European University Professors of Ophthalmology

EUPO 2016

Course on Neuro-ophthalmology and Strabismus

EUPO 2016

October 7-8, 2016
Nice, France

In conjunction with EVER 2016

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Aki KAWASAKI, EUPO course organizer

Dear colleagues,

This EUPO course 2016 will cover some of the essential topics in neuro-ophthalmology and strabismus. The topics are presented by a teaching faculty who are all experts in this domain. In addition, each faculty has distilled the essence of her/his topic into a short, readable handout with 3 multiple choice questions.

You can benefit most by reading the questions and handouts before attending the course. During the course, you are encouraged to ask questions and interact with the faculty.

I hope you will find this coursebook to be an educational tool and useful aid in your continued formation.

On behalf of the EUPO 2016 faculty, happy reading and see you at the courses!

Aki KAWASAKI
EUPO Course Organizer

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Programme EUPO 2016
Friday October 7, 2016

• Common Optic Neuropathies in Adults: Diagnosis, Treatment and Prognosis — 08:30 - 10:00

Antonella BOSCHI, Valerie PURVIN

		Course	Page
• 08:30	Idiopathic (demyelinating) optic neuritis *PURVIN V - United States*	1	10
• 08:50	Non-arteritic anterior ischemic optic neuropathy *SAARELA V - Finland*	2	19
• 09:10	Compressive optic neuropathy: pituitary adenoma *BOSCHI A - Belgium*	3	23
• 09:30	Leber hereditary optic neuropathy *YU WAI MAN P - United Kingdom*	4	29
• 09:50	Discussion		

• Break — 10:00 - 10:30

• Case Presentations I: Odd and Unusual Things in Neuro-ophthalmology — 10:30 - 11:00

Valerie PURVIN, Ville SAARELA

• Systematic Approach to the Ocular Motor System — 11:00 - 12:30

François-Xavier BORRUAT, Caroline TILIKETE

		Course	Page
• 11:00	Central disorders of ocular motitliy *BORRUAT FX - Switzerland*	5	34
• 11:25	Central disorders of ocular stability *TILIKETE C - France*	6	41
• 11:50	Myasthenia *LEE M - United States*	7	45
• 12:15	Discussion		

• Lunch — 12:30 - 13:30

Programme EUPO 2016
Friday October 7, 2016

• Uncommon but Important Causes of Visual Loss — 13:30 - 15:00
Fion BREMNER, Graham HOLDER

		Course	Page
• 13:30	Inatrogenic visual loss: toxicities *PURVIN V - United States*	8	51
• 13:50	Acquired autoimmune retinopathies *HOLDER G - United Kingdom*	9	69
• 14:10	Posterior reversible encephalopathy syndrome (PRES) *KAWASAKI A - Switzerland*	10	79
• 14:30	Neuromyelitis optica (NMO) and spectrum disorders *BREMNER F - United Kingdom*	11	85
• 14:50	Discussion		

• Break — 15:00 - 16:00

• Recognizing the Emergencies: From Symptom to Diagnosis — 16:00 - 17:30
Catherine VIGNAL CLERMONT, Michael LEE

		Course	Page
• 16:00	Transient monocular visual loss: carotid embolus vs giant cell arteritis *VIGNAL CLERMONT C - France*	12	90
• 16:20	Diagnosis and management of giant cell arteritis *LEE M - United States*	13	98
• 16:40	Acute diplopia: third nerve palsy *BREMNER F - United Kingdom*	14	104
• 17:00	Acute anisocoria: aneurysm vs Horner syndrome *KAWASAKI A - Switzerland*	15	109
• 17:20	Discussion		

• Case Presentations II: Odd and Unusual Things in Neuro-ophthalmology — 17:30 - 18:00
Patrick YU WAI MAN, Aki KAWASAKI

Programme EUPO 2016
Saturday October 8, 2016

• Paralytic Strabismus: Diagnosis, Evaluation and When to Treat — 08:30 - 10:00

Oliver EHRT, Heimo STEFFEN

		Course	Page
• 08:30	Acquired cranial nerve palsies *STEFFEN H - Switzerland*	16	117
• 08:55	Congenital cranial dysinnervation disorders *KAESER PF - Switzerland*	17	124
• 09:20	Surgical indications and management of paralytic strabismus *EHRT O - Germany*	18	134
• 09:45	Discussion		

