculus (MLF). | |
| | These internuclear fibers originate in the contralateral abducens nucleus and terminate in the ipsilateral medial rectus subnucleus of the third nerve nucleus. | |
| | In 1983 Michael Wall , who was a Fellow of mine at that time, reviewed all the patients whom I had seen with the one-and-a-half syndrome between 1968 and 1982. Films or video tapes of eye movements were available for review in 9 cases. In 12 of 20 patients, the lesion was on the right side. The patients ranged in age from 16 to 78 years. | |
| | Prior to our publication in Neurology there had been only 29 reported cases of the one-and-a-half syndrome in the literature: 6 proven and 6 probable infarctions, 8 hemorrhages (1 traumatic), 5 gliomas, 1 arteriovenous malformation, 1 metastatic melanoma, and 2 patients with MS. We added a further 20 patients. | |
| | Brainstem infarction was the most common cause in elderly adults (patients 17 to 20). Four patients were age 61 to 78 years (mean, 70 years). Two of them had hypertension. | |
| | Three patients presented with neurologic complaints and one with diplopia. | |
| | MS was the most common cause in 14 young adults age 18 to 52 years (mean, 32 years). Twelve had definite MS and 2 had possible MS. | |

Cardinal Manifestations and Presentation of Diseases

PART 2

| VIDEO e11-1 (Continued) | | | |
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| | In 4 patients the one-and-a-half syndrome represented the initial presentation of MS. Two of these patients com- plained first of diplopia and one of blurred vision. | | |
| | Only 7 of 14 MS patients had visual complaints as the major symptom. Nine had diplopia, 5 had blurred vision, 3 had oscillopsia, and 2 had difficulty looking to one side. | | |
| | Associated ocular motility signs: | | |
| | Gaze-evoked upbeat nystagmus | | |
| | Skew deviation | | |
| | Horizontal ipsilateral gaze nystagmus | | |
| | Rotary component to horizontal ipsilateral gaze nystagmus | | |
| | Spontaneous nystagmus to the contralateral side | | |
| | Absent or Impaired convergence | | |
| | Saccaulo vertical pursuit | | |
| | laze-evokeu uowiliseat hystagilius | | |
| | | | |
| | Esotronia | | |
| | Orthotronic | | |
| | In 10 MS patients whose eye position was documented in straight-ahead gaze, 4 had exotropia, 2 had an esotropia, and 4 were orthotropic. | | |
| | Associated Neurologic Signs: | | |
| | The most common associated cranial nerve lesions were an ipsilateral trigeminal sensory loss and a peripheral-type facial palsy. | | |
| | Seven patients had impaired coordination of the limbs. Only one patient had no neurologic abnormality other than the one-and-a-half syndrome. | | |
| | Of the 14 MS patients, 10 had recovery of eye movements: | | |
| | Recovery was complete in 8 patients between 4 and 16 weeks after onset, and partial recovery occurred in 2 other patients followed for 4 weeks and 9 weeks. | | |
| Neuroimaging | No neuroimaging studies were available on this patient. | | |
| Anatomy | The two constituents of the one-and-a-half syndrome (ipsilateral horizontal gaze palsy and INO) can be analyzed ana- tomically to provide the basis for topographic localization of the lesion at the bedside. | | |
| | Horizontal Gaze Palsy: | | |
| | There are four theoretical possibilities to account for the ipsilateral horizontal gaze palsy. It may be due to a single unilateral lesion affecting: | | |
| | 1. The ipsilateral paramedial pontine reticular formation (PPRF) only; | | |
| | 2. The ipsilateral abducens nucleus alone; | | |
| | Both the ipsilateral paramedial pontine reticular formation (PPRF) and the abducens nucleus; or, when two lesions are involved | | |
| | 4. The motoneuron root fibers of the ipsilateral abducens nucleus to the lateral rectus and the contralateral medial longitudinal fasciculus (MLF). | | |
| | Paramedial Pontine Reticular Formation: | | |
| | The medial portions of the nucleus reticularis magnocellularis (or nucleus centralis pontis oralis and caudalis) have been designated the "paramedian pontine reticular formation" (PPRF) , rostral to the abducens nucleus. The region extends from the abducens nucleus in a rostral direction toward the brachium conjunctivum and trochlear nucleus. It has been defined functionally because there are no distinct histologic boundaries. Anatomically, Graybiel, Büttner- Ennever, and Grantyn and colleagues all showed inputs from discrete areas. | | |
| | Two major oculomotor pathways originate from the PPRF. One pathway ascends rostrally, close to but outside of the MLF, to the rostral mesencephalon to coordinate horizontal and vertical gaze. The other pathway descends caudally and sends off a direct projection to the ipsilateral abducens nucleus. | | |
| | This excitatory pathway controls horizontal gaze to the ipsilateral side by stimulating motoneurons to the lateral rectus and internuclear abducens neurons, which project via the MLF to the medial rectus motoneurons of the contralateral oculomotor nucleus. Other major projections likely to be involved in gaze are projections from the PPRF to the nucleus prepositus hypoglossi and PPRF cerebellar pathways. | | |
| | No direct inhibitory pathway from the PPRF projects to the contralateral abducens nucleus. The inhibitory pathway from inhibitory burst neurons travels from the dorsomedial gigantocellular tegmental field just caudal to the abducens nucleus, crosses the brainstem, and terminates in the contralateral abducens nucleus. | | |
| | | | |

The importance of this pathway has been demonstrated for saccades and quick phases of vestibular nystagmus, but it is still unclear whether an analogous pathway exists to control smooth pursuit movements. In any case, the PPRF generates all ipsilateral-directed saccades (including the quick phases of vestibular nystagmus).

Abducens nucleus. The abducens nucleus contains typical motoneurons that give rise to root fibers that innervate the lateral rectus as well as internuclear neurons whose axons cross the midline and ascend via the contralateral MLF to the medial rectus subnucleus in the contralateral oculomotor (third nerve) nucleus. This projection is the main excitatory input to medial rectus motoneurons in lateral gaze.

An old clinicopathologic case published by **Bennett and Savill** described a unilateral gaze palsy with an associated "patch of softening" in the abducens nucleus without apparent involvement of neighboring structures.

Clinical distinction PPRF:

Abducens nucleus. At the bedside distinction can be made between the manifestations of gaze palsies in lesions of the PPRF in the upper pons from those of the PPRF in the lower pons at the level of the abducens nucleus.

With **PPRF lesions rostral to the abducens,** there is ipsilateral paralysis of saccades and pursuit, but the eyes can be driven to the side of the gaze palsy with vestibular stimulation.

At the level of the abducens nucleus, lesions of the PPRF are associated with ipsilateral gaze palsy and loss of reflex vestibular (and tonic neck) movements. This presumes that there is a critical synapse within the caudal PPRF for the vestibulo-ocular pathways or that, at the very least, the functional integrity of the PPRF at that level is necessary for vestibulo-ocular eye movements.

An associated sign with **abducens nuclear lesions**, however, is an **ipsilateral "peripheral" facial palsy** because the genu of the seventh nerve wraps around the abducens nucleus. The gustatory fibers are spared because these fibers are carried in the intermediate branch of the facial nerve to the nucleus solitarius of the medulla. This sign was present in four of our MS patients.

An identical ipsilateral gaze palsy can be produced by damage to axons of abducens neurons as they course through the brainstem—namely, the ipsilateral sixth nerve fascicle and those axons that ascend the contralateral MLF. Separation of these two anatomic sites suggests two lesions. A lateral gaze palsy that always remains conjugate is consistent with one lesion of the abducens nucleus, whereas one that is not conjugate at any time would better fit two lesions. Two examples, in our patient group, were both patients with definite MS.

Internuclear Ophthalmoplegia:

Both human and experimental data have established the localization of the lesion that causes INO. A unilateral INO is due to the interruption of the ipsilateral MLF after it has crossed the midline caudally in the pons from its site of origin in the contralateral abducens nucleus.

Clinically, the syndrome is characterized by:

- 1. Paresis or paralysis of adduction of the ipsilateral eye on attempted horizontal gaze to the contralateral side;
- 2. Horizontal jerk nystagmus in the contralateral abducting eye; and
- 3. Typically convergence is intact if the lesion does not extend to the mesencephalon.

Other associated findings are abnormalities in vertical smooth pursuit, OKN, the vertical VOR with normal vertical saccades if the INO is bilateral, and gaze-evoked vertical nystagmus on upward gaze more frequent than downgaze if the lesion is bilateral and skew deviation.

The one-had-a-half syndrome is characterized by, on horizontal gaze:

- 1. An ipsilateral gaze paresis or palsy;
- 2. An INO on contralateral gaze; and
- 3. At rest, an **exotropia of the eye contralateral to the lesion** in the acute phase, or no deviation at rest, or, less commonly, an **esotropia of the eye ipsilateral to the lesion** resulting from paresis of the sixth nerve.

Occasionally, **ocular bobbing** occurs; this may be periodic or limited to the ipsilateral eye. Anisocoria is also reported. **Personal Observation:**

All of our patients with the one-and-a-half syndrome showed a complete or partial ipsilateral horizontal gaze palsy and a clinical or subclinical INO on contralateral gaze.

Slow and incomplete adduction of the ipsilateral eye was attributed to deficient medial rectus excitation, and horizontal jerk nystagmus in the abducting eye was attributed to deficient tonic inhibition of the medial rectus. This interpretation is consistent with the results of oculographic studies.

The association of **exotropia in the one-and-a-half syndrome** was observed by **Fisher** and later termed **"paralytic pontine exotropia"** by **Sharpe and colleagues.** In this distinctive supranuclear syndrome, the deviated, exotropic eye shows abduction nystagmus during attempts to move it further laterally, and there is extreme slowness of adduction saccades when the eye is used to fixate to move it to the midline.

Paralytic pontine exotropia is attributed to tonic contralateral ocular deviation of the eyes, which implies acute ipsilateral involvement of the PPRF. Failure of the ipsilateral eye to deviate medially is explained by the INO. Three autopsy cases of paralytic pontine exotropia confirm the lesion site.

Esotropia of the ipsilateral eye may be due to a lesion of the fasciculus of the ipsilateral sixth nerve.

| VIDEO e11-1 (Continued) | | |
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| Metadata Element Field | Metadata | |
| Pathology | The anatomic localization of the lesion in the one-and-a-half syndrome has been confirmed at autopsy in seven patients. Six of them had a single unilateral lesion in the pontine tegmentum ipsilateral to the gaze palsy involving the PPRF and the ipsilateral MLF. The abducens nucleus was spared by discrete lesions and involved in extensive lesions resulting from infarction, hemorrhage, or glioma. | |
| | In Fisher's case, extensive pontine infarction involved both the PPRF and the abducens nucleus. | |
| | Crevits and colleagues correlated the gaze palsy with a single discrete infarct 3 by 2 mm in diameter in the ipsilateral PPRF and MLF. The lower fascicles of the ipsilateral sixth nerve passed through the necrotic area. This was probably the smallest lesion associated with the one-and-a-half syndrome. | |
| | Newman and colleagues reported a similar clinical case, but they found an ipsilateral PPRF lesion and "ischemic necrosis in the region of the abducens nucleus, although individual neurons could be identified." Partial damage to the contralateral PPRF was also found. | |
| | In another pathologically confirmed case evaluated clinically by electro-oculography, a hypertensive hemorrhage in the rostral pontine tegmentum had spread into the right basis pontis to destroy the ipsilateral PPRF and abducens nucleus. | |
| Etiology | Review (Wall, Wray, 1983) | |
| Treatment | | |
| Disease/Diagnosis | Multiple Sclerosis | |
| Further Readings | Bennett H, Savill TH: A case of permanent conjugate deviation of the eyes and head, the result of a lesion limited to the sixth nucleus, with remarks on associated lateral movements of the eyeballs, and rotation of the head and neck. Brain 12:102, 1889 | |
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VIDEO e11-2

| Metadata Element Field | Metadata |
|------------------------|---|
| Identifier | 166-2 |
| Title | Ocular Flutter |
| Ocular Movements | Ocular Flutter; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Ocular Flutter; |
| | Multiple Sclerosis; |
| Presenting Symptom | Blurred Vision |
| History | This patient was seen in the Neurovisual Clinic for evaluation of a monocular attack of optic neuritis that completely resolved. |
| | Six months later, she became unsteady walking and was found to have bilateral ataxia. She was given a diagnosis of multiple sclerosis (MS). |
| | Neuro-Ophthalmologic Examination: |
| | The examination was normal apart from the eye movements, which showed, in central gaze, episodic bursts of hori- zontal back-to-back saccades without an intersaccadic interval characteristic of ocular flutter. |
| | The patient was seen prior to the availability of neuroimaging by MRI. |
| | In 1954 Cogan first used the term <i>ocular flutter</i> to describe a rare disorder of horizontal eye movements characterized by rapid bursts of synchronous back-to-back horizontal oscillatory movements usually seen in the primary position of gaze. |
| | Since then, there have been more than 50 reports, usually single cases or small series, linking the phenomenon to a wide variety of brainstem and cerebellar conditions, e.g., post-enteroviral infection, cerebral malaria, cyclosporine treatment, and meningitis, but perhaps most frequently associated with parainfectious states or, with opsoclonus, as a paraneoplastic manifestation of occult malignancy. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2008 |
| Date Original | 1978 |
| Resource.Type | Video |
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| Source | 16-mm Film |
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| Relation-Is Part Of | 162-4, 166-1,931-1,936-7, 936-8 |
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| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |
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| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| Reviewer | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ |

| Metadata Element Field | Metadata |
|------------------------|--|
| Clinical | This patient with MS has ocular flutter characterized by the following: |
| | Horizontal saccadic oscillations are present without an intersaccadic interval; |
| | • The frequency of oscillations is usually high, typically 10-25 cycles per second, as evident in this case; |
| | • Ocular flutter is intermittent and mainly associated with voluntary saccades: flutter dysmetria; and |
| | • When the amplitude is very small, the oscillation can be detected only with an ophthalmoscope or on eye movement recordings, and then the term <i>microflutter</i> is used to describe the disorder. |
| | Ocular flutter occurs in: |
| | 1. Paraneoplastic opsoclonus/flutter due to an occult neoplasm; |
| | 2. MS; |
| | 3. Side effects of drugs: lithium, amitriptyline, cocaine, and phenytoin with diazepam; |
| | 4. Toxins: chlordecone, thallium, strychnine, toluene, and |
| | organophosphates; or |
| | 5. Complication of pregnancy |
| | In three reported cases from Japan of the opsoclonus-myoclonus syndrome (OMS) during pregnancy, the neurologic symptoms were entirely similar to those of OMS unrelated to pregnancy with opsoclonus/flutter, trunkal ataxia, and myoclonic jerks of the neck and limbs. The condition of the fetuses were good, except in the one case that miscarried. In all three cases the OMS occurred in the middle to late stages of pregnancy. Whether the symptoms improved because the pregnancy ended or because of corticosteroid therapy remains unclear. However, the OMS gradually improved after spontaneous miscarriage in one case. Taken together, the authors suggested that these results raise the possibility that pregnancy influences the appearance of OMS. |
| | When agents with a variety of potential effects on neurotransmitters have been excluded, a patient with ocular flutter warrants a careful evaluation for an occult neoplasm and long-term follow-up. |
| | In filming this short clip, the patient was asked to try to hold her gaze steady fixating on the camera. You will see that she is unable to do this because of bursts of spontaneous back-to-back horizontal saccades without a saccadic interval; this abnormality is characteristic of ocular flutter. |
| | Ocular flutter in the absence of other neurologic signs implies a paraneoplastic syndrome due to an occult neoplasm, most frequently cancer of the breast. |
| Neuroimaging | Ocular flutter has been hypothesized to be caused by loss of "pause" neuronal inhibition of burst neuron function in the paramedian pontine reticular formation (PPRF). However, there has only been one imaging study confirming this anatomic localization. |
| | The report is of a young woman with a definite relapse of her MS who developed prominent ocular flutter without any obvious ophthalmoplegia or nystagmus. |
| | An axial MRI FLAIR sequence through the pons and medulla showed a single prominent midline high signal lesion in the region of the PPRF. A sagittal midline section showing the same lesion demonstrated its craniocaudal distribution and its subventricular localization. Repeat axial and sagittal images through the same region months later showed the disappearance of the midline pontine lesion. The disappearance of the lesion followed acute treatment with a 3-day course of IV methylprednisolone, and the ocular flutter dramatically improved. |
| | The authors of this case referred to the MRI atlas by Kretschman and Weinrich and confirmed that the brainstem lesion was at the level of the sixth nerve nuclei and was virtually exactly occupying the position of the PPRF. There were other far less obvious small areas of abnormal signal in the posterior fossa, including two in the left cerebellar hemisphere and one each in the right cerebellar hemisphere and the superior medulla. |
| | As she recovered from the MS attack, both the midline pontine lesion and the ocular flutter dramatically improved. |
| | This case is the first clear evidence that at least some cases of ocular flutter are due to lesions involving the PPRF. |
| | (Schon F et al: Ocular flutter associated with a localized lesion in the paramedian pontine reticular formation. Ann Neurol 50:413, 2001) |

| Metadata Element Field | Metadata |
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| Anatomy | In 1979, Zee and colleagues studied a single patient with ocular flutter and related their findings to what was known about the anatomy and physiology of saccade generation in the monkey. |
| | They proposed that "pause" neurons normally prevent saccadic oscillations during fixation by inhibiting "burst" neuron firing and that this mechanism is disturbed in ocular flutter. |
| | They later proposed a similar disturbance in both voluntary and blink-induced saccadic oscillations. They hypothesized that the anatomic site involved in this group of eye movement disorders, which also includes opsoclonus, would be in the medial region of the PPRF, which is the human equivalent of the pontine raphe interpositus nucleus (RIN), in which pause neurons are located in the monkey. In humans, it lies adjacent to the midline and in the upper pons at the level of the sixth nerve nucleus but slightly ventral to it. |
| | However, experimental lesions of the omnipause region with excitotoxins caused slow saccades rather than oscilla- tions. One possible explanation is that burst neurons may also have been affected. |
| | The only case comparable to the MS patient reported by Schon and colleagues is one reported by Averbuch-Heller and colleagues. Their patient developed macrosaccadic oscillations 5 years after a head injury. |
| | MRI in this patient showed a lesion in the right side of the pons extending upward from the level of the sixth nerve nucleus into the tegmentum and basis pontis. |
| | It was proposed that the eye movement abnormality was caused by damage to the adjacent omnipause neuron projec- tions. |
| Pathology | Multiple sclerosis |
| Etiology | |
| Treatment | Ocular flutter ceased when the acute MS attack went into remission |
| Disease/Diagnosis | Multiple Sclerosis Ocular Flutter |
| Further Readings | Apsner R et al: Cyclosporin A induced ocular flutter after marrow transplantation. Bone Marrow Transplant 20:255, 1997 |
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| | Kretschmann HJ, Weinrich W: Cranial neuroimaging and clinical neuroanatomy. Stuttgart: Thieme Verlag, 1992 |
| | Leigh RJ, Zee DS: Diagnosis of nystagmus and saccadic intrusion, in <i>The Neurology of Eye Movements</i> , 4th ed. New York, Oxford University Press, 2006, pp 475-558 |
| | Orimo S et al: An autopsied case of purulent meningitis associated with ocular flutter. Brain Nerve 50:469, 1998 |
| | Reiji K et al: Opsoclonus-myoclonus syndrome during pregnancy. J Neuroophthalmol 24:273, 2004 |
| | Schon F et al: Ocular flutter associated with a localized lesion in the paramedian pontine reticular formation. Ann Neurol 50:413, 2001 |
| | Wiest G et al: Ocular flutter and trunkal ataxia may be associated with enterovirus infection. J Neurol 244:288, 1997 Zee DS, Robinson DA: A hypothetical explanation of saccadic oscillations. Ann Neurol 5:405, 1979 |