• Break — 10:00 - 10:30

• Case Presentations I: Odd and Unusual Things in Strabismus — 10:30 - 11:00

Dominique BREMOND GIGNAC, Camerson PARSA

• Amblyopia , Nystagmus and Secondary Strabismus — 11:00 - 12:30

Jan Tjeerd DE FABER, Pierre-François KAESER

		Course	Page
• 11:00	Amblyopia: physiologic basis and management *PARSA C - France*	19	140
• 11:20	Screening strategies for amblyopia *BREMOND GIGNAC D - France*	20	145
• 11:40	Infantile nystagmus *KAESER PF - Switzerland*	21	150
• 12:00	Secondary and iatrogenic strabismus *DE FABER JT - The Netherlands*	22	157
• 12:20	Discussion		

• Lunch — 12:30 - 13:30

Programme EUPO 2016
Saturday October 8, 2016

• Nonparalytic Esodeviations and Exodeviations — 13:30 - 15:00

Rosario GOMEZ de LIANO, Marcel TEN TUSSCHER

		Course	Page
• 13:30	Esotropia: Considerations in Infants and Adults *TEN TUSSCHER M - Belgium*	23	161
• 13:55	Exodeviations *GOMEZ DE LIANO R - Spain*	24	167
• 14:20	Nonsurgical management of strabismus *DE FABER JT - The Netherlands*	25	173
• 14:45	Discussion		

• Case Presentations II: Odd and Unusual Things in Strabismus — 15:00 - 15:30

Dominique BREMOND GIGNAC, Camerson PARSA

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Idiopathic (demyelinating) optic neuritis

Valerie PURVIN, United States

01

MCQ's

1. **Which of the following statements about isolated idiopathic optic neuritis is NOT true:**

   a. Pain is present in 90%
   b. Disc edema is present in 75% of cases
   c. Visual acuity returns to 20/40 or better in >90% of eyes
   d. The overall risk of future multiple sclerosis is about 50%

2. **Which of the following statements concerning the role of corticosteroid treatment for isolated idiopathic optic neuritis is true:**

   a. Intravenous steroids improve the visual outcome
   b. Oral steroid improve the visual outcome
   c. Intravenous steroids hasten recovery
   d. The beneficial effects of intravenous steroids persist for up to 10 years

3. **Which of the following is a common finding in isolated idiopathic optic neuritis:**

   a. Optic disc hemorrhages
   b. Worsening of vision when steroids are discontinued
   c. Optic nerve enhancement involving >50% of the nerve on MRI
   d. Decreased color vision
   e. Macular hard exudates

Definition and Etiologies

The term **optic neuritis** indicates an inflammatory process involving the optic nerve, usually centered on the myelin sheath. Optic neuritis is occasionally a manifestation of an infectious disease (e.g. syphilis, cryptococcosis, tuberculosis, Lyme disease) or a systemic inflammatory process such as sarcoid or lupus erythematosus. It also occurs as a post-viral or post-immunization event. These are uncommon causes. Most often optic neuritis occurs as a manifestation of multiple sclerosis (MS) or as a forme fruste of MS, termed isolated idiopathic optic neuritis.

Pathophysiology

Activated peripheral T cells migrate across the blood–brain barrier and release cytokines and other inflammatory mediators leading to demyelination. This loss of myelin slows conduction and accounts for the sensitivity of Visual Evoked Response testing in optic neuritis. Following the attack there is, in addition, variable axonal degeneration, accounting for residual visual loss. Ocular coherence tomography (OCT) has provided an objective measure of this axonal loss, which correlates with visual impairment [Trip]. Thus, OCT can be an additional parameter with which to evaluate the efficacy of future therapies for both ON and for MS, in addition to frequency of exacerbations and level of disability [Costello].