VIDEO e11-3

| Metadata Element Field | Metadata |
|---------------------------|---|
| Identifier | 168-6 |
| Title | Downbeat Nystagmus |
| | Periodic Alternating Nystagmus |
| Ocular Movements | Downbeat Nystagmus Periodic Alternating Nystagmus |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Downbeat Nystagmus |
| | Multiple Sclerosis |
| Presenting Symptom | Blurred vision |
| History | This patient carries a diagnosis of multiple sclerosis (MS). |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2008 |
| Date Original | 1973 |
| Resource.Type | Video |
| Format.Creation | |
| Source | 16-mm Film |
| Language | En |
| Relation-Is Part Of | 932-4, 946-8 |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002. For further information regarding the rights to this collection, please visit http://medlib.med.utah.edu/neuroophth/Wray/copyright.htm |
| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |
| Catalogue | http://library.med.utah.edu/NOVEL/Wray |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| Reviewer | David S. Zee, MD, Johns Hopkins Hospital 2009 |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ |

| Metadata Element Field | Metadata |
|---------------------------|---|
| Clinical | This is a unique patient with MS who has periodic downbeat nystagmus and periodic alternating nystagmus (PAN). |
| | The combination of downbeat nystagmus and PAN was first reported in a case of multiple sclerosis by Keane in 1974. |
| | It is also reported to occur in the setting of severe hypomagnesemia possibly associated with thiamine deficiency (Du Pasquier and colleagues, 1998). |
| | The eye movements show: |
| | 1. No nystagmus initially in primary gaze; |
| | 2. A period of downbeat nystagmus in central gaze; |
| | 3. A period of PAN; and |
| | 4. No nystagmus on upgaze. |
| | Partway through the period of downbeat nystagmus, the direction of the nystagmus changes to a spontaneous horizontal jerk nystagmus present in central gaze, which reverses direction approximately every 2 min; this is diagnostic of PAN. |
| | Periodic Alternating Nystagmus: |
| | Because the period of oscillation in one direction is long, about 4 min, the diagnosis of PAN may be missed unless the exam- iner observes the nystagmus for several minutes. |
| | As the nystagmus finishes one cycle of right beating nystagmus, a brief transition period occurs during which there may be brief beats of downbeat nystagmus before the next half cycle starts of left beating nystagmus. |
| | Although rare, acquired PAN is perhaps the best understood of all forms of nystagmus and was the first for which an effective treatment was identified with the drug baclofen. |
| | Convergence can be used to suppress PAN in some patients. |
| | The pathogenesis of PAN is due to a lesion of the cerebellar nodulus and uvula. |
| | Acquired PAN has been reported in association with a number of conditions. |
| Neuroimaging | Neuroimages were not available in this patient. |
| Anatomy | Lesions of the cerebellar nodulus and uvula |
| Pathology | Demyelination |
| Etiology | |
| Treatment | The GABAergic drug baclofen (30 mg/d) abolishes acquired PAN in most patients but helps only occasional patients with the congenital form of PAN. |
| | This patient was seen prior to the availability of baclofen to treat PAN. |
| Disease/Diagnosis | Multiple Sclerosis |
| | Downbeat Nystagmus |
| | Periodic Alternating Nystagmus |
| Further Readings | Du Pasquier R et al: Periodic downbeat nystagmus. Neurology 51:1478, 1998 |
| | Furman JM et al: Vestibular function in periodic alternating nystagmus. Brain 113:1425, 1990 |
| | Garbutt S et al: Effects of visual fixation and convergence in periodic alternating nystagmus due to MS. Neuroophthalmol 28:221, 2004 |
| | Halmagyi GM et al: Treatment of periodic alternating nystagmus. Ann Neurol 8:609, 1980 |
| | Jay WM et al: Periodic alternating nystagmus clearing after cataract surgery. J Clin Neuroophthalmol 5:149, 1985 |
| | Keane JR: Periodic alternating nystagmus with downward beating nystagmus. Arch Neurol 30:399, 1974 |
| | Leigh RJ et al: A hypothetical explanation for periodic alternating nystagmus: Instability in the optokinetic-vestibular system. Ann NY Acad Sci 374:619, 1981 |
| | Leigh RJ, Zee DS: Diagnosis of nystagmus and saccadic intrusion, in The Neurology of Eye Movements, 4th ed. New York, |
| | Oxford University Press, 2006, pp :475-558 |

VIDEO e11-4

| Metadata Element Field | Metadata | Metadata Elen Field | nent |
|---------------------------|--|------------------------|------|
| Identifier | 933-1 | | |
| Title | Bilateral Internuclear Ophthalmoplegia | | |
| Ocular Movements | Bilateral Internuclear Ophthalmoplegia; | | |
| | Abducting Nystagmus; | | |
| | Normal Convergence; | | |
| | Gaze-Evoked Upbeat Nystagmus; | | |
| | Gaze-Evoked Downbeat Nystagmus; | | |
| | Saccadic Dysmetria; | | |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital | | |
| Subject | Bilateral Internuclear Ophthalmoplegia; | | |
| | Abducting Nystagmus; | | |
| | Normal Convergence; | | |
| | Gaze-Evoked Upbeat Nystagmus; | | |
| | Gaze-Evoked Downbeat Nystagmus; | | |
| | Saccadic Dysmetria; | | |
| | Multiple Sclerosis; | | |
| Presenting Symptom | Blurred vision | | |
| History | The patient is a 25-year-old woman who was in excellent health until 4 days prior to admission, when she noted blurred vision | Publisher | |
| | and horizontal double vision on lateral gaze | Date Digital | |
| | to right and left. | Date Original | |
| | Past History: | Resource.Type | |
| | No previous episodes of transient neurologic | Format.Creation | n |
| | symptoms. | Source | |
| | Family History: | Language | |
| | Negative for neurologic diseases. | Relation-Is Part | t Of |
| | Neuro-Ophthalmologic Examination: | | |
| | Visual acuity 20/20 OU | Rights Manage | men |
| | Visual fields, pupils and fundus examination normal | | |
| | Ocular Motility: | | |
| | Paresis of adduction of the right eye on gaze left | Holding.Institut | ion |
| | Abducting nystagmus of the left eye on gaze left | | |
| | Paresis of adduction of the left eye on gaze | Annotation | |
| | Right | Collection | |
| | qaze right | Catalogue | |
| | Normal convergence | Contributor Prin | nary |
| | Upbeat nystagmus on upgaze | Contributor Sec | cond |
| | Downbeat nystagmus on downgaze | | |
| | Saccadic dysmetria | Reviewer | |
| | Hypermetria of the adducting eye | | |
| | Hypometria of the abducting eye | Context URL | |

VIDEO e11-4 (Continued)

| Field | Metadata | |
|-----------------------|--|--|
| | Diagnosis: | |
| | Bilateral internuclear ophthalmoplegia (INO) | |
| | Saccadic dysmetria | |
| | Brain CT with and without Contrast: | |
| | Normal. | |
| | Prognosis: | |
| | ments were normal. | |
| | Diagnosis: | |
| | Multiple Sclerosis (MS) | |
| | The diagnosis of MS was suspected and discussed with the patient and her parents. The rapid recovery of her motility disorder was consistent with the diagnosis. | |
| | MS is the most common cause of <i>bilateral</i> internuclear ophthalmoplegia in a young adult. | |
| | Brainstem infarction is the commonest cause of <i>unilateral</i> internuclear ophthal-moplegia in middle-aged and elderly adults. | |
| | A bilateral internuclear ophthalmoplegia in a child raises the possibility of a fourth- ventricle tumor. | |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah | |
| Date Digital | 2006 | |
| Date Original | 1990 | |
| Resource.Type | Video | |
| Format.Creation | | |
| Source | 3/4" Umatic master videotape | |
| Language | En | |
| Relation-Is Part Of | 163-6, 163-15,168-6, 906-4, 937-8, 941-2, 941-3 | |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002. For further information regarding the rights to this collection, please visit http://medlib.med.utah.edu/neuroophth/ Wray/copyright.htm | |
| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 | |
| Annotation | No | |
| Collection | Neurology/Neuro-ophthalmology | |
| Catalogue | http://library.med.utah.edu/NOVEL/Wrav | |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP | |
| Contributor Secondary | Ray Balhorn, Video compressionist | |
| Deviewer | Devid Zee MD, Johns Harding Harris | |
| Keviewer | 2006 David Zee, MD, Jonns Hopkins Hospital, | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ | |
| | (continued) | |

| Metadata Element Field | Metadata | Meta Field |
|---------------------------|---|---------------|
| Clinical | This patient with MS had a bilateral INO with: | |
| | Paresis of adduction of the right eye on gaze left; | |
| | Abducting nystagmus of the left eye on gaze left; | |
| | Paresis of adduction of the left eye on gaze right; | |
| | Abducting nystagmus of the right eye on gaze right; | |
| | Normal convergence; | |
| | Upbeat nystagmus on upgaze; | |
| | Downbeat nystagmus on down gaze; and | |
| | Saccadic dysmetria | |
| | Hypermetria (overshoot) of the adducting eye | |
| | Hypometria (undershoot) of the abducting eye | |
| | The Clinical Features of an INO are: | |
| | Medial rectus muscle weakness ipsilat- eral to the side of the lesion with paresis of adduction or adduction lag; | |
| | Abducting nystagmus of the eye con- tralateral to the lesion—dissociated nystagmus; | |
| | 3. Normal convergence; | |
| | Skew deviation—hypertropia on the side of the lesion; and | |
| | 5. Dissociated vertical nystagmus—down- beat with greater torsional component in the contralateral eye. | Neuro |
| | Bilateral INO with bilateral lesions of the MLF may also have: | Anato |
| | Gaze-evoked vertical nystagmus; | |
| | Impaired vertical pursuit; | |
| | Decreased vertical vestibular response; and | |
| | Small-amplitude saccadic intrusions sug- gesting involvement | |
| | of the brainstem adjacent to the MLF. | |
| | Weakness of adduction is due to impaired conduction in axons from the abducens internuclear neurons, which project to the medial rectus motor neurons in the contral- ateral oculomotor (third nerve) nucleus. | |
| | Adduction weakness is most evident during saccades, and adduction lag is brought out clinically by asking the patient to look all the way to the right and all the way to the left (i.e., to make large saccades) back and forth across the midline. The speed of the adducting eye depends on a strong agonist contraction. The adducting saccade may be slow and hypometric. | |
| | in the abducting eye, abducting saccades are | |

In the abducting eye, abducting saccades are hypometric with centripetal drifts of the eye and slowing. A series of small saccades and drifts have the clinical appearance of **abducting nystagmus**—**dissociated nystagmus**.

VIDEO e11-4 (Continued)

| adata Element I | Metadata |
|--------------------|---|
| | Dissociated nystagmus may be due to: |
| | Impaired ability to inhibit the affected medial rectus; or |
| | 2. The brain's attempts to compensate for the adduction weakness. |
| | (For further discussion, review Leigh JR, Zee DS: Diagnosis and central disorders of ocular motility, in The Neurology of Eye Movements, 4th ed. New York, Oxford University Press, 2006, pp 620-627.) |
| | Skew deviation, commonly seen in uni- lateral INO, is due to interruption of central projections in the otolithic pathway ascend- ing in the MLF to the midbrain. The higher eye (hypertrophic) is usually on the side of the MLF lesion. |
| | Interruption of pathways mediating the vertical vestibulo-ocular reflex (VOR) may cause downbeat nystagmus with a greater torsional component in the eye contralateral to a unilateral INO. |
| | Oscillopsia, an illusion of movement of the visual world, is a common presenting symptom of INO. |
| | Horizontal oscillopsia usually occurs from either the adduction lag or the abducting nystagmus. |
| | Vertical oscillopsia occurs during head movements and is caused by a deficient vertical VOR or, as in this case, by pendular vertical oscillations. |
| roimaging | Neuroimaging studies were not available in this patient. |
| omy | The medial longitudinal fasciculus (MLF) is a major pathway in the brainstem extend- ing from the pons up to the midbrain. The MLF carries signals for the control of hori- zontal eye movements. |
| | For horizontal gaze: |
| | 1. The MLF contains axons from the abducens internuclear neurons and carries signals for |
| | horizontal saccades, the vestibulo-ocular reflex (VOR), and smooth pursuit. |
| | 2. These axons project to the medial rectus motor neurons in the contralateral oculo- motor (third nerve) nucleus. |
| | For vertical gaze: |
| | 1. The MLF contains axons from the rostral interstitial MLF (riMLF), which carry vertical saccadic signals. |
| | 2. The MLF also contains ascending axons from the vestibular nuclei, which carry signals for the vertical VOR, smooth pursuit, gaze holding, and otolith-ocular reflex. |
| | Axons project to the oculomotor and trochlear (fourth nerve) nuclei, as well as to the interstitial nucleus of Cajal. |

(continued)

| | • |
|---------------------------|---|
| Metadata Element Field | Metadata |
| Pathology | Review (7) |
| Etiology | |
| Treatment | Review (3) |
| Disease/Diagnosis | Multiple Sclerosis |
| Further Readings | Gordon RM, Bender MB: Visual phenomenon in lesions of the medial longitudinal fascicu- lus. Arch Neurol 15:238, 1966 |
| | Gresty MA et al: Disorders of the vestibu- loocular reflex producing oscillopsia and mechanisms compensating for loss of laby- rinthine function. Brain 100:693, 1977 |
| | Hauser SL, Goodin DE: Multiple Sclerosis and other demyelinating diseases, in Harrison's Principals of Internal Medicine, 16th ed, DL Kasper et al (eds). New York, McGraw-Hill, 2005 |
| | Keane JR: Internuclear ophthalmoplegia: Unusual causes in 114 of 410 Patients. Arch Neurol 62:714, 2005 |
| | Leigh JR, Zee DS: Diagnosis of central dis- orders of ocular motility, in <i>The Neurology of</i> <i>Eye Movements</i> , 4th ed. New York, Oxford University Press, 2006. pp 598-718 |
| | Muri RM, Meienberg 0: The clinical spec- trum of internuclear ophthalmoplegia in multiple sclerosis. Arch Neurol 42: 851, 1985 |
| | Strominger MB et al: Bilateral internuclear ophthalmoplegia with absence of conver- gence eye movements. Clinico-pathological correlations. J Clin Neuro-ophthalmol 6:57, 1986 |

VIDEO e11-5

| Metadata Element Field | Metadata |
|------------------------|---|
| Identifier | 163-1 |
| Title | Unilateral Ptosis |
| Ocular Movements | Unilateral Ptosis; Unilateral Lid Retraction; Myasthenic Lid Twitch; External Ophthalmoplegia; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Unilateral Ptosis; Unilateral Lid Retraction; Myasthenic Lid Twitch; External Ophthalmoplegia; Myasthenia Gravis; Tensilon Test; Thymolipoma; Generalized Myasthenia Gravis; |

| Metadata Element Field | Metadata |
|------------------------|--|
| Presenting Symptom | Transient double vision |
| History | The patient is a 46-year-old woman who presented in July 1977 with horizontal double vision lasting 2 weeks; 3 weeks later the left upper eyelid started to droop and by the end of the day the eye was closed. She had no ptosis of the right eye and no generalized fatigue. |
| | She consulted an internist; a glucose tolerance test was normal. |
| | She was referred to a neurosurgeon, who noted weakness of the medial rectus muscle—third nerve palsy. |
| | CT Brain Scan: |
| | Normal. |
| | She was referred to the Neurovisual Clinic, Massachusetts General Hospital. |
| | Past History: |
| | Negative for previous attacks of diplopia, ptosis, or fatigue. |
| | Neuro-Ophthalmologic examination: |
| | Visual acuity: 20/30, J1 OU |
| | Visual fields, pupils, and fundus examination normal |
| | Eyelids: |
| | Partial ptosis left eye (OS) |
| | Lid retraction right (OD) |
| | Bilateral overaction of the frontalis muscle |
| | Myasthenic lid twitch OS |
| | Slight increase in ptosis OS on fatigue |
| | No recovery of ptosis on gentle eye closure |
| | Impaired ability to bury eyelashes fully |
| | Ocular Motility: |
| | Mild weakness of the medial rectus muscle bilaterally, left > right |
| | Poor convergence |
| | Vertical gaze normal |
| | Intravenous Tensilon Test (Edrophonium Chloride): |
| | The test dose of 0.2 mL was adequate to produce a positive response with elevation of the ptotic left eyelid and cor- rection of lid retraction OD. |
| | The response lasted 30 s and then the left eyelid drooped. A further 0.3 mL of edrophonium again resulted in correction of ptosis OS. The full 1-mL (10-mg) dose of edrophonium was not given. |
| | Diagnosis: |
| | Ocular myasthenia gravis. |
| | Hematologic Tests: |
| | Thyroid studies normal |
| | Anti-skeletal muscle antibodies positive |
| | (The presence of antibodies to striatal muscle suggests that the patient harbors a thymoma.) |
| | Tests for antibodies to the nicotinic acetylcholine receptor (AChR) were not available at that time. |
| | Chest X-Ray PA and Lateral: |
| | A large anterior mediastinal mass was found consistent with an enlarged thymus gland. |
| | CBT of Thorax: |
| | Multiple transverse sections through the mid-thorax showed the presence of a softly demarcated rounded mass in the anterior mediastinum directly contiguous and anterior to the inferior portion of the transverse aortic arch. The mass measured approximately 4 cm and was surrounded by fat; it had diminished attenuation in the center, indicating the presence of a moderate amount of fat or liquid within the tumor. |
| | Tomograms revealed the mediastinal mass to be homogeneous without evidence of calcification or lobulation. There was no hilar adenopathy. |
| | (continued) |

| Metadata Element Field | Metadata |
|------------------------|--|
| | Diagnosis: |
| | Thymoma |
| | Thymectomy: |
| | On August 8, 1977 a thymectomy was performed and encapsulated tumor completely excised. |
| | Pathology: |
| | The specimen contained a partially cystic mass and a solid portion that constituted approximately one-half of the |
| | tumor. The cystic mass was $5 \times 4 \times 1$ cm, and the overall dimensions of the tumor $11 \times 5 \times 1$ cm, weighing 45 g. |
| | Postonerative Status: |
| | On day one, the patient complained of diplopia in mid-afternoon and marked drooping of her eyelids. At that time she |
| | • Rilateral asymmetrical provide $\Omega S > \Omega D$: |
| | • Delaberal fiscure OD 0, OS 7: |
| | Taipebrai fissure 00 9, 00 7, Increased storic bilatorally on prolonged upgazo; |
| | Increased prosis bilaterally on profonged upgaze, Euli barizontal and vartical gaza; |
| | I di honzontal and venteal gaze, No facial weakness: |
| | Normal hulbar muscles: |
| | Normal bubbli muscles, Normal bubbli muscles, |
| | Good provimal strength in the limbs: and |
| | Normal ventilatory capacity |
| | Patient made an excellent recovery and was discharged home without any medication |
| | Second Admission |
| | In September 1977, 6 weeks post-op, she was readmitted with increasing ptosis, diplopia and generalized fatigue. At the end of the day she had fatigue chewing and weakness of the jaw and neck |
| | Importantly, she had no difficulty swallowing or breathing and no change in the quality of her voice. She had become depressed and anxious. |
| | Ocular Motility: |
| | Bilateral symmetrical prosis with weakness of the orbicularis oculi, and an inability to bury her evelashes |
| | Increased ptosis on fatigue |
| | Mvasthenic lid twitch OS |
| | • Fatigue of horizontal saccades after rapid gaze right and left, to the point where the eves came to a standstill |
| | Neurologic Examination: |
| | • A mild bulbar palsy |
| | Bilateral facial weakness with difficulty pursing her lips |
| | Inability to sustain the arms elevated for long periods |
| | Normal vital capacity |
| | Electrophysiologic Studies: |
| | The technique for repetitive stimulation studies is similar to motor nerve conduction studies. Rather than a single supramaximal stimulus, trains of repetitive stimuli are delivered at a rate of 3 stimuli per second, with 6–10 stimuli in a train. The compound muscle action potential of the first response is compared with the fifth response and the percentage decrement measured. A decrement of greater than 10% represents a positive test for myasthenia gravis (MG). |
| | In this patient the study revealed decrements in the right deltoid, right biceps, and inferior orbicularis oculi muscle, confirming a diagnosis of generalized myasthenia gravis. |
| | Stimulated Single-Fiber EMG (SF-EMG) was performed in the right digitorum communis. Seven pairs were recorded. Jitter was abnormal in one pair. MCD ranged from 15.7 to 134.8 µs. |
| | Blocking was present. |

| Metadata Element Field | Metadata |
|------------------------|---|
| | SF-EMG is the more sensitive electrophysiologic method for the diagnosis of myasthenia. This is a special technique for the recording of single-muscle-fiber action potentials and is used to measure fiber density and so-called jitter. Jitter is the variability of the interpotential interval of successive discharges of two single muscle fibers belonging to the same motor unit. This phenomenon is due largely to the very slight variability of delay at the branch points in the distal axon and by synaptic delay at the neuromuscular junction. |
| | Diagnosis: |
| | Myasthenia gravis |
| | Treatment: |
| | Mestinon (pyridostigmine bromide) 60 mg q3h |
| | Prednisone 40 mg daily |
| | Hospital Course: |
| | Twenty-four h after starting medication there was striking improvement. By day four, she had fully recovered. |
| | In July 1980 she was admitted for the third time with acute difficulty swallowing, shortness of breath, ptosis, diplopia, and limb weakness. Her relapse was due to her starting to taper her own prednisone dose down from 5 mg/d to 2.5 mg/d because she was mildly cushingoid. |
| | In the emergency department she had on examination: |
| | A mild bulbar palsy; |
| | Moderate weakness of proximal muscles; |
| | Bilateral ptosis; |
| | Easy fatigue of her eye movements; and |
| | Normal vital capacity. |
| | Medication: |
| | Prednisone was increased to 10 mg bid |
| | Pyridostigmine 60 mg 4x/d |
| | She rapidly recovered back to her normal baseline and was discharged nome. |
| | In May 1998 she was admitted as an emergency with occlusion of the right dorsalls peaks and anterior libralis arteries. |
| | A unonnectority was performed. Hematologic studies revealed a hypercoagulable state: |
| | Prothrombin time 15.6 |
| | Partial thromhonlastin time 24 1 |
| | CEA level 120 |
| | Hematocrit 26.7 |
| | The presence of a hypercoagulable state and elevated CEA level led to a workup for an occult malignancy. |
| | Colonoscopy revealed a sigmoid mass approximately 2×2 cm obstructing the colon. A left colectomy and colorectal anastomosis were performed. Observations during surgery revealed metastatic spread with four nodules located in the right lobe of the liver. |
| | Adenocarcinoma of the colon with 18/18 positive mesenteric lymph podes |
| | Patient died in 1999 |
| Publisher | Spencer S. Eccles Health Sciences Library University of Itah |
| Date Digital | |
| Date Digital | 1077 |
| | |
| Resource.Type | VIGEO |
| Format.Creation | |
| Source | 16-mm Film |
| Language | En |
| Relation-Is Part Of | 163-10, 166-25, 920-1, |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002. For further information regarding the rights to this collection, please visit http://medlib.med.utah.edu/neuroophth/Wray/copyright.htm |

| Metadata Element Field | Metadata |
|------------------------|--|
| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |
| Catalogue | http://library.med.utah.edu/NOVEL/Wray |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| Reviewer | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ |
| Clinical | The video of this patient illustrates eyelid signs of ocular myasthenia gravis. Partial ptosis OS Retraction of the upper eyelid OD Myasthenic lid twitch OS (overshoot of the upper lid on looking up after full gaze down) Full eye movements A positive IV Tensilon test showed: Full recovery of ptosis OS Loss of lid retraction OD Watering of the eyes Frequent blinking Lid Twitch—Cogan's Sign: In 1965 Cogan described a transient eyelid retraction occurring during refixation from downgaze to straight ahead gaze. The twitch is an "overshoot" of the eyelid. Cogan's lid twitch sign is not pathognomonic for MG. It may occur with brainstem or peripheral ocular motor disorders. Hering's Law of Equal Eyelid Innervation: Unilateral ptosis and contralateral lid retraction demonstrate Hering's law of equal eyelid innervation. Thus, when the ptotic lid is manually raised, the contralateral lid falls to a normal position since a large innervation is no longer required. Ptosis is defined as the lid covering more than 2 mm of the cornea. Ptosis is measured by documenting the width of the palpebral fissure in millimeters with the eyes in primary gaze and the eyebrows held down straight. Approximately 50% of patients with MG present with ptosis. More than 90% eventually develop eye movement abnormalities and typical ocular MG. Of those patients who present with only ocular symptoms, half persist with purely ocular myasthenia and half go on to develop generalized MG. Or those who develop generalized MG, most do so within 2 years of the onset of the ocular |
| Neuroimaging | symptoms as in this patient. CT and MRI of the mediastinum are the most sensitive radiologic techniques for detecting a thymoma. CT is superior in screening for thymoma. MRI may, however, offer better resolution in evaluating the extent or spread |
| | of a thymoma to the pleural cavity. |
| Anatomy | Both thymic hyperplasia and thymoma are associated with MG. Thymic hyperplasia occurs in as many as 65–70% of all myasthenic patients, particularly younger patients. It is characterized by infiltration of the thymus with lymphocytes and plasma cells and the formation of lymphoid follicles (germinal centers). Thymoma occurs in 5–20% of myasthenic patients. The incidence of this tumor increases with age. Patients with thymoma tend to have more severe disease, higher serum titers of AChR antibodies, and more severe abnormalities on EMG than patients without a thymoma. Associated Autoimmune Diseases: |
| | There is a 23% incidence of associated autoimmune disease in patients with thymoma, although no sex predisposition or HLA antigen has been found. |

| | innou |
|------------------------|--|
| Metadata Element Field | Metadata |
| Pathophysiology | MG is an autoimmune disease caused by sensitized T helper cells and an IgG-directed attack on the nicotinic acetyl- choline receptor of the neuromuscular junction (NMJ). |
| | The mechanism of antibody damage to the receptor and motor endplate probably involves several steps. |
| | 1. There is a complement-directed attack with the destruction of acetylcholine receptor and the junctional folds. |
| | 2. Binding of the antibody to the receptor can cause receptor blockade. |
| | 3. The abnormal and reduced numbers of acetylcholine receptors lead to impaired NMJ transmission. |
| | In postsynaptic disorders such as MG, the number of quanta of acetylcholine released by each nerve stimulus is normal, but the effect of each quantum on its receptor is reduced. |
| | 5. The net result is a lower endplate potential and a reduced safety factor of transmission at the NMJ. Clinically this manifests as pathologic fatigability, i.e., progressive muscle weakness with use—the hallmark of MG. Patients typically improve after rest or upon arising in the morning, with worsening as the day passes. |
| | 6. In MG, fatigue is limited to muscular fatigue alone and often progresses to frank muscle weakness. |
| Etiology | Autoimmune |
| Treatment | See above |
| Disease/Diagnosis | Generalized myasthenia gravis |
| | Thymolipoma |
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VIDEO e11-6

| Metadata Element Field | Metadata |
|------------------------|--|
| Identifier | 906-2 |
| Title | Progressive External Ophthalmoplegia |
| Ocular Movements | Bilateral Ptosis; |
| | Facial Weakness; |
| | Complete External Ophthalmoplegia; |
| | Normal Pupils; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Bilateral Ptosis; |
| | Facial Weakness; |
| | Complete External Ophthalmoplegia; |
| | Normal Pupils; |
| | Progressive External Ophthalmoplegia (PEO); |
| | Mitochondrial Myopathy; |
| Presenting Symptom | Droopy eyelids |
| History | The patient is an 18-year-old girl first seen in 1990 with a 6-year history of progressive ptosis. |
| | In 1986, at age 14, she was seen by an ophthalmologist and pediatric neurologist and investigated. |
| | Myasthenia gravis was ruled out by a negative Tensilon test, negative anti-acetylcholine receptor antibodies, and normal electromyography and repetitive nerve stimulation studies of the right upper extremity. |
| | She was given a trial on pyridostigmine 50 mg tid and 180 mg time span overnight for 1 month without any improvement. |
| | In 1987 , at age 15 , she had bilateral ptosis surgery repeated on the right eye in August 1990. By this time she had developed limitation of all conjugate eye movements due to progressive external ophthalmoplegia (PEO). |
| | In 1990, at age 18, a muscle biopsy performed at Johns Hopkins showed ragged-red fibers and scattered atrophic myofibers. |
| | Diagnosis: Mitochondrial Myopathy |
| | The fundus exam showed no abnormality. |
| | Cardiac and endocrine evaluations were normal. |
| | The patient moved out of Boston and was lost to follow-up. |
| | The term mitochondrial cytopathy has been used to emphasize multisystem involvement in PEO. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2004 |
| Date Original | 1990 |
| Resource.Type | Video |
| Format.Creation | |
| Source | 3/4" Umatic master videotape |
| Language | En |
| Relation-Is Part Of | 926-2, 926-3, 945-3, 946-1 |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002. For further information regarding the rights to this col- lection, please visit http://medlib.med.utah.edu/neuroophth/Wray/copyright.htm |
| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |
| Catalogue | http://library.med.utah.edu/NOVEL/Wray |
| Contributor Primarv | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| | Steve Smith, Videographer |

| Metadata Element Field | Metadata |
|------------------------|---|
| Reviewer | |
| Context LIRI | http://library.med.utab.edu/NOVEL/Wray |
| Clinical | This 18-year-old girl with PEO presented with the insidious onset of bilateral prosis |
| omnour | Muscle involvement is diagnostic. |
| | The myopathic signs illustrated are: |
| | 1. Bilateral ptosis with overaction of the frontalis muscle; |
| | 2. Weakness of the orbicularis oculi muscle with impaired eye closure; |
| | 3. No recovery of ptosis on gentle eye closure (which is a sign seen in ptosis due to myasthenia gravis); |
| | 4. No fatigue of the eyelids with increased ptosis on sustained up gaze; |
| | No overaction of the eyelid on suddenly looking up (a technique used to detect a myasthenic lid twitch, a sign described by Dr. David Cogan); |
| | 6. A complete external ophthalmoplegia with gaze fixed in primary position (noteworthy that the patient was unaware that she could not move her eyes fully until the time of her neurovisual examination); and |
| | 7. Weakness of the lower face, impairing the ability to grip the lips tightly together. |
| Neuroimaging | Neuroimaging studies were not done in this case. |
| | Wray and colleagues (1995) provided MR images in Kearns-Sayre syndrome (KSS) and PEO. The figures included: |
| | A 61-year-old woman (patient 1) with KSS, moderately severe truncal and appendicular ataxia, and a documented mtDNA deletion. |
| | A. T1-weighted sagittal image demonstrates severe cerebellar vermian atrophy (arrow). |
| | A 23-year-old man (patient 2) with KSS, cognitive impairment, ataxia, and an mtDNA deletion. |
| | A. T2-weighted image demonstrates regions of hyperintense signal (arrows) in the subcortical white matter. The periventricular regions were spared. |
| | B. T2-weighted image shows foci of hyperintense signal (arrows) in the dorsal midbrain. |
| | A 37-year-old woman (patient 8) with CPEO manifested by external ophthalmoplegia, ataxia, and sen- sorineural hearing loss. |
| | A. Long-repetition-time/short-echo-time (proton density) axial image. In the frontal lobes, abnormal hyper- intense signal predominates in the subcortical white matter (arrows), whereas in the posterior temporal and parietal lobes the abnormal signal extended from the subcortical regions to the ventricular surface (curved arrows). |
| | B. T2-weighted axial MR image demonstrates bilateral hyperintense signal abnormalities in the globus pal- lidus (arrows). Hyperintense white matter abnormalities and ventricular dilatation are also present. |
| | C. T1-weighted sagittal image demonstrates cerebral cortical and cerebellar vermian atrophy (arrow) and thinning of the corpus callosum. |
| | Other PEO patients are reported show predominantly white matter damage that correlated with spongiform degeneration of the brain verified by autopsy examinations. |
| Anatomy | |
| Pathology | A skeletal muscle biopsy is diagnostic in mitochondrial myopathy due to an mtDNA deletion. |
| | In mitochondrial myopathy, defective oxidative phosphorylation results in mitochondrial proliferation in type 1 and 2A muscle fibers. |
| | Fibers with the most severe biochemical defects may degenerate, and adjacent fibers with less severe or no defects may appear normal. |
| | The combination of a patchy moth-eaten appearance in individual muscle fibers along with mitochondrial pro- liferation gives rise to the ragged-red fiber seen on modified Gomori trichrome staining. NADH staining shows abnormal subsarcolemmal mitochondria in the muscle fibers. |
| | The electron microscopic sections of skeletal muscle show abnormal mitochondria. |