Studies

Much of what we know about optic neuritis comes from the NIH-funded multi-center Optic Neuritis Treatment Trial (ONTT), first published in 1988 with subsequent follow-up reports including the 15-year follow-up data in 2008. The study was a prospective, randomized trial involving 455 patients with acute unilateral optic neuritis (ON). Although the primary objective was to assess the efficacy of steroid treatment, the trial also provided invaluable information about other aspects of ON. Patients were randomly assigned to treatment with oral steroids, IV methylprednisolone followed by oral prednisone or oral placebo for 14 days. Measurements of visual function were made at entry, at follow-up visits for the first 6 months, yearly for 4 years, then at 5, 10 and 15 years. Information regarding the subsequent development of clinically definite multiple sclerosis (CDMS) was also tracked.

Information regarding the natural history of optic neuritis is also provided by a number of other studies including those from Boston [Rizzo], Sweden [Soderstrom], Milan [Ghezzi], Queens Square [Brex] and Barcelona [Tintore]. Other studies have addressed the response to treatment, including the long term outcome from the ONTT [LONS], the CHAMPS and CHAMPIONS studies that addressed the benefit of interferon beta-Ia (Avonex) in high-risk patients following a clinically isolated syndrome, and the ETOMS study of a similar group of patients treated with interferon beta-1a (Rebif) [ETOMS] or interferon beta-1b [BENEFIT]. These studies indicate a benefit from earlier treatment, in keeping with evolving evidence of early axonal loss in MS vs the older view that progressive neurologic impairment was a long-term consequence of multiple exacerbations.

Clinical Features

Optic neuritis usually affects young adults with a strong female predilection (77%). Onset is acute onset with pain on eye movement in 90% (typically absent when the nerve is involved in its intra-cranial segment). Central vision is typically involved manifest as loss of acuity and color vision and presence of a relative afferent pupillary defect if unilateral or asymmetric. Visual field testing usually reveals a central scotoma when tested with Goldmann (kinetic) perimetry but the pattern is more variable when tested with automated perimetry, including generalized depression and altitudinal patterns. The disc is normal in 2/3 of cases (termed "retrobulbar ON") and swollen in the remainder, typically without hemorrhages or exudates. Visual loss worsens over several days, stabilizes for about 2 weeks and then shows progressive improvement over the next several months.

In children disc swelling is more common and the condition is more often bilateral (60 – 70%) [Brady]. Initial visual loss is often more profound but conversion to MS is less common [Lucchinetti]. Many cases of childhood optic neuritis are whereas para-infectious or post-infectious.

Prognosis

The **visual prognosis** is overall excellent with recovery to 20/40 or better in > 90%. However, despite good visual acuity, most patients experience persistent deficits of optic nerve function, particularly affecting color vision, brightness and contrast sensitivity. Most patients will still have a RAPD (if unilateral) and disc pallor after their attack.

The **neurologic prognosis** tells a different story. The overall risk of MS 15 years after an episode of optic neuritis is approximately 50%. MRI remains the best prognostic indicator of the future development of MS. Data from the ONTT indicates that after 15 years, the risk of clinically definite MS is 25% in those with a normal MRI and 72% in those with 1 or more white matter lesions. Certain clinical features of the acute attack confer a better prognosis for remaining free of MS however the significance of these features (male gender, absence of pain, severe disc edema, and disc hemorrhages/ exudates) is that they point to a diagnosis of something other than optic neuritis (e.g. neuroretinitis or papillophlebitis).

Management

MRI of the orbits with fat suppression and gadolinium is useful for confirming the diagnosis, revealing optic nerve enhancement in 90% of cases. MRI of the head provides useful information regarding the future risk of MS. Lumbar puncture is indicated if there are features suggesting meningitis or encephalitis (fever, stiff neck, other cranial nerve palsies) but the usefulness of cerebrospinal fluid (CSF) examination is limited. Oligoclonal bands are more often present in those who go on to develop MS but in the presence of an abnormal MRI, CSF testing doesn't offer additional prognostic information. Visual Evoked Potential testing, while sensitive to the demyelinative changes of optic neuritis, does not provide useful information in typical cases. OCT provides information regarding axonal loss and is

Treatment

Based on the results of the ONTT, we know that intravenous corticosteroid treatment speeds recovery but does not change the prognosis for visual recovery, which remains excellent regardless of treatment. In the group at high risk of MS (those with white matter lesions on MRI) treatment with intravenous steroids decreased the conversion rate by 50% compared to that of the placebo group. Those treated with oral prednisone alone did not show this positive response and in fact were more likely to experience a repeat attack. Based on these data, treatment with oral steroids alone is discouraged. Since publication of the ONTT results, it has been suggested that the different outcome in the two treated groups was not due to the mode of administration but the magnitude of treatment. Levels comparable to those of the intravenous group can be attained with administration of ultra high dose oral methylprednisolone.