| Metadata Element Field | Metadata |
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| Etiology | Mutations in mtDNA are maternally inherited in a graded fashion. A single mtDNA mutation can lead to dra- matically different clinical phenotypes, creating a very large spectrum of expressivity. |
| | For example, the A3243G mutation associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) can also cause cardiomyopathy, diabetes and deafness, or external ophthal-moplegia. |
| | Deletions of mtDNA in skeletal muscle, ranging in size from 3.8 to 9.1 kb, were found in an identical loca- tion on muscle biopsy in 5 of 11 personal cases (3 KSS, 8 PEO). The deletion encompasses structural genes for the mitochondrial respiratory chain and is associated with impaired mitochondrial function. The variable involvement of multiple organs, (e.g. heart, brain and retina in PEO and KSS) may be attributable to a mixed population of mutant and normal genomes in varying amounts in different tissues. |
| | Both muscle and brain are also involved in patients with the MELAS syndrome, which is characterized by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; and MERRF , characterized by myoclonic epilepsy associated with ragged-red fibers. |
| | In MELAS, dysfunction of the central nervous system dominates the clinical picture. |
| | While there is considerable overlap of symptoms and signs between PEO , KSS , MELAS , and MERRF , there is general agreement that cases of mitochondrial myopathy, PEO and KSS , with or without clinical involvement of the brain, should be considered separately. |
| | The term mitochondrial encephalomyopathy or cytopathy has been applied to the multisystem diseases involving brain, skeletal muscle, and other organs. These disorders and the clinical phenotypes of mtDNA disease span the spectrum of all known oxidative phosphorylation disorders and include PEO , deafness, cardiomyopathy, MELAS , and MERRF . |
| Treatment | Coenzyme Q (ubiquinone) deficiency is present in KSS; treatment strategies for KSS are based on supplying electron transport chain cofactors and substrates, as well as antioxidants, in an attempt to protect against mtDNA free-radical damage. |
| | The literature best supports the efficacy of coenzyme Q10 (ubiquinone) 4 mg/kg per day in mitochondrial disease. |
| Disease/Diagnosis | Progressive External Ophthalmoplegia; |
| | Mitochondrial Cytopathy |
| References | DiMauro S et al: Mitochondrial myopathies. Ann Neurol 17:521, 1985 |
| | Evans OB, et al: Clinical and Laboratory Features of Mitochondrial Encephalomyopathy Syndromes. In Inborn Errors of Metabolism of the Nervous System, in <i>Neurology in Clinical Practice</i> , 3rd ed. Philadelphia, Butterworth Henemann 2000, 1595-1662. |
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VIDEO e11-7

| Metadata Element Field | Metadata |
|------------------------|---|
| Identifier | 212-3 |
| Title | Paraneoplastic Upbeat Nystagmus |
| Ocular Movements | Upbeat Nystagmus; Lid Nystagmus; Opsoclonus; Saccadic Dysmetria; Saccadic Pursuit; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Upbeat Nystagmus; Lid Nystagmus; Saccadic Dysmetria; Oscillopsia; Saccadic Pursuit; Paraneoplastic Cerebellar Syndrome; Pancreatic Endocrine Carcinoma; Anti-Hu–Associated Paraneoplastic Encephalitis Paraneoplastic Opsoclonus; |
| Presenting Symptom | Dizziness |
| History | This case was presented to the Clinical Eye Movement Society at the American Neurological Association Meeting in October 2009. The patient is a 65-year-old woman who was in good health until 7 weeks prior to admission. On June 22, 2009, on the return flight from her daughter's wedding in Oregon, she began to feel "dizziness" that she characterized as an "inability to sense herself in space." This progressed insidiously over the course of hours and became intense enough to cause difficulty in standing and an inability to walk unassisted off the plane on arrival. Fully upright she felt as though "there is a sensation of backwards motion, with someone trying to push me off my heels." She also reported difficulty with short-term memory, intermittent blurring of vision, and "eyes bobbing up and down," a prominent feature that "caused quite a stir among physicians." She had no impairment in her speech or swallowing, no motor or sensory changes, and no hearing loss, tinnitus, or headache. On return home, she consulted an ENT specialist on Cape Cod who diagnosed an inner ear problem and prescribed meeizine. Her PCP diagnosed vestibular neuritis and prescribed a short course of prednisone. Her symptoms progressed and she was referred to the Massachusetts Eye and Ear Infirmary and then admitted to the Massachusetts General Hospital. Past Medical History: Hypertension Family History: Hypertension and alcoholism in both parents Social History: Retired but working in the family business Smoted 1 to 2 packs per day for 25 years |

| Metadata Element Field | Metadata |
|------------------------|---|
| | Neurologic Examination: |
| | Alert, appropriately interactive, normal affect |
| | Orientation: Oriented to person, states "MEEI" for place and "Cambridge" for city |
| | Oriented to 2009 but states "June" for month (August) |
| | Attention: WORLD backwards without error |
| | Speech: Fluent |
| | Followed simple and complex commands |
| | Repetition, naming, comprehension intact |
| | Memory: 3/3 at registration and 0/3 at 5 min. |
| | Normal fund of knowledge |
| | Calculations: Intact |
| | Praxis: Normal |
| | Cranial Nerves: |
| | Normal apart from ocular motility |
| | Motor System: |
| | 5/5 throughout |
| | 2+ symmetric reflexes |
| | Plantar responses flexor |
| | Sensory System: |
| | Impaired vibration sense in the toes |
| | All other modalities normal |
| | Coordination: |
| | No titubation |
| | Prominent trunkal ataxia |
| | Ataxic gait with tendency to sway backwards |
| | Neurovisual Consult: |
| | Patient complained of marked oscillopsia and difficulty reading. |
| | Neuro-Ophthalmologic Examination: |
| | Visual acuity: 20/60 with difficulty |
| | Confrontation fields, pupil reflexes, and fundoscopy normal. |
| | Ocular Motility: |
| | Upbeat nystagmus in primary position |
| | Lid nystagmus |
| | Full horizontal and vertical eye movements |
| | Normal convergence |
| | Upbeat nystagmus suppressed on convergence |
| | Horizontal and vertical saccadic dysmetria |
| | Saccadic pursuit in all directions |
| | Horizontal optokinetic nystagmus (OKN) present |
| | Absent vertical OKN |
| | Horizontal and vertical oculocephalic reflex normal |
| | No skew deviation |
| | Blood Studies: |
| | WBC 12,100/mm ³ (4.5–11.0) |
| | Polys 94% |
| | Neuts 11,340/mm ³ (1.8–7.7) |
| | Serum electrolytes normal |
| | Brain MRI without Gadolinium: |
| | Nonspecific white matter foci representing chronic small vessel ischemic change |

(continued)

11-23

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| Metadata Element Field | Metadata |
|------------------------|--|
| | Brain MRI Thin Slices through the Brainstem/Cerebellum: |
| | Stable scattered T2/FLAIR hyperintensities in the periventricular and deep white matter that are nonspecific. |
| | A demyelinating process cannot be fully excluded. |
| | Head and Neck MRI with 3D Reformatting: |
| | Normal studies |
| | CT Scan of the Chest with IV Contrast: |
| | Normal study |
| | Bone Scan: |
| | Skeletal degenerative changes |
| | No suspicious lytic or blastic lesions |
| | Lumbar Puncture: |
| | Cerebrospinal fluid protein 69 mg/dL (elevated) |
| | Sugar 60 mg/dL |
| | WBC 7 |
| | 97% lymphs |
| | 3% monos |
| | Elevated IgG 22.5 mg/dL (0-8.0) |
| | CSF albumin 33.2 mg/dL (normal) |
| | Paraneoplastic Markers: |
| | Serum was sent to the Mayo Clinic for a paraneoplastic panel of antibodies including anti-Ma1, anti-Ma2, anti-Ri, anti-Yo, anti-Hu, anti-Zic4, anti-CV2. |
| | Result: Anti-Hu antibody positive—titer 1:15,360 |
| | Transabdominal and Transvaginal Ultrasound: |
| | Heterogeneous, thickened endometrial stripe measuring 17 mm |
| | Endometrial tissue biopsy negative |
| | CT of Abdomen and Pelvis with IV Contrast: |
| | Solid-appearing $3.8 \times 2.9 \times 3.5$ cm well-defined heterogeneous mass (measuring 80 Hounsfield units post-contrast) arising from the tail of the pancreas |
| | Biopsy: |
| | Pancreatic mass core biopsy positive for pancreatic endocrine carcinoma |
| | Pathology: |
| | The tumor was relatively well circumscribed but extended focally into the peripancreatic soft tissue and focally involved the edge of the specimen at its inferior aspect (confirmed by synaptophysin stain). The proximal resection margin was free of tumor. |
| | Immunohistochemical study revealed that ki-67 proliferative index was <2%, and no lymphovascular invasion was identified on D2-40-stained sections. |
| | Based on its size and the presence of lymph node metastasis |
| | (1 of 23 lymph nodes) the lesion was best classified into well-differentiated endocrine carcinoma. |
| | The diagnosis was confirmed with histochemical stains that showed strong tumor cell positivity for cytokeratin cocktail, chromogranin, and synaptophysin, and no significant tumor cell staining with trypsin. |
| | Diagnosis: |
| | Anti-Hu-associated paraneoplastic encephalomyelitis with limbic encephalitis |
| | Brainstem encephalitis causing upbeat nystagmus |
| | 8/20/1990 Surgery: |
| | Distal pancreatectomy with splenic preservation. |
| | A 3.2 \times 3.2 \times 2.5 cm heterogeneous mass was palpable in the tail of the pancreas. |

Metadata Element Field Metadata

Treatment:

- 1. Appropriate therapy for carcinoma
 - Distal pancreatectomy
 - Chemotherapy with cyclophosphamide (one dose of 600 mg/m² IV)
- 2. Immune modulation
 - IV methylprednisolone (total 5 g)
 - IV immunoglobulin for 5 days
- 3. Symptomatic treatment for oscillopsia
 - Trial of clonazepam
- 4. Other medication
 - IV thiamine

Hospital Course:

The patient became very anxious. Impairment in cognition progressed rapidly, leading so severe confusion and inability to hold a conversation and answer questions.

There was no significant response to IV IgG.

She was discharged to rehab on 9/14/09.

Follow-Up:

The progressive deterioration in her mental function and gait ataxia stabilized and in fact improved 5 days prior to her follow-up visit on **9/28/09:** 6 weeks after IV steroid therapy, 5 weeks post-tumor resection, and 3 weeks following IV IgG/ cyclophosphamide.

On examination, although she still had significant memory impairment, trunkal ataxia, opsoclonus and upbeat nystagmus, she was more attentive, oriented $\times 3$, and conversational. She asked specific questions and had considerable insight into her illness. She was able to walk with a walker.

Blood Studies:

Serum for repeat anti-Hu antibody titer

Pathology Studies:

Pathologic paraffin sections of the pancreatic tumor and serum samples were sent to **Dr. Dalmau, Dept of Neurology, University of Pennsylvania, Philadelphia, PA, who kindly agreed to study Hu immunoreactivity.**

I also consulted Dr. Dalmau regarding long-term therapy.

He responded:

"I usually treat my patients with metronomic

doses of cytoxan (1mg/kg per day) for a very long

time (months). They usually tolerate the treatment very well. The treatment should focus on the cytotoxic T cell immune response, not the antibodies. The antibodies often remain detectable for several years. **Rituximab** may help, not because of antibody reduction, but because of B cell depletion. (B cells are very good antigen presenters to the T cells.) I have not personally used both rituximab and cytoxan for this disorder, although I used it in other disorders and they were usually well tolerated."

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| Date Original | 2009 |
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| Source | 3/4" Umatic master videotape |
| Language | En |
| Relation-Is Part Of | 166-1, 931-1, 936-8, 941-5 |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002. For further information regarding the rights to this collection, please visit http://medlib.med.utah.edu/neuroophth/Wray/copyright.htm |
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| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |

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|------------------------|--|
| Catalogue | http://library.med.utah.edu/NOVEL/Wray |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| Reviewer | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ |
| Clinical | This 65-year-old patient with pancreatic cancer and a paraneoplastic cerebellar syndrome had oscillopsia. Ocular motility signs: Upbeat nystagmus in primary position Lid nystagmus Upbeat nystagmus and opsoclonus under closed eyelids Full horizontal and vertical eye movements Normal convergence Upbeat nystagmus suppressed on convergence Horizontal and vertical saccadic dysmetria Saccadic pursuit in all directions Horizontal and vertical saccadic dysmetria Saccadic pursuit in all directions Horizontal and vertical oculocephalic reflex normal No skew deviation The clinical features of upbeat nystagmus illustrated by this case are: Nystagmus is present in central gaze and increases on looking up; Convergence is almost completely suppressed the nystagmus; It is associated with abnormal smooth pursuit; and Opsoclonus is present. View additional cases of upbeat nystagmus alongside this case: ID917-5 Post-resection of a cerebellar astrocytoma ID942-3 Post-infectious brainstem encephalitis ID906-4 Multiple sclerosis ID208-1 Wernicke's encephalopathy post-stomach stapling for morbid obesity Saccadic Hypermetria: Lesions of the dorsal cerebellar vermis and fastigial nuclei cause saccadic dysmetria—typically hypometria if the vermis alone is involved and typically hypermetria if the fastigial nuclei are involved. View additional cases of paraneoplastic syndromes alongside this case: ID931-7 Paraneoplastic couse clonus, CA breast (the index case of the anti-Ri antibody) ID936-7 Paraneoplastic cousel futter, CA lung ID936-7 Paraneoplastic cousel futter, CA lung |
| Neuroimaging | See text |
| Anatomy | Upbeat nystagmus is reported most commonly with lesions in the caudal medulla, which variably involve the peri- hyperglossal group of nuclei, including the nucleus intercalates, the nucleus of Roller, and the nucleus para- raphales. |

(continued)

PART 2

Cardinal Manifestations and Presentation of Diseases

| Metadata Element Field | Metadata |
|------------------------|---|
| Pathophysiology | Graus and colleagues (2001) analyzed 200 patients with anti-Hu–associated paraneoplastic encephalomyelitis (PEM). |
| | The mean age of the 200 patients was 63 years (range, 28–82 years), and 75% were men. The predominant neurologic syndromes were sensory neuropathy (54%), cerebellar ataxia (10%), limbic encephalitis (9%), and multifocal involvement (11%). |
| | Pathologic or x-ray evidence of a tumor was obtained in 167 patients (83%) and was a small-cell lung cancer in 74% of those with histologic diagnosis. |
| | PEM preceded the diagnosis of the tumor in 71% of patients (mean delay, 7 months; range, 0.1–47 months). |
| | The location and histologic diagnosis of neoplasms in 167 patients in this group included 3 patients with carcinoma of the breast, 6 with carcinoma of the prostate, 1 with carcinoma of the ovary, and 2 with carcinoma of the pancreas (1 small cell). |
| | The predominant neurologic symptom of PEM in this study was a sensory neuropathy. The sensory symptoms in PEM patients are usually due to a lesion in the dorsal root ganglia rather than in the peripheral nerves, and in our patient the only finding of a sensory neuropathy was loss of vibration sense in the toes. |
| | Previous work suggested that when a tumor other than a small cell lung carcinoma (SCLC) was discovered in PEM patients the possibility of a concomitant SCLC was high and appropriate studies should be made to rule out this tumor, as in our case. |
| | The authors hypothesize that a positive Hu immunoreactivity by the extrathoracic tumor would support that the tumor was responsible for the PEM. |
| | Further studies currently conducted by Dr. Dalmau are underway in our patient. |
| | Prognosis: |
| | The prognosis of PEM remains poor in terms of survival and neurologic disability. In the Graus and colleagues series, up to 53% of patients were severely disabled at the time of diagnosis and only a minority (5%) had a benign indolent course. |
| | Regarding therapy, although immunotherapy alone is probably not effective in the majority of patients, four patients in the series improved with different immunotherapies. No specific immunotherapy treatment can be recommended, how-ever; ideally, all PEM patients should be offered the possibility of inclusion in therapeutic protocols. |
| | Autopsy Studies: |
| | Dalmau and Graus and colleagues, in a clinical analysis of anti-Ma2–associated encephalitis, obtained pathologic studies in 12 patients. In 11 patients the microscopic studies showed perivascular lymphocytic cuffing and interstitial infiltrates of lymphocytes with variable gliosis and neuronal degeneration. The inflammatory infiltrates were mainly composed of T cells with a smaller number of B cells, macrophages, and microglial activation. |
| | The autopsy of four patients showed a correlation between the clinical MRI findings and the degree of pathologic involvement. The areas with major pathologic abnormalities were always the most symptomatic, but all four patients had abnormal findings in areas that were clinically asymptomatic. In a patient whose symptoms appeared restricted to limbic and hypothalamic dysfunction, the autopsy showed severe involvement of the hippocampus and entorhinal cortex, and mild chronic inflammation in numerous areas including frontal and parietal cortex, midbrain, substantia nigra, pontine nuclei, dorsal grey matter of the medulla, olivary nuclei, and occasional dropout of Purkinje cells with Bergmann's gliosis. |
| | The spinal cord was spared, but the dorsal root ganglia showed several small aggregates of reactive lymphocytes. |
| Etiology | |
| Treatment | The approach to treatment in paraneoplastic opsoclonus syndromes is: |
| | 1. Appropriate therapy for the cancer |
| | • Surgery |
| | Chemotherapy and/or radiation |
| | |
| | Plasmanheresis |
| | Immunoadsorption therapy |
| | Steroids |
| | 3. Symptomatic treatment for vertigo |
| Disease/Diagnosis | Paraneoplastic Upbeat Nystagmus |

| Metadata Element Field | Metadata |
|------------------------|--|
| Further Readings | Bataller L, Dalmau J: Paraneoplastic neurologic syndromes: Approaches to diagnosis and treatment. Semin Neurol 23:215, 2003 |
| | Budde-Steffen C et al: An anti-neuronal autoantibody in paraneoplastic opsoclonus. Ann Neurol 23:528, 1988 |
| | Byrne T et al: Spontaneous neurological improvement in anti-Hu associated encephalomyelitis. J Neurol Neurosurg Psychiatry 62:276, 1997 |
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| | Dropcho E, Payne R: Paraneoplastic opsoclonus-myoclonus. Association with medullary thyroid carcinoma and review of the literature. Arch Neurol 43:410, 1986 |
| | Graus F et al: Anti-Hu-associated paraneoplastic encephalomyelitis: Analysis of 200 patients. Brain 124:1138, 2001 |
| | Hierons R et al: The late effects of necrotizing encephalitis of the temporal lobes and limbic areas: A clinico-pathological study of 10 cases. Psychol Med 8:21, 1978 |
| | Leigh RJ, Zee DS: Diagnosis of nystagmus and saccadic intrusion, in <i>The Neurology of Eye Movements</i> , 4th ed. New York, Oxford University Press, 2006, pp 521-534. |
| | Pierrot-Deseilligny C, Milea D: Vertical nystagmus: Clinical facts and hypotheses. Brain 128:1237, 2005 |
| | Pierrot-Deseilligny C et al: Upbeat nystagmus due to a caudal medullary lesion and influenced by gravity. J Neurol 254:120, 2007 |
| | Sanders MD: Lid nystagmus evoked by ocular convergence: An ocular electromyographic study. J Neurol Neurosurg Psychiatry 1968;31:368, 1968 |
| | Tilikete C et al: Saccadic lateropulsion and upbeat nystagmus: Disorders of caudal medulla. Ann Neurol 52:658, 2002 |
| | Voltz R: Intravenous immunoglobulin therapy in paraneoplastic neurological syndromes. J Neurol 253:33, 2006 |
| | Wong AM et al: Opsoclonus in three dimensions: Oculographic, neuropathologic and modeling correlates. J Neurol Sci 2001;189:71, 2001 |

VIDEO e11-8

| Metadata Element Field | Metadata |
|------------------------|--|
| Identifier | 936-7 |
| Title | Paraneoplastic Ocular Flutter |
| Ocular Movements | Ocular Flutter; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Ocular Flutter; Oscillopsia; Trunkal Ataxia; Paraneoplastic Cerebellar Syndrome; Small Cell Carcinoma of the Lung; |
| Presenting Symptom | Unsteady walking |
| History | The patient is a 58-year-old woman with known hypertension. In 1994, 2 weeks prior to admission she had a dramatic change in behavior with insomnia, agitation and depression. This was accompanied by "wringing of hands and anxiety for no apparent reason." She became anorexic, lost 15 lb, and developed increasing headache, dizziness, head shaking, unsteadiness walking, and a feeling of generalized weakness. She denied nausea, vomiting, lethargy, or syncope. |
| | After consulting her doctor she came to the emergency department. She was seen by Medicine, Psychiatry and Neurology, and admitted to Psychiatry with the chief complaint, "I cannot stand up." |
| | Psychiatry considered her unsteady gait to be histrionic and related to depression and her perception that she was unable to walk. |
| | On examination she was extremely agitated and cooperated poorly with the examiner. She was able to walk only with the use of a walker and two nursing assistants. At that time, she also complained of difficulty focusing and an abnormality of her eye movements were noted. |
| | A neuro-ophthalmology consultation led to her transfer from Psychiatry to Neurology. |

| Metadata Element Field | Metadata |
|------------------------|--|
| | Past History: |
| | Significant for a previous episode of depression treated with antidepressant medication and alcohol abuse in the past. |
| | She was a heavy smoker, smoking a pack per day for more than 30 years. |
| | Family History: |
| | Significant for alcohol abuse in both parents. |
| | Social History: |
| | Eldest of six siblings, unmarried and living alone. Worked as a secretary until 10 years prior to admission when she lost her job. |
| | Neurologic Examination: |
| | She was oriented in time, place, and person but failed to obey three-step commands She had: |
| | Fluctuating level of alertness and attentiveness; |
| | Motor impersistence and perseveration: and |
| | Impaired short-term memory. |
| | A constellation of cerebellar signs: |
| | Dysarthria |
| | • Titubation |
| | Fine tremor of the face and chin |
| | Ocular flutter with occasional spontaneous obtrusive saccades (no continuous opsoclonus) |
| | Marked trunkal ataxia sitting and standing |
| | Gait ataxia with inability to walk without support |
| | The motor system was intact. |
| | Reflexes symmetric, slightly brisk, with flexor plantar responses |
| | Coordination intact in the limbs |
| | Sensory examination showed no abnormality |
| | The electronystagmogram showed: |
| | Spontaneous and gaze nystagmus—intermittent ocular flutter epochs (5 Hz), 1- to 2-cycle sinusoids in duration throughout the record. |
| | Ocular flutter occurred without any rhythmic pattern, with highest frequency on saccades to the left and on eye closure. |
| | She had normal vertical excursions and normal vertical vestibulo-ocular reflex. |
| | 2. Saccades: normal velocity and latency; gaze-evoked nystagmus with large saccades in either direction. |
| | 3. Pursuit (tracking) |
| | 0.2 Hz: Sinusoidal. Ocular flutter intrusions. |
| | 0.3 Hz: Saccadic breakdown to the right and left. |
| | Vertical pursuit gain was negligible. |
| | 4. Optokinetic nystagmus: Poor gain in each direction. |
| | 5. Positional testing: |
| | a. Hallpike's; eyes open in the light: Dizziness with brief burst of right beating nystagmus on the first positioning. |
| | b. Static; eyes open in the dark: No nystagmus or dizziness. |
| | c. Static; eyes closed: No nystagmus or dizziness. |
| | The study showed: |
| | Ocular flutter epochs; |
| | Loss of vertical pursuit tracking; |
| | Lateral gaze-evoked nystagmus; |
| | Saccadic breakdown of pursuit tracking at higher frequencies; and |
| | • A brief burst of right beating nystagmus with accompanying dizziness upon Hallpike positioning to a head hanging right position. |
| | These findings were consistent with brainstem and cerebellar dysfunction affecting fixation and saccadic and pursuit pathways. |

| Metadata Element Field | Metadata |
|------------------------|--|
| | Diagnosis: Paraneoplastic Cerebellar Syndrome |
| | Ocular Flutter |
| | Investigations: |
| | The workup was directed toward detection of an occult neoplasm in breast, ovary, or lung. |
| | Serum electrolytes were abnormal: |
| | Sodium 125 mmol/L (135–145) |
| | Potassium 2.8 mmol/L (3.4–4.8) |
| | Osmolality 262 mOsm/kg (280–296) |
| | Hyponatremia was secondary to the syndrome of inappropriate ADH Secretion (SIADH). |
| | The diagnosis of SIADH is made by finding a concentrated urine sodium (>20 mmol/L) in the presence of hypona- tremia or low plasma osmolality (<260 mmol/kg). |
| | The causes of SIADH include malignancy such as small cell carcinoma of the lung, as in this patient. |
| | Electroencephalogram normal. |
| | Lumbar puncture showed normal cerebrospinal fluid (CSF) with 4 WBC, negative cytology, and no oligoclonal bands |
| | Mammogram normal. |
| | Abdominal and pelvic CT normal. |
| | Bone scan negative for metastases. |
| | Brain MRI focal nonenhancing periventricular T1 hypointensity and T2 hyperintensity noted adjacent to the left lateral ventricle. |
| | Differential Diagnosis: |
| | Nonspecific demyelination versus gliosis. |
| | Chest X-Ray: |
| | X-ray revealed a well-circumcised 6-cm mass consistent with adenocarcinoma of the lung without significant hilar lymphadenopathy. |
| | Chest CT: |
| | In the region of the superior segment and basilar segments of left lower lung, a large, well-rounded, smooth, homogeneously soft-tissue, dense, noncalcified mass was found: approximately $5 \times 3 \times 5$ cm with a single pleural tag. |
| | (Figures 1 and 2) |
| | Diagnosis: |
| | Primary bronchogenic carcinoma. |
| | Surgery: |
| | The patient had a left lower lobe lobectomy and excision of a number of hilar lymph nodes. |
| | Pathology: |
| | Small cell undifferentiated carcinoma of the lung with metastatic carcinoma in 2/5 hilar lymph nodes. |
| | (Figures 3 and 4) |
| | Paraneoplastic Markers: |
| | A fresh-frozen segment of the lung tumor, a sample of CSF, and three samples of serum were sent to Dr. Posner at the Memorial Sloan Kettering Cancer Center for antibody studies (Anti-Ri, Anti-Yo, Anti-Hu). No antibodies were detected. |
| | Yo Autoantibody Test: Negative |
| | Antibodies to the Yo antigen are the most common paraneoplastic antibodies to Purkinje cells. |
| | A negative result for the Yo autoantibody test proved that the cause of the disease was not due to this para- neoplastic antibody but did not rule out paraneoplastic cerebellar degeneration as the cause of the symptoms (Clouston et al. 1992; Hammack et al. 1992). |
| | Ri Autoantibody Test: Negative |
| | Anti-Ri is a highly specific antineuronal antibody that reacts with nuclei of neurons in the central nervous sys- tem. The presence of anti-Ri antibody identifies the subset of patients with paraneoplastic ataxia and opsoclo nus who suffer from breast or gynecologic cancer. The antibody when present is a useful marker for this type of underlying malignancy. The relative amount of anti-Ri was found always to be higher in CSF than in serum (Anderson et al. 1988; Budde-Staffen et al. 1988; Lugue et al. 1989) |

(continued)

PART 2

Cardinal Manifestations and Presentation of Diseases

| Metadata Element Field | Metadata |
|------------------------|--|
| | Protein-A Immunoadsorption: |
| | In spite of the absence of known paraneoplastic antibodies, the patient was treated twice weekly for three weeks with protein-A immunoadsorption: 250 mL of plasma was passed through a disposable column of staphylococcal protein-A covalently bound to a silica matrix that bound both the Fc portion of IgG molecules and immune complexes. The plasma was then returned to the patient. |
| | The first treatment was given in hospital because of the possible risk of cutaneous immune complex vasculitis. |
| | In addition she received prednisone 80 mg daily and haloperidol 2.5 mg PO qhs to minimize the risk of steroid psychosis. |
| | The mechanism of action of the immunoadsorption therapy is not clear, but it may have removed small quantities of immune complexes or antineuronal antibodies or facilitated the formation of anti-idiotype antibodies. |
| | Oncology: She had a limited stage small cell lung cancer, stage T2, N1, MO of the left lower lobe, treated initially with a left lower lobectomy and six cycles of postoperative chemotherapy and then with subsequent radiation to the chest (50.4 Gy in 28 fractions). |
| | Prognosis: |
| | The patient has been followed up for more than 10 years. When last seen in 2006, she was under treatment for chronic obstructive pulmonary disease and anxiety. She was still smoking one pack of cigarettes per day. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2004 |
| Date Original | 1994 |
| Resource.Type | Video |
| Format.Creation | |
| Source | 3/4 Umatic master videotape |
| Language | En |
| Relation-Is Part Of | 166-1, 931-1, 936-8, |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002-2004. For further information regarding the rights to this collection, please visit http://medlib.med.utah.edu/neuroophth/Wray/copyright.htm |
| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neuro-ophthalmology |
| Catalogue | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist Steve Smith, Videographer |
| Reviewer | David Zee, MD, The Johns Hopkins University Hospital, 2007. |
| | Frederick Hochberg, MD, Massachusetts General Hospital, 2007. |
| Context URL | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Clinical | This 58-year-old woman with paraneoplastic ocular flutter is slow to obey commands to move her eyes. Her speech is slurred and she has very little spontaneous conversation. |
| | Titubation is best seen at the start of the video. |
| | Ocular flutter and flutter dysmetria are the major diagnostic signs. |
| | • Intermittent epochs of ocular flutter—horizontal back-to-back saccadic oscillations without an intersaccadic interval. |
| | • Flutter dysmetria most evident when the eyes make voluntary saccadic movements to the left |
| | Occasionally the amplitude of flutter is very small— microflutter —and the oscillations detected only with an ophthal- moscope or eye movement recordings (Cogan, 1954). |
| | Commont Dr. Zoo (DZ) March 2007 |
| | SHW: David, I neglected to test for ocular flutter under closed lids by asking the patient to look to the right and back to center and to the left and back to center. Would Lexpect to see flutter with eves closed? |
| | DZ: Good question. This would seem to be very likely since eye closure shuts off the pause cells, and flutter itself can often be triggered by making a saccade, even in the light. |

| Metadata Element Field | Metadata |
|------------------------|--|
| Neuroimaging | Neuroimaging studies are unavailable in this case. |
| Pathophysiology | Paraneoplastic opsoclonus/ocular flutter is thought to be humorally mediated, and antibodies to diverse autoantigens have been reported, but most patients are seronegative as in this case. The antineural antibodies associated with opsoclonus include Anti-Ri, Anti-Hu, Anti-Yo, Anti-Mal, and Anti-amphiphysin antibodies. |
| Treatment | The approach to treatment in paraneoplastic syndromes is: 1. Appropriate therapy for the cancer • Surgery • Chemotherapy and/or radiation 2. Immune modulation • Plasmapheresis • Immunoadsorption therapy • Intravenous immunoglobulin • Steroids 3. Symptomatic treatment for vertigo, etc. |
| Disease/Diagnosis | Small Cell Carcinoma of the Lung |
| Further Readings | Anderson NE et al: Paraneoplastic cerebellar degeneration: Clinical-immunological correlations. Ann Neurol 24:559, 1988 Bataller L, Dalmau J: Paraneoplastic neurologic syndromes: Approaches to diagnosis and treatment. Semin Neurol 23:215, 2003 Budde-Steffen C et al: An anti-neuronal autoantibody in paraneoplastic opsoclonus. Ann Neurol 23:528, 1988 Ciavarella D: The use of protein A columns in treatment of cancer and allied diseases. Int J Clin Lab Res 21:210, 1992 Cher LM et al: Therapy for paraneoplastic neurologic syndromes in six patients with protein A column immunoadsorption. Cancer 75:1678, 1995 Clouston PD et al. Paraneoplastic cerebellar degeneration. III. Cerebellar degeneration, cancer, and the Lambert-Eaton myasthenic syndrome. Neurology 42:1944, 1992 Cogan DG: Ocular dysmetria, flutter-like oscillations of the eyes and opsoclonus. Arch Ophthalmol 51:318, 1954 Ellenberger C et al: Opsoclonus and parenchymatous degeneration of the cerebellum. The cerebellar origin of an abnormal eye movement. Neurology 18:1041, 1968 Hammack J et al: Paraneoplastic cerebellar degeneration. II. Clinical and immunologic findings in 21 patients with Hodgkin's disease. Neurology 42:1938, 1992 Helmchen C et al: Cerebellar activation in opsoclonus: An fMRI study. Neurology of <i>Eye Movements</i>, 4th ed. New York, Oxford University Press, 2006, pp 521-534 Luque AF et al:. Anti-Ri: An antibody associated with paraneoplastic opsoclonus and breast cancer. Ann Neurol 29:241, 1991 |
| | Luque A et al: Ann Neurol 26:178, 1989 (Abstract) Nitschke M et al: Opsoclonus-myoclonus in small cell lung cancer: Detection of an autoantibody and improvement after protein A Column immunoadsorption therapy. N Engl J Med, 1994 (Letter) |
| | Ridley A et al: Omnipause neurons in two cases of opsoclonus associated with oat cell carcinoma of the Lung. Brain 110:1699, 1987 |
| | Wong AM et al: Opsoclonus in three dimensions: Oculographic, neuropathologic and modeling correlates. J Neurol Sci 189:71, 2001 |
| | Zee D: Personal communication, 2007. |