Putting this together, steroid treatment is appropriate for speeding recovery, e.g. for those with severe pain, with bilateral involvement or with occupational needs and for patients with a steroid responsive disease such as sarcoidosis. For those whose MRI shows white matter lesions, steroids may be offered in hopes of decreasing the chance of a second demyelinating episode, however noting that in the ONTT this beneficial effect wore off after two years. Such patients should be referred to a neurologist for consideration of long-term immuno-modulatory treatment (e.g. Avonex, Rebif). For patients with a normal MRI, expectant management (no treatment) may be followed; treatment with IV steroids is considered optional and should be weighed against the loss of the diagnostic information gained from observing the natural history.

Although patients in the ONTT were hospitalized during the course of their IV treatment, the occurrence of serious adverse reactions was so low that this is no longer recommended. Patients can be treated on an out patient basis consisting of 1 gram of Solu-Medrol infused over 30 – 60 minutes each day for 3 days followed by 60 mg per day of prednisone for 10 days.

Differential Diagnosis

Other forms of optic nerve inflammation should be considered. **Optic perineuritis** is a form of orbital inflammatory disease that targets the optic nerve sheath [Purvin 2001]. Pain is more intense, visual loss less severe (central vision is preserved in 50%) and age range more broad than in ON. The diagnosis can be made with MRI that shows characteristic donut-like peri-neural enhancement. Unlike demyelinating ON, visual loss does not usually resolve spontaneously but is quite responsive to steroids. Most cases are idiopathic although several specific systemic diseases have been reported [Purvin 2009]. Treatment consists of high dose oral prednisone.

Neuroretinitis is an inflammatory disorder in which the target tissue is the optic disc vasculature. Prominent disc edema is accompanied by peri-papillary serous retinal detachment. Resorption of the aqueous component leaves lipid exudates that are subsequently ingested by macrophage, which then track to the macula with a stellate configuration. This distinctive "macular star" appears 9 – 12 days after onset. The most commonly identified cause is Bartonella (cat scratch disease) but a number of different infectious etiologies have been reported [Purvin 2011]. Compared to ON, pain is less common and visual loss is out of proportion to the relative afferent pupil defect. Antibiotic treatment is usually given but resolution is usually good regardless of treatment. In this condition and in optic perineuritis there is no increased risk of demyelinating disease.

Some patients, however, experience recurrent attacks with cumulative sometimes severe visual loss [Sundaram].

Neuromyelitis Optica is an antibody-mediated inflammatory disease of the central nervous system with a predilection for the optic nerves, spinal cord, and certain brain regions. Originally considered an MS variant, identification of pathogenic antibodies to aquaporin-4 has delineated NMO as a separate autoimmune condition and enabled testing for the disorder. Although initially defined as optic neuritis and myelitis with normal MRI, diagnostic criteria have continued to evolve [Wingerchuk] and we now recognize that there are cases consisting of just optic neuritis. Features that would lead one to suspect (and test for) NMO rather than "garden variety" optic neuritis include: severe vision loss, poor visual recovery, simultaneous or rapidly sequential bilateral involvement of both eyes, chiasmal lesions, and severe retinal nerve fiber layer loss demonstrated using optical coherence tomography (OCT). On MRI there is often enhancement of more than half of the optic nerve and or chiasm (comparable to the characteristic longitudinally extensive spinal cord lesions in this condition) [Khanna]. NMO antibodies are not uniformly positive in patients with clinical features of the disease. Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been identified in 15-40% of such seronegative patients [Ramanathan]. Treatment is different from that of MS, usually consisting of high dose steroids, azathioprine, mycophenolate mofetil, and rituximab [Papadopoulos].

Chronic Recurrent Optic Neuritis (CRION) is an inflammatory optic neuropathy that is responsive to corticosteroids and relapses when steroids are withdrawn [Petzold]. CRION is currently a diagnosis of exclusion, meaning that diseases such as MS, NMO, sarcoidosis have been ruled out. While the diagnosis cannot be made without evidence of recurrence, it may be suspected after a single attack based on steroid responsiveness and/or poor recovery. **Autoimmune Optic Neuropathy** shares these clinical features but associated with laboratory markers of autoimmunity, such as a positive ANA and/or skin biopsy.

The differential also includes non-inflammatory disorders. **Lebers Hereditary Optic Neuropathy (LHON)** should be suspected in any patient who seems to have acute optic neuritis but without pain. A **central retinal artery occlusion** seen in the hyper-acute stage, before development of characteristic retinal whitening, may mimic retrobulbar optic neuritis. Again, the absence of pain should be a tip-off. **Pituitary apoplexy** and an expanding or ruptured **ophthalmic artery aneurysm** can present with the clinical features of retrobulbar optic neuritis. Headache is usually more severe, with features of meningeal irritation (photosensitivity, neck stiffness) and visual field testing often reveals a temporal hemianopic pattern.

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MCQ answers page 10

1. **Answer: b**

2. **Answer: c**

3. **Answer: d**

MCQ's

1. **Which of the following therapies has level A evidence (several randomised clinical trials with corresponding results) as an effective treatment for NAION?**

   a. High-dose intravenous corticosteroids
   b. Aspirin
   c. Optic nerve sheat decompression
   d. None of the above

2. **Which of the following medications have been implicated as risk factors for NAION?**

   a. Sildenafil
   b. Amiodarone
   c. Vasoconstricting drugs (e.g., nasal decongestants)
   d. Insulin

3. **Which of the following are typical symptoms or signs of NAION?**

   a. Elevated intraocular pressure
   b. Swollen optic nerve head
   c. Visual field defect
   d. Temporal head ache

Risk factors

- arterial hypertension, diabetes, hypercholesterolemia
- small, crowded disc (disc at risk), optic disc drusen
- acutely raised IOP (e.g. related to cataract surgery)
- amiodarone, medication for erectile dysfunction (e.g. sildenafil), vasoconstricting drugs (e.g., nasal decongestants)
- acute hypotension (e.g. during surgery), anemia, migraine
- possible risk factors: sleep apnea, nocturnal hypotension, hypercoagulability, vitreous separation

Epidemiology

- yearly incidence 2 – 10/ 100 000 in patients over 50 years of age
- men and women equally affected
- patients mostly caucasians

Symptoms and signs

- typically acute, painless monocular loss of central or periferal vision
- visual acuity below 0.3 in half of the patients
- swollen optic disc (sectoral or diffuse)
- optic disc hemorrhages may be present
- visual field defects (arcuate, altitudinal, central)
- relative afferent pupillary defect may be present

Differential diagnosis

- AAION, optic neuritis, diabetic papillopathy
- other causes of optic neuropathy: toxic, nutritional, compressive, paraneoplastic …

Treatment

- no treatment has been proven effective in randomised clinical trials
- reports on possibly beneficial effect: systemic corticosteroid, intravitreal triamcinolone

Prevention of NAION of the second eye

- aspirin might be beneficial
- discontinuing medications associated with increased risk: amiodarone and silfenadil
- avoiding nocturnal hypotension; antihypertensive medication administered in the morning
- corticosteroids might even increase the risk of NAION of the second eye

Prognosis

- spontaneous improvement of vision in up to 43% of patients
- Ischemic Optic Neuropathy Decompression Trial: in six months the visual acuity is less than 0.1 in 36% and better than 0.3 in 35%
- The risk of NAION in the second eye is 15 % in 5 years

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MCQ answers page 19

1. Answer: d

High-dose intravenous corticosteroids have been evaluated retrospectively in a non-randomised study that showed no statistically significant treatment benefit. Aspirin did not show a statistically significant improvement in visual function in NAION in the Ischemic Optic Neuropathy Decompression Trial (IONDT). Optic nerve sheath decompression was evaluated as the treatment of NAION in the IONDT. This randomized clinical trial showed no benefit from surgical intervention.