VIDEO e11-9

| Metadata Element Field | Metadata |
|------------------------|--|
| Identifier | 939-8 |
| Title | Bilateral Sixth Nerve Palsy |
| Ocular Movements | Bilateral Sixth Nerve Palsy; |
| | Bilateral Esotropia; |
| | Paraneoplastic Opsoclonus/Flutter; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Bilateral Sixth Nerve Palsy; |
| | Bilateral Esotropia; |
| | Paraneoplastic Opsoclonus/Flutter; |
| | Paraneoplastic Cerebellar Syndrome; |
| | Carcinoma of the Breast; |
| Presenting Symptom | Double vision and ataxia |
| History | This patient is a 62-year-old woman with a 6-month history of double vision and difficulty walking. |
| | In August 1996 , she first noted her right upper eyelid twitching followed by dizziness, nausea and vomiting. Soon after her voice became "shaky" and she experienced mild difficulty walking. She consulted her primary care physician and was prescribed sertraline for depression. |
| | In November 1996, she developed double vision and increasing unsteadiness walking. |
| | In December 1996, she consulted a neurologist. |
| | Brain MRI at an outside hospital reported to be normal |
| | In January 1997, she was admitted to Massachusetts General Hospital. |
| | Past History: |
| | Significant for right breast cancer in 1986, status post lumpectomy and radiation therapy |
| | Family History: |
| | |
| | Neurologic Examination: |
| | Normal cognitive function |
| | Spontaneous myoclonus and hilateral hand tremore |
| | Mild left heminaresis with hyperreflevia and extensor plantar response |
| | Right flevor nlantar resonnse |
| | Rilateral limb ataxia and nait ataxia |
| | Neuro-Onbthalmologic Examination: |
| | Visual acuity 20/20 OU |
| | Visual fields, pupils, and fundus examination no abnormality |
| | Ocular Motility: |
| | Intermittent opsoclonus with multivectorial conjugate saccades without an intersaccadic interval and |
| | Ocular flutter with horizontal back to back saccades in central gaze |
| | • Esotropia OS > OD |
| | Weakness of abduction OS—left sixth nerve palsy |
| | Weakness of adduction OS |
| | Weakness of abduction OD—right sixth nerve palsy |
| | Full upgaze with upbeat nystagmus |
| | Full downgaze with no nystagmus |
| | Pursuit movements normal |
| | resung tor ocular dysmetria snow slow renxation saccades. No dysmetria. |
| | Diagnosis. |
| | raraneoprasul cerebenar synurome with opsocionus/nutter. |
| | The following sequences were obtained: |
| | Axial FLAIR, T1, FSE T2, diffusion-weighted images, and post gadolinium. |

| Metadata Element Field | Metadata |
|------------------------|---|
| | The study showed areas of T2 and FLAIR hyperintensity involving the tegmen and extending cranially to the midbrain adjacent to the midline and just inferior to the cerebellar peduncle. |
| | Also noted were areas of FLAIR and T2 hyperintensity within the corona radiata and centrum semiovale bilaterally, left greater than right. Similar signal abnormalities were seen within the right putamen and globus pallidus. |
| | Impression: |
| | Diffuse white matter process consistent with a paraneoplastic syndrome. |
| | Lumbar Puncture: |
| | Cerebrospinal fluid protein 36 mg/dL |
| | Sugar 68 mg/dL |
| | 136 RBC |
| | 12 WBC |
| | 95% lymphs |
| | 4% monocytes |
| | Positive for oligoclonal bands |
| | Cytology negative for malignant cells twice |
| | Chest/Abdomen/Pelvic CT |
| | Normal |
| | Bone Scan and Bone Marrow Biopsy: |
| | Normal |
| | Mammogram: |
| | Bilateral mammogram |
| | Cluster of microcalcifications in the subareolar region of the lateral aspect of the left breast suspicious for intraductal carcinoma |
| | Procedure: |
| | Needle-guided left breast biopsy |
| | Pathology: |
| | Intraductal adenocarcinoma in situ in the left breast, the primary breast cancer being in the right breast. |
| | Paraneoplastic Markers: |
| | CSF and serum were sent to Dr. Posner at the Memorial Sloane Kettering Cancer Center for antibody studies (Anti-Ri, Anti-Yo). No antibodies were detected. |
| | Ri Autoantibody Test: Negative |
| | Anti-Ri is a highly specific antineuronal antibody that reacts with nuclei of neurons in the central nervous system. The presence of anti-Ri antibody identifies the subset of patients with paraneoplastic ataxia and opsoclonus who suffer from breast or gynecologic cancer. The antibody when present is a useful marker for this type of underlying malignancy. The relative amount of anti-Ri was found always to be higher in CSF than in serum. (Anderson et al, 1988; Budde-Steffen et al, 1988; Luque et al, 1989.) |
| | All diagnostic antibody tests should be considered within the context of clinical findings (Dalmau et al, 1992). |
| | Diagnosis: |
| | 1. Paraneoplastic opsocionus/ocular flutter |
| | 2. Paraneoplastic cerebellar syndrome |
| | A. Bilataral sixth narve nalsy |
| | 5. Intraductal adenocarcinoma in situ left breast |
| | Surgical resection of the intraductal adenocarcinoma in situ was done |
| | Therany: |
| | Ten days of IV solumedrol 1 g/d |
| | Five-day course of IV IgG |
| | Hospital Course: |
| | Over a period of 10 days the opsoclonus and flutter completely resolved and there was significant improvement in her ophthalmoplegia. The left eye regained almost full abduction and the right eye was able to cross the midline looking right. |
| | The spontaneous myoclonus stopped, hand tremors waxed and waned but overall improved, and the gait instability was markedly improved. She was able to walk in her room without a walker and in the hallway with a wheeled walker. |
| | She was hospitalized for 3 weeks and then discharged to a rehabilitation hospital. |
| | (continued) |

(C 1)

| Metadata Element Field | Metadata |
|------------------------|---|
| | Discharge Medication: |
| | Prednisone 10 mg daily, three times a day and on a tapering dose to stop after 2 weeks. |
| | The patient was followed by the neuro-oncology team. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2008 |
| Date Original | 1997 |
| Resource.Type | Video |
| Format.Creation | |
| Source | 3/4" Umatic master videotape |
| Language | En |
| Relation-Is Part Of | 163-3, 169-34, 944-5, 946-2 |
| Rights Management | Shirley H. Wray, MB, ChB, PhD, FRCP, Copyright 2002. For further information regarding the rights to this collection, please visit http://medlib.med.utah.edu/neuroophth/Wray/copyright.htm |
| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |
| Catalogue | http://library.med.utah.edu/NOVEL/Wray |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| | Steve Smith, Videographer |
| Reviewer | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ |
| Clinical | This 62-year-old woman with paraneoplastic opsoclonus/flutter and diplopia due to bilateral sixth nerve palsy describes the visual disturbance of oscillopsia. |
| | At the time the video was made she had no opsoclonus/flutter. |
| | The eyes show: |
| | • Esotropia OS > OD |
| | Weakness of abduction OS—left sixth nerve palsy |
| | Weakness of abduction OD—right sixth nerve palsy |
| | Impaired adduction US Full upgage with upbeet pystagmus |
| | Full downgaze with no pystagmus Full downgaze with no pystagmus |
| | Pursuit movements normal |
| | Testing for ocular dysmetria showed slow refixation saccades. No dysmetria. |
| | In addition this patient had: |
| | Bilateral ataxia on finger/nose test and heel-knee-shin |
| | Loss of rhythm hand tapping |
| | • Gait ataxia |
| | Ocular flutter and flutter dysmetria are the major diagnostic signs. |
| | • Intermittent epochs of ocular flutter —horizontal back-to-back saccadic oscillations without an intersaccadic interval |
| | Flutter dysmetria most evident when the eyes make voluntary saccadic movements to the left |
| | thalmoscope or eye movement recordings (Cogan, 1954). |
| | Comment Dr. Zee (DZ). March 2007 |
| | SHW: David Linealected to test for ocular flutter under closed lids by asking the patient to look to the right and back |
| | to center and to the left and back to center. Would I expect to see flutter with eyes closed? |
| | can often be triggered by making a saccade, even in the light. |

| Metadata Element Field | Metadata |
|------------------------|---|
| Neuroimaging | Neuroimaging studies are unavailable in this case. |
| | |
| Anatomy | |
| Pathology | Paraneoplastic opsoclonus/ocular flutter is thought to be humorally mediated, and antibodies to diverse autoantigens have been reported, but most patients are seronegative as in this case. The antineural antibodies associated with opsoclonus include Anti-Ri, Anti-Hu, Anti-Yo, Anti-Mal, and Anti-amphiphysin antibodies. |
| | It is not known whether opsoclonus is a cerebellar or brainstem disorder. |
| | Cerebellum: |
| | Wong and colleagues (2001) have suggested, on theoretical grounds, that the deep cerebellar nuclei should be activated in patients with opsoclonus. |
| | Helmchen and colleagues (2003) assessed this hypothesis with fMRI in two patients with opsoclonus and com- pared them with healthy subjects. They used three-dimensional scleral search coil recordings to characterize the pathologic eye oscillations. Fortuitously, both patients showed a decrease of or no OC with the eyes closed, so fMRI signals under two conditions (open eyes with OC and closed eyes without OC) could be compared. |
| | A comparison of these two states revealed neither cerebellar vermal nor brainstem activation but showed, for the first time, bilateral functional activation of the deep cerebellar fastigial nuclei. |
| | This result supports the recent hypothesis of Wong and colleagues that OC results from a disinhibition of the fastigial ocular motor region (FOR). |
| | FOR contains saccade-related neurons that augment the ongoing discharge of pontine excitatory and inhibitory burst neurons. Because the cerebellar ocular motor vermis physiologically inhibits FOR, the authors concluded that the absence of vermal activation during OC may reflect a cause of OC. |
| | Brainstem: |
| | Glycine has been identified as the neurotransmitter of omnipause neurons, and poisoning with a glycine antagonist, strychnine, is reported to produce opsoclonus and myoclonus. |
| | Zee postulates that an immune-mediated glycine channelopathy affecting the membrane of omnipause cells may be the underlying mechanism for ocular flutter and opsoclonus and that it may be possible that membrane- stabilizing drugs may have a therapeutic role for flutter and opsoclonus in the future. |
| | (Personal communication, 2007.) |
| Ftiology | Intraductal adapacarcinoma of the broast |
| Treatment | |
| | |
| Disease/Diagnosis | Paraneoplastic opsocionus/inuter |
| | Paraneonlastic brainstem encenhalitis |
| | Rilateral sixth nerve nalsy |
| | Intraductal adenocarcinoma of the breast |
| Further Readings | Alderson LM: Neurologic complications of breast cancer, in <i>Office Practice of Neurology</i> , 2nd ed, MA Samuels, SK Feske (eds) Philadelphia Churchill Livingstone, 2003, pp. 1181-1186 |
| | Anderson NE et al: Paraneoplastic cerebellar degeneration: Clinical-immunological correlations. Ann Neurol 24:559, 1988 |
| | Bataller L, Dalmau J: Paraneoplastic neurologic syndromes: Approaches to diagnosis and treatment. Semin Neurol 23:215, 2003 |
| | Budde-Steffen C et al: An anti-neuronal autoantibody in paraneoplastic opsoclonus. Ann Neurol 23:528, 1988 |
| | Cogan DG: Ocular dysmetria, flutter-like oscillations of the eyes and opsoclonus. Arch Ophthalmol 51:318, 1954 |
| | Dalmau J et al: Anti-Hu–associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) 71:59, 1992 |
| | Helmchen C et al: Cerebellar activation in opsoclonus: An fMRI study. Neurology 61:412, 2003 |
| | Leigh RJ, Zee DS: Diagnosis of peripheral ocular motor palsies and strabismus, in <i>The Neurology of Eye Movements</i> , 4th ed. New York, Oxford University Press, 2006, pp. 385-474 |
| | Luque A et al: Ann Neurol 26:178, 1989 (Abstract) |
| | Wong AM et al: Opsoclonus in three dimensions: Oculographic, neuropathologic and modeling correlates. J Neurol Sci 189:71, 2001 |
| | |

PART 2

VIDEO e11-10

| Metadata Element Field | Metadata |
|------------------------|---|
| Identifier | 944-1 |
| Title | Bilateral Ptosis |
| | Facial Diplegia |
| Ocular Movements | Bilateral Ptosis; |
| | Total External Ophthalmoplegia; |
| | Facial Diplegia; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Subject | Bilateral Ptosis; |
| , | Total External Ophthalmoplegia; |
| | Facial Diplegia; |
| | Areflexia; |
| | Acute Inflammatory Demyelinating Neuropathy; |
| | Guillain-Barré Syndrome—Miller Fisher Syndrome; |
| Presenting Symptom | Double vision |
| History | The patient is a 47-year-old attorney who was transferred from an outside hospital to the Massachusetts General |
| | Hospital (MGH) for treatment of the Miller Fisher variant of Guillain-Barré syndrome (GBS). |
| | On the morning of September 14, 1993, the patient awoke feeling dizzy and he was unsteady walking. He went back to sleep and felt better when he got up and went to work. |
| | The next day, he noted horizontal double vision driving to work and he returned home to bed. Later that day, he |
| | nurse, and she told him to go to the hospital. |
| | He was admitted to a local hospital. |
| | Head and Neck MRA: |
| | Normal. |
| | Lumbar Puncture: |
| | Cerebrospinal fluid protein 102 mg/mL |
| | No white blood cells. |
| | Hospital Course: |
| | The patient got progressively worse. |
| | On day 5 , he had the sensation that "someone injected my whole mouth with Novocain" and his speech was pro- foundly worse. He also reported that his reflexes, which were normal on admission, became decreased. |
| | On day 10 , he was transferred to the MGH. At this time he had mild headache and dizziness and he could no longer hold his eyes open. He recalled that he had had a period of diarrhea one week prior to the onset of these symptoms. |
| | On admission he complained of generalized weakness and marked weakness of the face and arms, less in the legs. He was able to chew using the left side of his mouth but needed to drink with a straw. He had no difficulty swallow- ing or breathing. |
| | Family History: |
| | Negative for neurologic disease |
| | Neurological/Neuro-Ophthalmic Examination: |
| | Speech dysarthric |
| | Cranial Nerves: |
| | Complete bilateral ptosis |
| | Total external ophthalmoplegia |
| | Only a trace of vertical movements up and down |
| | Pupils equal, minimally reactive to light and near |
| | Facial sensation—slight decrement of pin sensation bilaterally in all three divisions of the trigeminal nerve |
| | Severe taciai diplegia |
| | Motor System: |
| | He leit generally weak and fatigued, muscle strength 4+ to 5/5 bilaterally |
| | Plantar responses flexor |

| Metadata Element Field | Metadata |
|------------------------|--|
| | Coordination: |
| | Impaired in all four limbs and marked gait ataxia |
| | Sensation: |
| | Light touch and temperature decreased distally in the hands and feet |
| | Brain CT Noncontrast: |
| | Normal |
| | Brain MRI: |
| | Normal |
| | Chest X-Ray: |
| | Normal |
| | ECG: |
| | Normal sinus rhythm, normal trace |
| | Diagnosis: |
| | Miller Fisher syndrome (MFS) |
| | The constellation of signs: |
| | 1. Bilateral ptosis |
| | 2. External ophthalmoplegia |
| | 3. Facial diplegia |
| | 4. Limb and gait ataxia |
| | 5. Pupils sluggishly reacting to light |
| | Investigations: |
| | The most important investigations in suspected cases of GBS or its variant, MFS, are: |
| | 1. Electrodiagnostic studies; and |
| | 2. Examination of the cerebrospinal fluid (CSF). |
| | Met the criteria for MFS. |
| | The most frequent early electrodiagnostic findings in GBS and MFS are: |
| | 1. A reduction in the amplitude of muscle action potentials; |
| | 2. Slow nerve conduction velocity; |
| | Conduction block in motor nerves singly or in combination; |
| | 4. Prolonged distal latencies (reflecting distal conduction block); |
| | Prolonged or absent F-responses (indicating involvement of proximal parts of nerves and roots) and reflecting focal demyelination; and |
| | 6. Delayed or absent H-reflex (which merely confirms the loss of ankle jerks). |
| | A limited electrodiagnostic examination may be normal early in the illness, as in this case. A more thorough study, which includes measurement of late responses, almost invariably shows disordered conduction in an affected limb within days of the first symptom. |
| | Electrophysiologic Studies: |
| | Nerve conduction in the lower extremities normal on day 14. |
| | Lumbar Puncture: |
| | Protein 108 mg/mL |
| | No white cells |
| | Usually, the CSF protein is normal in the first few days of the illness. Then the protein level begins to rise, reaching a peak in 4–6 weeks and persisting elevated for several weeks. |
| | In Dr. Ropper's experience patients with MFS have a higher incidence of normal or only slightly elevated CSF protein during the course of their illness. |
| | Stool Cultures: |
| | Positive for <i>Campylobacter jejuni</i> |
| | Serum protein electrophoresis revealed IgG kappa M components in the slow gamma region and there were oligo- clonal bands present as well. |
| | Antibody Studies: |
| | To check for Anti-GQ _{1b} antibody, I sent the serum of this patient and the serum from a second case of MFS, a young man presenting with bilateral sixth nerve palsy, (ID944-5) to Professor Newsom-Davis in Oxford to study. Both of these patients were found to have the Anti-GQ_{1b} IgG antibody. |