2. Answer: a, b, c

Phosphodiesterase type 5 inhibitors (including sildenafil), amiodarone and vasoconstricting drugs have been implicated as risk factors for NAION. However, most patients have concurrent vascular and other risk factors and showing a direct relationship between the use of a specific medication and NAION may be difficult. Diabetes (not insulin) is a risk factor for NAION.

3. Answer: b, c

Swollen optic nerve head and visual field defects are typical signs of NAION. Acutely raised IOP is a risk factor for NAION. Temporal head ache is not a symptom of NAION and it should raise the suspicion of giant cell arteritis when related to ischaemic optic neuropathy.

Compressive optic neuropathy: pituitary adenoma

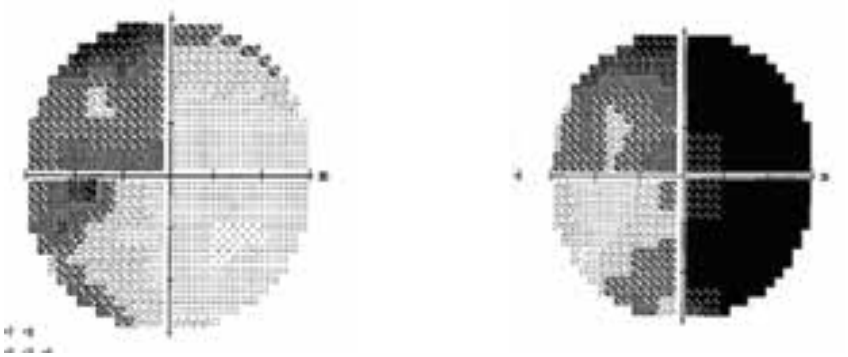
Antonella BOSCHI, Belgium

03

MCQ's

1. A young man of 40 yo complained of progressive visual loss since several months. VA in the RE 3/10, in the LE 10/10, Color perception was 0/10 in RE, 9/10 in LE, RAPD RE, Fundus: Pale R optic nerve, L ON looks normal. The visual field

LE **RE**



Based on the clinical data where do you localize the lesion?

a. On the middle of the chiasm
b. On the right optic tract
c. Near the junction of the right optic nerve and the chiasm
d. Anterior part of the chiasm

2. Which of the following Neuro-Imaging technic is the most suitable technic for chiasmal syndrome diagnosis?

a. Sellar MRI
b. Coronal+Axial Ct scan
c. CT-angiography
d. Echography

3. Which of the following features is not an early sign of chronic chiasmal compression:

a. Color desaturation
b. Unilateral visual loss
c. Unilateral RAPD
d. Superior temporal quadrant visual field loss
e. Papilledema

Objectives

- Revision of neuroanatomy of sellar/chiasmal region.
- Revision of Clinical features of compressive/ chiasmal optic neuropathy
- Management of pituitary adenoma

Introduction

Compressive optic neuropathy is typically characterized by a progressive visual loss in one or both eyes. Color perception defect may be the first sign of the visual dysfunction. Visual field defect, like central scotoma, altitudinal, and fascicular defect may be reported. Optic disc is frequently pale in chronic, slowly progressive compressive disease. Presence of optic disc oedema suggests a more acute and usually intraorbital process.

Chiasmal disorders must be considered in the differential diagnosis of anterior visual pathway lesion. Visual loss is usually progressive, but may have an acute onset (pituitary apoplexia).

A monocular or bilateral temporal hemianopia associated or not with endocrine dysfunction must suggest a chiasmal involvement. A monocular central visual loss with a controlateral temporal quadrant defect can also be observed in disorders involving the optic nerve–chiasma jonction.

Oculomotor palsies, nystagmoid eye movements or non-paretic transient diplopia can also be associated with chiasmal disorders.

The most frequent causes of chiasmal dysfunction are compressive sellar masses: pituitary adenoma are the most common, representing 10-15% of all intracranial tumors. About 70% of pituitary adenoma occurs in individual with age 30-50 yo.

Other causes of the chiasmal syndrome are Craniopharyngioma (20-25%),Meningioma (10%),Glioma (7%)

Anatomic aspects and physiopathology of chiasmal involvement will be reviewed. The neuro-ophthalmic signs and symptoms and management of pituitary adenomas will be discussed

Neuroanatomy

The chiasma, made by convergence and crossing of nasal fibres of the optic nerve, is 12mm wide, 8mm anteroposterior and 4mm tick.

Is tilted forward of 45° and lies in the subarachnoid space of the suprasellar cistern. In 80% of the individuals, the chiasma is located just above the pituitary gland, located in a recess of the sphenoid bone called the sella turcica (in 15% is prefixed, above

the tuberculum sellae, or post-fixed over the dorsum sellae in other 15%). The cavernous sinus, containing the cranial nerves III, IV, V1,V2 and the VI the internal carotid arteries, and the sympathetic fibers, form the lateral walls of the sella. The diaphragma sellae is a horizontal fold of dura mater that separates the pituitary gland from the suprasellar cistern.

At the chiasma, axons from the nasal retinal ganglion cells from both eyes cross, and the temporal axons remain ipsilateral (ratio of crossed/uncrossed fibers 53:47). About 90% of chiasmal fibers originate from the macula, the crossed ones stay superiorly and posteriorly within the chiasm. The retinal superior axons stay superior in the chiasm and the inferior remain inferior. Most of the axons exit in the optic tracts; a few exit in the hypothalamus are responsible of the diurnal variations of various neuroendocrine systems. The vascular supply of the chiasm takes origin mainly inferiorly from superior hypophyseal, posterior communicating, and posterior cerebral arteries.

Neuro-ophthalmic symptoms and signs

Headaches are one of the most common symptoms reported in pituitary adenomas, with an incidence of 45%. These headaces are often localized to the brow or periorbital region

Progressive, insidious visual loss is the most frequent manifestation of chiasmal disturbance. This is in relation to a slowly compressive lesions being the most frequent cause of chiasmal disorder.

Visual symptoms are usually vague, difficult in focusing and reading. However, many patients are asymptomatic, until severe abnormal visual acuity or visual field defects occurred.

Color vision is diffusely or selective altered in the defect fields.

The temporal visual field defect, with respect of the vertical meridian, is the hallmark of chiasmal dysfunction. However, in the large majority of patients with pituitary adenoma the asymmetric temporal hemianopia with mixed defects are the most common(42%), likely because the chiasm and the optic nerve are compressed.

The large majority of these patients have been reported with a moderate (>/= 3mm) displacement of the visual pathway. It is unclear why the crossing fibers are so vulnerable(LeeIH et al AJR AmJ Roentgenol 2015 Nov;205(5))Likely mechanical distortion of nerve bundles and vascular supply impairment are both involved.

If the chiasm is postfixed or the lesion affects the anterior part of chiasm, the visual field defect may be a monocular with a central or arcuate scotoma, with or without a supratemporal defect in the other eye. Central bitemporal scotomas or optic tract syndromes may be the product of prefixed chiasm or a posterior lesion.

Disorders that may cause bitemporal visual field defects without respect of the vertical meridian include : tilted optic disc, sectoral retinitis pigmentosa, and enlarged blind spots.

Binasal defects respecting vertical meridian due to chiasm lesions is very unusual: bilateral ectatic carotid artery, compression from a variety of chiasmal tumors or third ventricular enlargement. Usually binasal defects have ocular cause like glaucoma, retinitis pigmentosa, and ischemic optic neuropathy.

Some patients **with complete bitemporal hemianopsia** will complain of **a complete loss of depth perception**. This has been termed "post-fixational blindness and is caused by the two blind temporal hemifields overlapping during convergence.

Optic disc may be diffusely pale or a « transverse » horizontal band optic atrophy (compression of crossing fibers) have being reported. Nevertheless, disc pallor is not associated with a poorer prognosis for vision improvement after treatment.

Macular ganglion cell analysis with OCT is useful tool for an early detection of chiasmal compression by detecting nasal macular Ganglion cell thining.

Eye movement abnormalities are unusual. Oculomotor palsy accompanied chiasmal involvement when the tumor extends in the cavernous sinus, sometimes also suggested by facial pain.