Cardinal Manifestations and Presentation of Diseases

VIDE0 e11-10 (Continued)

| Metadata Element Field | Metadata |
|------------------------|---|
| | Treatment: The patient received a total of six sessions of plasmapheresis with replacement with albumin. Ciprofloxacin 500 mg P0 bid Hospital Course: Initially, the patient was too weak to get out of bed and became areflexic. He started to improve while receiving plasmapheresis and physical therapy to the point that at 5 weeks post onset of his illness he regained a few degrees of eye movement in all directions, the ptosis resolved, and he was able to open his eyes. He also gained more control of his mouth and lips, resulting in improvement in his speech, but he was unable to smile or whistle. Follow-Up: The patient was seen in the clinic at 5 weeks, 12 weeks, and 4 months after the onset of his illness. By 4 months, the ptosis and ophthalmoplegia had resolved completely and he had minimal facial weakness and speech was 90% back to normal. He had 5/5 muscle strength and no ataxia. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2004 |
| Date Original | 1993 |
| Resource.Type | Video |
| Format.Creation | |
| Source | 3/4 Umatic master videotape |
| Language | En |
| Relation-Is Part Of | 925-2, 944-5 |
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| Holding.Institution | Spencer S. Eccles Health Sciences Library, University of Utah, 10 N 1900 E, Salt Lake City, UT 84112-5890 |
| Annotation | No |
| Collection | Neuro-ophthalmology |
| Catalogue | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| | Steve Smith, Videographer |
| Reviewer | |
| Context URL | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Clinical | This patient with a severe attack of MFS was followed over a period of 4 months. I had the opportunity to film him on four occasions. In the first clip, made on day 15 , he had: Complete ptosis Total external ophthalmoplegia Inability to close his eyes tightly Inability to close his eyestightly Inability to raise his eyebrows Severe facial diplegia with inability to show his teeth or smile Dysarthric speech due to inability to articulate his words The second clip was made at 5 weeks . At this time: Ptosis had started to improve Patient was able to open and close his eyes Patient was not able to blink—definite paucity of blinking Facial diplegia still pronounced and unable to show his teeth |

| Metadata Element Field | Metadata |
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| | The third clip was made at 12 weeks. At this time he reported: |
| | General strength recovering |
| | Full use of his hands and arms |
| | Speech a good deal clearer |
| | Ptosis had recovered and he was aware of diplopia |
| | Able to close his eyes fairly tightly |
| | Able to raise his eyebrows up |
| | Able to grip his lips together but not whistle |
| | The fourth clip was made at 4 months. At this time, there was striking improvement and the patient was a much happier man. |
| | Speech clearer but still not precise |
| | External ophthalmoplegia has completely recovered with full horizontal and vertical eye movements |
| | Lip movements improved |
| | Able to grip his lips together |
| | Eye closure now tight and able to open and close his eyes normally |
| | Able to raise his eyebrows up and frown |
| | Lower face weakness improved, able to show his teeth and smile |
| | No gait ataxia |
| | Reflexes 1+ throughout |
| | In 1956 Miller Fisher published a paper in the New England Journal of Medicine describing an unusual acute idio- pathic polyneuritis characterized by: |
| | 1. Total external ophthalmoplegia; |
| | 2. Severe ataxia; and |
| | 3. Loss of the deep tendon reflexes. |
| | The nature of the illness was not recognized until he saw the third case, when, in association with a mild peripheral neuropathy, the cerebrospinal fluid showed an albuminocytologic dissociation with a total protein of 348 mg/100 mL and no cells. |
| | The syndrome Miller Fisher described proved to be a variant of acute idiopathic polyneuritis (GBS) in which limb involvement was minimal or absent. |
| | In two of Miller Fisher's cases (cases 1 and 2), external ophthalmoplegia was complete and the eyes fixed in primary gaze. Case 3 had bilateral sixth nerve paralysis and slight rotary nystagmus on attempted lateral gaze. Bilateral ptosis was added to the picture 2 days later. |
| | GBS is now viewed as a group of distinct disorders including the following variants. |
| | Regional |
| | Fisher syndrome of ophthalmoplegia, ataxia, and areflexia |
| | Cervico-brachial-pharyngeal, often with ptosis |
| | Oculopharyngeal weakness |
| | Predominant paraparesis |
| | Bilateral facial or abducens weakness with distal paresthesias |
| | Ophthalmoplegia with ${ m GQ}_{ m th}$ autoantibodies |
| | Functional |
| | Generalized ataxia without dysarthria or nystagmus |
| | Pure sensory |
| | Pure motor |
| | Pandysautonomia |
| | Axonal |
| | The degree of ophthalmoparesis is variable but certain patterns suggest involvement of either the peripheral or cen- tral nervous system. |
| | The ophthalmoplegia may resemble: |
| | Horizontal or vertical gaze palsy |
| | Internuclear ophthalmoplegia |
| | |

| Metadata Element Field | Metadata |
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| | Ptosis is often absent even in the presence of significant ophthalmoparesis. |
| | Bell's phenomenon is often preserved even when vertical eye movements are absent. |
| | Signs pointing to cerebellar dysfunction are: |
| | Rebound nystagmus |
| | Impairment of smooth pursuit |
| | Suppression of the vestibular ocular reflex |
| | Dr. Fisher was himself impressed by the presence of ataxia unaccompanied by sensory loss and "reluctantly interpreted" the clinical signs as "manifestations of an unusual and unique disturbance of peripheral neurons." |
| Neuroimaging | No imaging studies are available in this patient. |
| | The MRI findings in another patient with MFS have been reported. |
| | The patient was a 25-year-old woman with complete external ophthalmoplegia, ptosis, limb ataxia, and areflexia. |
| | Brain MRI: |
| | T1-weighted images with Gd-DTPA on day 15 of her illness demonstrated enhancement of the posterior nerve roots of the cauda equina. |
| | MRI on day 32 revealed swelling and enhancement of the bilateral ocular motor nerves as well as the facial nerves and the abducen nerves. |
| | The patient received high-dose IV immunoglobulin therapy and had marked improvement in her ophthalmoplegia. |
| | Repeat MRI with gadolinium, after recovery, showed no enhancement of the cauda equina nor of the cranial nerves. |
| | In this patient IgG anti-GQ1b and GD _{1b} antibodies were detected. |
| Anatomy | |
| Pathology | In 1993, Chiba and colleagues reported the presence of serum IgG antibody against ganglioside GQ _{1b} in patients in the acute phase of MFS and pointed out that this immunologic feature was common to both MFS and GBS. |
| | To check for Anti-GQ _{1b} antibody, I sent the serum of this patient and the serum from a second case of MFS, a young man presenting with bilateral sixth nerve palsy (ID944-5), to Professor Newsom-Davis in Oxford to study. Both these patients were found to have the Anti-GQ _{1b} IgG antibody . |
| | Both GBS and the MFS are cell-mediated immunologic diseases directed at peripheral nerve resulting in acute inflammatory demyelinating neuropathy. |
| | Autoantibodies: A number of autoantibodies directed at components of nerve ganglioside are detected inconsistently in patients with GBS. Anti-GQ _{1b} IgG is the most important and is the autoantibody found in almost all patients with ophthalmoplegia. |
| | Antibodies against the ganglioside GQ _{1b} have also been detected in patients with Bickerstaff's brainstem encephalitis. Bickerstaff's encephalitis is characterized by ophthalmoplegia and ataxia but is also accompanied by pyramidal and sensory tract findings and cerebrospinal fluid pleocytosis. |
| | GM1 autoantibody may be found in approximately one-third of patients with GBS early in their course, corresponding in most instances to a predominantly motor presentation and to axonal damage. |
| | The highest titers of anti-GM1 antibody are usually associated with cases that follow Campylobacter infections. |
| | Autoantibodies directed against GD1a or GT1b have been associated in some cases with the pharyngeal-brachial- cervical variant. |
| | Pathologic studies in cases of GBS have failed to demonstrate any changes within the neuroaxis, and there is thus no morbid anatomic basis for attributing the clinical picture to a disturbance within the brainstem. |
| | Virtually all cases have shown perivascular (mainly perivenous) lymphocytic infiltrates scattered throughout the cranial nerves, ventral and dorsal nerve roots, and dorsal root ganglia and along the entire length of the peripheral nerves. Swelling of nerve roots at the site of their dural exit has been emphasized by some authors and theorized to cause root damage. |
| | In patient's whose electrophysiologic tests display severe axonal damage early in the illness, the pathologic findings cor- roborate the predominately axonal nature of the disease with secondary myelin damage and little inflammatory response. |
| Etiology | <i>Campylobacter jejuni</i> may be the responsible trigger in GBS and MFS since anti-GQ1b antibodies bind to surface epitopes on this organism, and its lipopolysaccharide fraction may molecularly mimic the ganglioside. |
| Treatment | Specific treatment of the presumed immune disorder that underlies GBS and MFS include plasma exchange and IV immunoglobulin (0.4 g/kg per day for 5 consecutive days). |
| | Approximately 3–5% of patients do not survive an attack of GBS. |
| Disease/Diagnosis | Miller Fisher syndrome |
| - | Acute inflammatory demyelinating neuropathy |
| | (continued) |

| Metadata Element Field | Metadata |
|------------------------|--|
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| | |

VIDE0 e11-11

| Metadata Element Field | Metadata |
|------------------------|--|
| Identifier | 16-1 |
| Title | Retinal Emboli |
| Ocular Movements | |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Retinal Emboli Transient Monocular Blindness Ogular Streke |
| Presenting Symptom | |
| Presenting Symptom | Transient monocular bindness |
| History | Temporary loss of vision in one eye, termed transient monocular bindness (TMB), is the most important visual symptom of arteriosclerotic vascular disease, arteritis, and states of altered coagulability and thrombo-cytosis. In most patients, the visual disturbance during each individual attack of TMB is stereotypic. It may recur over a period of months or over a much briefer span of hours, days, or weeks. A meticulous history of the attack and duration of the visual disturbance will permit classification of the TMB occurrence into one of four types. Type I is due to transient retinal ischemia. Type II is due to retinal vascular insufficiency. Type III is due to vasospasm. Type IV occurs in association with antiphospholipid antibodies but includes cases of unknown cause. |
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| Format Creation | |
| Source | 16-mm Film |
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| Annotation | No |
| Collection | Neurology / Neuro-ophthalmology |
| Catalogue | http://library.med.utah.edu/NOVEL/Wray |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Ray Balhorn, Video Compressionist |
| Reviewer | |
| Context URL | http://library.med.utah.edu/NOVEL/Wray/ |

| Metadata Element Field | Metadata |
|------------------------|---|
| Clinical | A unique film of retinal emboli passing through the microcirculation of the retina recorded by Roger Lancaster (photographer) in 1967 with Dr. Cogan and his two fellows, Dr. Philip Zweifach and Dr. David Haining, is shown here. I believe this is the only film in existence showing moving emboli in branches of the central retinal artery. |
| | A retinal embolus is virtually diagnostic of localized disease of the ipsilateral internal carotid artery (ICA) when a typical carotid bruit is present, when aortic or cardiac disease is absent, and when there is no exogenous source of emboli, as, for example, in IV drug use (talc and microcrystalline cellulose), severe trauma, or injection (air). |
| | Cholesterol emboli (Hollenhorst plaques) appear in the branches of the central retinal artery as bright or shiny bodies whose diameter seems to exceed the intraluminal diameter of the arteriole. |
| | These emboli tend to lodge at arterial bifurcations. They may be invisible except on ocular compression or by varying the incidence angle of the ophthalmoscope light. They may be permanent or quite transient, moving on to the next bifurcation or disappearing before the next examiner can verify them. The presence of a cho- lesterol embolus is a poor prognostic sign: 93% of such patients have vascular disease at presentation; 15% die within the first year and 55% within 7 years. The cause of death is usually heart disease, 6:1 compared with stroke. |
| | Pale white platelet plugs can also be seen transiently within retinal arteries. In a hypertensive patient, the caliber of the retinal arteries on the side of an ICA stenosis may be reduced and will show fewer hypertensive changes than the retinal vessels of the opposite eye. Focal cotton-wool spots (cystoid bodies), in the absence of hypertensive retinopathy, are due to embolic microinfarction and may be seen when no emboli are visible. |
| Neuroimaging | |
| Anatomy | |
| Pathology | |
| Etiology | |
| Treatment | |
| Disease/Diagnosis | Transient Monocular Blindness Retinal Emboli |
| Further Readings | Beal MF et al: Cholesterol embolism as a cause of transient ischemic attacks and cerebral infarction. Neurology 31:860, 1981 |
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VIDE0 e11-12

| Metadata Element Field | Metadata |
|------------------------|--|
| Identifier | 939-2 |
| Title | Third Nerve Palsy |
| Ocular Movements | Ptosis; |
| | Third Nerve Palsy; |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Ptosis; |
| | Third Nerve Palsy; |
| | Microinfarct Third Nerve; |
| | Oculomotor Nerve; |
| Presenting Symptom | Double vision |
| History | The patient is a 57-year-old man who carried a diagnosis of atrial fibrillation and coronary artery disease post CABG. |
| | He was seen in the Massachusetts General Hospital ER with acute double vision and headache and was admitted. |
| | Four days prior to admission (PTA) he developed a bifrontal headache accompanied by double vision looking down. He reported that the double vision involved "diagonal images" and was worse on looking to the left. He had no nausea, vomiting, or eye pain. |
| | One day PTA he developed ptosis of the left eye (OS). |
| | Past History: |
| | Notable for coronary artery disease with multivessel coronary artery bypass grafts in 1991. |
| | Hypercholesterolemia |
| | Atrial fibrillation (not on anticoagulation) |
| | A history of previous episodes of diplopia |
| | Ten years PTA, he developed diplopia on left lateral gaze lasting three days. He was seen by an ophthalmolo- gist but no diagnosis was made. His vision returned to normal. |
| | One year PTA, he had another attack of double vision and was seen by an ophthalmologist who diagnosed a left sixth nerve palsy. |
| | Workup included a brain MRI, which was normal. |
| | The sixth nerve palsy recovered completely. |
| | Social History: |
| | Heavy cigarette smoker in the past. |
| | General Examination: |
| | Normal. |
| | BP 120/70 |
| | Temporal artery pulses normal |
| | No carotid or orbital bruits |
| | Neuro-Ophthalmologic Examination: |
| | Visual acuity 20/20 00 |
| | Pupils equal reacting briskly to light and near |
| | Visual fields and fundus examination normal |
| | Ucular Molliny: |
| | r was us Marked parasis of superior rectus and inferior oblique |
| | Markey parests of superior recus and interior oblight |
| | Parecis of medial rectus, able to adduct only 20 degrade past the midline |
| | Inferior rectus naretic, able to depress the eve only 20 degrees |
| | Cranial nerves 4 and 6 intact |
| | No prophosis or ocular pulsation |
| | Ocular motility OD normal |

VIDE0 e11-12 (Continued)

| Metadata Element Field | Metadata |
|------------------------|--|
| | Motor System: |
| | Normal |
| | Sensory System: |
| | Normal |
| | Brain MRI: |
| | Normal |
| | MR Angiogram: |
| | Normal |
| | Blood Studies: |
| | Complete blood count, differential, and platelet count normal |
| | Erythrocyte sedimentation rate normal |
| | C-reactive protein and fibrinogen normal |
| | Tests for diabetes negative |
| | Test for syphilis negative |
| | Chest X-Ray: |
| | Normal |
| | Lumbar Puncture: |
| | Cerebrospinal fluid clear |
| | Protein 39 mg/mL |
| | |
| | |
| | Lidyilosis. |
| | Etiology |
| | Microinfarction |
| | Close observation of all patients with a third nerve palsy, particularly those with a progressive history, as in this patient, should be watched carefully with pupil examinations checked regularly. Anisocoria greater than 2 mm may be considered grounds for an arteriogram. |
| | Prognosis for Recovery: |
| | Good |
| | The patient was discharged on the third hospital day. He returned 5 weeks later 95% recovered with full eye movements and only partial left ptosis. One month later he was fully recovered. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2004 |
| Date Original | 1996 |
| Resource.Type | Video |
| Format.Creation | |
| Source | 3/4 Umatic master videotape |
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| Relation-Is Part Of | 5-1 932-6 940-3 946-6 |
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| Annotation | Νο |
| Collection | Neuro-ophthalmology |
| Catalogua | http://medstat.med.utah.edu/neuroonhth/Mrau/ |
| Cantributer Driver | http://meusiai.meu.ulaii.euu/meuloopinii/wilay/ |
| Contributor Primary | Siliriey H. Wray, MB, UNB, PND, FKUP |
| Contributor Secondary | kay Bainorn, Video Compressionist Steve Smith, Videographer |

| Metadata Element Field | Metadata |
|------------------------|---|
| Reviewer | |
| Context URL | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Clinical | This patient with a microinfarct of the trunk of the left third nerve had: Ptosis OS Paresis of all the muscles innervated by the third nerve, with marked paresis of the inferior oblique and superior rectus In primary gaze, left eye deviating down and out due to the unopposed action of the intact lateral rectus and superior oblique muscles Pupil normal A second video clip taken 5 weeks after the onset of the palsy showed 95% recovery with: Minimal ptosis OS |
| | Minimal paresis of elevation of the eye Cover/uncover test showed an alternating exophoria Review alongside this case: ID163-21 Nuclear third nerve palsy ID919-2 Nuclear third nerve palsy with isolated bilateral ptosis ID166-25 Fascicular third nerve palsy—Claude's syndrome |
| Neuroimaging | Normal studies |
| Anatomy | The diagnosis of a third nerve palsy is straight forward but it is important to consider whether it is: 1. A nuclear lesion; 2. A complete or partial lesion of the nerve trunk; or a 3. Superior division of the third nerve; or an 4. Inferior division of the third nerve. A lesion involving the superior division of the third nerve results in paresis of the levator palpebrae muscle and the superior rectus so that the patient will have partial ptosis and paresis of elevation in the line of action of the superior rectus. A lesion involving the inferior division of the third nerve involves all the extraocular muscles innervated by the third nerve, except the levator palpebrae and the superior rectus, with or without pupil involvement. |
| Pathology | |
| Etiology | In adults, the most common cause of a progressive painful pupil sparing the third nerve palsy is microinfarc- tion of the nerve in association with diabetes, hypertension, temporal arteritis, or syphilis. The most common cause of a progressive painful third nerve palsy involving the pupil is an aneurysm of the posterior communicating or posterior cerebral artery, until proved otherwise and an emergency CT angio- gram and/or MR angiogram is indicated. Patients with partial involvement of the pupil and complete paresis of the extraocular muscles and eyelid should also undergo MRI/MRA study and be closely observed. MRA will reveal some but not all aneurysms compressing the third nerve. |
| Treatment | Control of risk factors for stroke |
| Disease/Diagnosis | Third nerve palsy Microinfarction of the nerve |
| Further Readings | Blake PY et al: MR of oculomotor nerve. Am J Neuroradiol 16:1665, 1995 Chou KL et al: Acute ocular motor mononeuropathies: Prospective study of the roles of neuroimaging and clinical assessment. J Neurol Sci 219:35, 2004 Ettl A, Salomonowitz E: Visualization of the oculomotor cranial nerves by magnetic resonance imaging. Strabismus 12:85, 2004 Eustace P: Partial nuclear third nerve palsies. Neuro-ophthalmology 1985;5:259, 1985 Leigh JR, Zee DS: Diagnosis of peripheral ocular motor palsy and strabismus, in <i>The Neurology of Eye Movements</i>, 4th ed. New York, Oxford University Press, 2006. pp. 385-474 |

VIDE0 e11-13

| Metadata |
|---|
| 932-3 |
| Apraxia of Evelid Opening |
| Apraxia of Eyelid Opening Impaired Initiation of Horizontal Saccades Slow Hypometric Horizontal Saccades Supranuclear Paralysis of Up and Downgaze Square Wave Jerks |
| Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Apraxia of Eyelid Opening Impaired Initiation of Horizontal Saccades Slow Hypometric Horizontal Saccades Supranuclear Paralysis of Up and Downgaze Square wave Jerks Progressive Supranuclear Palsy—Tauopthay Steele Richardson Olszewski Syndrome CNS—Degeneration |
| Frequent falls |
| In January 1997, this 73-year-old patient was referred to the Neurovisual Clinic. At that time his speech was slurred and he stated that his eyes were his "biggest" complaint because: 1. He had impaired focusing "close up"; 2. His eyes shut spontaneously much of the time; 3. Bright sunlight provoked eye closure; 4. The frequent closure of his eyes made it difficult for him to hold a conversation with anybody; and 5. With his eyes open his vision was clear. Neuro-Ophthalmologic Examination documented: Visual acuity: 20/40 OU Eyelids: Age-related bilateral ptosis Infrequent blinking Positive glabella tap Able to close his eyes but very slow opening his eyes Mild blepharoclonus Ocular Motility: Slow hypometric horizontal saccades Slow vertical saccades Absent convergence Saccadic pursuit in all directions Convergence insufficiency with exophoria at near Within 6 months his wife noted that his condition had deteriorated in that he: Seemed to have lost his motivation Rarely spoke unless spoken to Tended to sit longer without moving Did not appear to wish to read anything Had more difficulty feeding himself and dressing |
| |

| Metadata Element Field | Metadata |
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| | Neurologic Examination at that time showed: |
| | Striking paucity of movements |
| | Rigidity of the neck |
| | Difficulty getting up out of a chair, toppling backwards |
| | Slowness walking, needing to make several small |
| | steps in order to turn |
| | Speech that had become dysphonic more than dysarthric |
| | Tollgue that moved well Absence of jaw jerk and facial jerks |
| | Diagnosis |
| | Progressive supranuclear palsy |
| Publisher | Spencer S. Eccles Health Sciences Library. University of Utah |
| Date Digital | 2004 |
| Date Original | 1996 |
| Besource Type | Video |
| Format Creation | |
| Source | 3/4" Umatic master videotane |
| | |
| Balation-Is Part of | 166-18 168-3 024-2 036-5 030-3 |
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| Annotation | No |
| Collection | Neurology/Neuro-ophthalmology |
| Catalogue | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributor Secondary | Tessa Hedlev-Whyte, MD, Massachusetts General Hospital, Pathology: |
| ; | Anne Osborn, MD, University of Utah, Neuroimaging; |
| | Ray Balhorn, Video Compressionist |
| | Steve Smith, Videographer |
| Reviewers | David Zee, MD, Johns Hopkins University, 2005 |
| Context URL | http://medstat.med.utah.edu/neuroophth/Wray/ |
| Clinical | This patient with progressive supranuclear palsy (PSP) has: |
| | Supranuclear saccadic and pursuit paralysis of upward gaze |
| | Square wave jerks looking up |
| | Slow hypometric horizontal saccades |
| | Slow eyelid closure and impaired voluntary eyelid opening with striking inability to open his eyes on command (apraxia) |
| | Dysphonic and dysarthric speech |

VIDE0 e11-13 (Continued)

| Metadata Element Field | Metadata |
|------------------------|---|
| | Comment: |
| | The inability to initiate eyelid opening is a dysfunction of voluntary lid control due, in this patient, to disease of the extrapyramidal system. The patient can close his eyes slowly on command and reopen them normally after blinking. |
| | However, the major problem was a difficulty in voluntarily opening his eyes on command (eyelid apraxia). |
| | The term <i>eyelid apraxia</i> is a misnomer and should not be used to describe the eyelid dysfunction in this case of PSP because the motor system is affected. |
| | Confirmation that the vertical gaze disorder is supranuclear and localized to the rostral interstitial nucleus of the MLF (riMLF) in the midbrain is the presence of: |
| | 1. Upward deviation of the eyes on forced eye closure (intact Bell's) and |
| | 2. Full upward eye movements when the head is bent forward—the oculocephalic or doll's eye reflex. |
| | At the onset of PSP: |
| | Vertical saccades are slow |
| | Vertical saccadic range is progressively reduced |
| | Initiation of vertical saccades is impaired |
| | Vertical smooth pursuit is impaired (reduced range) |
| | • Vertical optokinetic stimulation can cause gaze to tonically deviate in the direction of the stripe movement |
| | (Personal communication, Zee 2005.) |
| | Additional PSP signs are: |
| | 1. Positive glabella tap (inability to inhibit a blink when the forehead is tapped) |
| | 2. Myerson's sign (inability to inhibit a blink to a bright pen light shown in the eyes) |
| | 3. Blepharoclonus (tremor of the lids on gentle eye closure) |
| | 4. Square wave jerks |
| | 5. Bilateral ophthalmoparesis in the late stages of the disease |
| Neuroimaging | PSP has characteristic changes on neuroimaging. |
| | In another case a sagittal T2-weighted MR scan shows the tectal plate is markedly thinned and atrophic (Figure 1). Functional MRI reveals global metabolic reduction most pronounced in the frontal lobes, anterior cingulate gyrus, the basal ganglia, the ventrolateral and dorsomedial nuclei of thalamus, and the upper brainstem. PET scans using fluorodopa demonstrate diminished striatal dopamine formation and storage. In addition to hypometabolism in the putamen, severe caudate involvement on PET scanning distinguishes PSP from Parkieses (Figure 2 and 2). |
| Anatomy | Supranuclear paralysis of vertical gaze localizes to the midbrain and to the rostral interstitial nucleus of the madial localizes to the midbrain and to the rostral interstitial nucleus of the |
| | The riMLF is a wing-shaped structure that lies dorsomedial to the red nucleus and rostral to the interstitial nucleus of Cajal. The riMLF contains burst neurons for vertical and torsional saccades. The riMLF projects predominantly to the ipsilateral oculomotor (third nerve) and trochlear (fourth nerve) nuclei. |
| Pathology | In an autopsy case of PSP, a pale locus coeruleus and substantia nigra are two typical gross features on inspection of the brainstem. |
| | Neuronal loss, granulovacuolar degeneration, and fibrillary gliosis are present in areas of neuronal change. There is widespread neuronal and glial tau accumulation in the cortex, basal ganglia, periaqueductal gray matter, subthalamic nucleus, red nucleus, substantia nigra, pedunculopontine nucleus, superior colliculus, and the dentate nucleus of the cerebellum. |
| | Microscopically, globose neurofibrillary tangles are observed on LHE stain. |
| | The neuronal cytoplasmic inclusions are strongly immunoreactive for tau. |
| | Tufted astrocytes are a specific finding in PSP. They are often binucleate and have long tau reactive processes. The intracellular aggregation of tau in PSP may be sufficient to cause nerve cell degeneration. |
| Etiology | PSP is a "tauopathy." |
| | Studies suggest that it is a recessive disorder in linkage disequilibrium with the tau gene. Rare familial forms of PSP exist including an autosomal dominant transmission with incomplete penetrance. |
| | The relationship to the tau gene further suggests a relationship to frontotemporal dementia/Pick's disease (FTDP), and some families carrying the FTDP-17 mutation (chromosome 17) have affected members with PSP-like phenotypes. |

| Metadata Element Field | Metadata |
|------------------------|--|
| Treatment | There is no cure for PSP. Once the disease has begun, its course is relentlessly progressive. |
| Disease/Diagnosis | Progressive Supranuclear Palsy-tauopathy |
| Further Readings | Buttner-Ennever JA, Horn AK: Pathways from cell groups of the paramedian tracts to the floccular region. Ann NY Acad Sci 781:532, 1996 |
| | Daniel SE et al: The clinical and pathological spectrum of Steele-Richardson-Olszewski syndrome (progres- sive supranuclear palsy): A reappraisal. Brain 118:759, 1995 |
| | Friedman DI et al: Neuro-ophthalmic findings in progressive supranuclear palsy. J Clin Neuroophthalmol 12:104, 1992 |
| | Growdon JH, Rossor MN: <i>The Dementias. Blue Books of Practical Neurology</i> , Vol 19. Philadelphia, Butterworth-Heinemann, 1998 |
| | Leigh RJ, Zee DS: Diagnosis of central disorders of ocular motility, in <i>The Neurology of Eye Movements</i> , 4th ed. New York, Oxford University Press, 2006, pp 598-718 |
| | Mendez MG, Cummings JL: <i>Dementia: A Clinical Approach</i> . 3rd ed. Philadelphia, Butterworth Heinemann, 2003 |
| | Richardson JC et al: Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia. A clinical report on eight cases of heterogenous system degeneration. Trans Am Neurol Assoc 88:25, 1963 |
| | Stanford PM et al: Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene: Expansion of the disease phenotype caused by tau gene mutations. Brain 123:880, 2000 |
| | Sir Charles Bell (http://www.whonamedit.com/doctor.cfm/2103.html) |

VIDE0 e11-14

| Metadata Element Field | Metadata |
|------------------------|--|
| Identifier | 925-4 |
| Title | Restrictive Orbitopathy |
| Ocular Movements | Bilateral Lid Retraction |
| | Lid Lag |
| | Restricted Upgaze |
| Creator | Shirley H. Wray, MB, ChB, PhD, FRCP, Professor of Neurology, Harvard Medical School; Director, Unit for Neurovisual Disorders, Massachusetts General Hospital |
| Subject | Bilateral Lid Retraction Lid Lag Bilateral Exophthalmos Restrictive Orbitopathy of Graves' disease |
| Presenting Symptom | Prominent eyes |
| History | This 71-year-old woman was referred with bilateral optic neuropathy and thyroid-associated ophthalmopathy (TAO) of Graves' disease. She had been treated for primary hyperthyroidism on three occasions with radioactive iodine and was taking methima- |
| | Neuro-Onbthalmologic Examination: |
| | Vision was reduced to 20/200 in each eve with bilateral central scotoma and mild disc hyperemia. |
| | She had the classical signs of Graves' disease: |
| | A prominent stare. |
| | Retraction of all four eyelids |
| | Bilateral exophthalmos |
| | Hertel exophthalmometer 25 0D, 28 0S, base 108. |
| | Tight orbits/reduced orbital resilience |
| | Restricted horizontal eye movements |
| | Marked limitation of upward gaze |
| | Mild limitation of downgaze |
| | Lid lag (persistent elevation of the upper eyelid in |
| | downgaze)—von Graefe sign |
| | Positive forced duction test |
| | Prominent congested scleral blood vessels |
| | A visible rim of sciera on gentie eye closure |
| | Beil's reflex absent, eyes fail to move up under closed |
| | lius) |
| | |
| | Thuroid tests showed TT3 elevated to 243 (6/7/90) and 324 (7/3/90) |
| | CT Orbits: |
| | Greatly enlarged extraocular muscles crowding the optic |
| | nerves at the apex |
| | Considerable bilateral proptosis right > left. |
| | The inferior rectus and medial rectus muscles were especially enlarged with fusiform dilatation of the midposition of the muscle. |
| | Diagnosis: |
| | Advanced Graves' disease |
| | Thyroid-associated orbitopathy |
| | Bilateral compressive optic neuropathy |
| | Therapy: |
| | Patient received a course of oral steroids |

| Metadata Element Field | Metadata |
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| | Surgery: |
| | Bilateral orbital decompression and ethmoidectomy. |
| | CT Orbits Post-Op: |
| | The scan confirmed adequate removal of the medial orbital walls and the orbital floors over the maxillary sinuses. |
| | The surgeon also partly divided the levator muscles because of severe upper lid retraction. Her vision recovered to 20/40 OD and 20/30 OS. |
| | Comment: |
| | Compressive optic neuropathy is the most serious complication of TAO. |
| | requiring orbital decompression, as in this case, optic neuropathy occurs in up to 50% of patients. |
| | Vision loss from optic nerve compression requires immediate management. |
| Publisher | Spencer S. Eccles Health Sciences Library, University of Utah |
| Date Digital | 2004 |
| Date Original | 1990 |
| Resource.Type | Video |
| Format.Use | Video/RealMedia/0:0:00 minutes ; Video/QuickTime/0:0:00 minutes; |
| Format.Creation | |
| Source | 3/4" Umatic master videotape |
| Language | En |
| Relation-Is Part of | 4-3 |
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| Annotation | No |
| Collection | Neuro-ophthalmology |
| Catalogue | http://medstat.med.utah.edu/NOVEL/Wray/ |
| Contributor Primary | Shirley H. Wray, MB, ChB, PhD, FRCP |
| Contributory Secondary | Ray Balhorn, Video Compressionist Hugh Curtin, M.D., Massachusetts Eye and Ear Infirmary, Boston, MA Steve Smith, Videographer |
| Reviewer | Arthur Grove, MD, Massachusetts Eye and Ear Infirmary, Boston, MA. |
| Context URL | http://medstat.med.utah.edu/NOVEL/Wray/ |
| Clinical | This 71-year-old woman with TAO of Graves' disease has: A prominent stare Retraction of all four eyelids Bilateral exophthalmos Hertel exophthalmometer 25 0D, 28 0S, base 108 |
| | Tight orbits/reduced orbital resilience Restricted horizontal eye movements Marked limitation of upgaze Mild limitation of downgaze |
| | Lid lag (persistent elevation of the upper eyelid in |
| | downgaze)—von Graefe sign |
| | rusiuve iureeu uuelluir lest Prominent congested scleral blood vessels |
| | A visible rim of sclera on gentle eve closure |
| | |

Metadata Element Field Metadata

Neuroimaging

Anatomy

Pathology

Etiology

Also illustrated is:

- The use of a Hertel exophthalmometer to measure the forward protrusion of the proptotic eye
- How to evaluate reduced orbital resilience by digital pressure on the globe
- The absent Bell's reflex

Comment:

TAO can be differentiated from ocular myasthenia gravis by the lack of ptosis and the presence of proptosis, lid retraction, lid-lag, and periorbital edema.

TAO can, however, co-exist with ocular myasthenia gravis. As a result, screening thyroid studies are essential prior to treatment even when the clinical diagnosis of TAO together with ocular myasthenia gravis seems clear.

Forced Duction Test:

In TAO the limitation of upgaze is due to tethering of the eyeball in the floor of the orbit by soft tissue changes. Tethering of the eyeball inferiorly can be confirmed by performing a forced duction test. The test requires anesthetizing the eyeball with topical anesthesia. Inability to move the eye up despite pushing on the globe with a cotton tip swab or pulling with a small pair of blunt tweezers, suggests mechanical restriction—interpreted as a positive forced duction test. CT of the orbit is the gold standard for the diagnosis of TAO. The classic finding is enlargement of the extraocular muscle belly with relative sparing of the tendon. Proptosis may be recognized without extraocular muscle enlargement, presumably resulting from an increased volume of intraorbital fat. Te advected the arbit, the recommended ecourses is chart to impression recovery (CTIP, to bicklight the extraoc

- To order an MRI of the orbit, the recommended sequence is short tau inversion recovery (STIR, to highlight the extraocular muscles. CT Orbit:
- Images in another case of TAO showed on Figure 1: Axial CT through the orbit without contrast shows enlargement of the medial rectus muscle bilaterally. The tendinous insertion is spared.
 - Figure 2: The coronal CT (reformatted from axial data set) without contrast showed enlargement of the medial rectus muscle, inferior rectus muscle, and upper muscle complex on both sides.
- Orbit—enlargement of extraocular muscles Graves' disease is an autoimmune condition. For unknown reasons, the extraocular muscles develop lymphocytic and plasmacytic infiltration with secondary production of acid mucopolysaccharides. In the acute stages, the changes are largely inflammatory. In the chronic inactive stage, there is often fatty infiltration of muscles. Autoimmune disorder
- TreatmentTreatment of TAO associated with Graves' disease is extremely successful. Irritation and swelling can be treated with a
short (1- to 2-month) course of systemic corticosteroids or with low-dose (1500 to 2000 cGy) orbital radiation therapy.
Proptosis can be treated with orbital decompression using a variety of techniques.
(For a full discussion of therapy, see reference Galetta et al, 1996; Jacobson, 1995; and Riddick, 1991.)Disease/DiagnosisRestrictive orbitopathy of Graves' DiseaseFurther ReadingsBahn RS, Heufelder AE: Pathogenesis of Graves' ophthalmopathy. N Engl J Med 329:1468, 1993
Galetta SL et al: Pretectal eyelid retraction and lag. Ann Neurol 33:554, 1993
 - et al: Eyelid lag without eyelid retraction in pretectal disease. J Neuroophthalmol 16:96, 1996
 Garrity JA et al: Results of transantral orbital decompression in 428 patients with severe Graves' ophthalmopathy. Am J Ophthalmol 116:533, 1993
 Hoffman PN: in *Walsh and Hoyt's Clinical Neuro-Ophthalmology*, 6th ed, NR Miller, NJ Newman (eds). Philadelphia, Lippincott Williams & Wilkins, 2005
 Jacobson DM. Acetylcholine receptor antibodies in patients with Graves' ophthalmopathy. J Neuroophthalmol 15:166, 1995
 Kennerdell JS et al: Apical optic nerve compression of dysthyroid optic neuropathy on computed tomography. Arch
 - Ophthalmol 99:807, 1981 Liu GT et al: Orbit disease in neuro-ophthalmology, in *Neuro-ophthalmology Diagnosis and Management*. Philadelphia, WB Saunders Company, 2001

Neigel JM et al: Dysthyroid optic neuropathy. The crowded orbital apex syndrome. Ophthalmology 95:1515, 1988 Riddick FA Jr: Update on thyroid diseases. Ophthalmology 88:467, 1981

Trobe JD et al: Dysthyroid optic neuropathy: Clinical profile and rationale for management. Arch Ophthalmol 96:1199, 1978

Wiersinga WM: Advances in medical therapy of thyroid-associated ophthalmopathy. Orbit 15:177, 1996