In patient with a complete bitemporal hemianopia, transient veritical or horizontal diplopia may be due to « hemifield slide phenomena ».

Chiasmal lesions of any kind can be associated with **seesaw nystagmus**, a very rare form of nystagmus in which one eye elevates and intorts while the other eye synchronously depresses and extorts, then alternates. The exact pathophysiology of this phenomenon is unknown

Diagnostic Studies:

Neuroimaging

MRI focused on sellar area with axial, coronal and sagittal thin sections with and without enhancement is the preferential exam.

In case of acute visual loss, optic disc swelling, sever head-ache which may suggest a pituitary apoplexy, an MRI should be performed as an emergency.

If MRI is contraindicated or not tolerated, CT scan is still useful.

MRI or CT angiography is necessary when aneurysm is suspected.

Endocrine Testing

About 1/4 or 1/3 of patient with pituitary adenoma are non-functional. Most of the macroadenoma causing visual loss are non-functioning.

The most common hypersecreting adenomas are: Prolactinomas and GrothH secreting tumors. Those secreting tumors are more commonly diagnosis because the endocrine symptoms.

The endocrinologic testing that should be performed in patient with suspicion of chiasmal compression: Prolactin, cortisol AM, TSH, T4, LH, FSH, estradiol (in women), testosterone (in men) levels.

Treatment

In Prolactinomas: medical therapy with **In Prolactinomas: medical therapy** with dopamine agonist (cabergoline, bromocriptine) which inhibit the synthesis of prolactin is the first-line treatment.

For all other symptomatic adenomas the first –line treatment is trans-**sphenoidal neurosurgery.**

The prognosis for visual improvement is usually excellent in the large majority of patients.

Prognostic signs associated with **lack of visual improvement** are: long delay prior diagnosis, optic nerve atrophy, and poor visual acuity .

Complications

Pituitary apoplexy a life-threatening complication of pituitary adenoma caused by a sudden hemorrhage or infarction of the tumor. Predisposing factors : arterial hypertension, anticoagulant therapy, and major surgery.

Clinical picture comprises headache, visual impairment, cranial nerve palsies and hypopituitarism. Subarachnoid hemorrhage and impaired consciousness can be associated. In acute phase glucocorticoid replacement, electrolyte support are mandatory. Surgery if vision or/and consciousness are impaired.

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MCQ answers page 23

1. Answer: c

based on the anatomy of the chasm a lesion that cause right visual loss with a right temporal field defect and a central scotoma and a left temporal quadrant defect has to be located in the anterior right side of the chiasm. In this location the right optic nerve in entering in the chiasm and the nasal fibres of the L optic nerve curve forward (Wilbrand's knee) before entering in the opposite optic tract.

2. Answer: a

MRI with and without Gadolinium. It allows thin (3-mm) axial, coronal and saggital sections. Anatomical details of sellar area are very well defined. The only disadvantage is absence of visualisation of small calcifications and bone erosion. Brain CT scan can be useful to better define suspected sellar lesions (like craniopharyngioma, bone erosion by metastasis or aggressive pituitary adenoma..). When aneurysm is suspected an Ct or MRI angiography should be performed.

3. Answer: e

Early sign of compressive chiasm is loss of color perception, uni or bilateral visual loss, temporal field defect. Papilledema is a late and rare manifestation due to obstructive hydrocephalus and intracranial hypertension induce by sellar lesion expansion.

MCQ's

1. Which mitochondrial DNA mutation is the most common cause of LHON?

a. m.3243G>A
b. m.3460G>A
c. m.11778G>A
d. m.14484T>C
e. m.14459G>A

2. Which of these statements is incorrect with regards to the clinical manifestations of LHON?

a. LHON shows a marked male bias
b. LHON is characterised by incomplete penetrance
c. The peak age on onset is in the fifth decade of life
d. Visual loss is painless and subacute
e. Both optic nerves are invariably involved

3. Which of these neurological complications have been associated with LHON?

a. Dystonia
b. Myoclonus
c. Multiple-sclerosis like illness
d. None of the above
e. All of the above

Objectives

- To become familiar with the clinical features and management of LHON
- To understand the molecular genetic basis of LHON

Epidemiology and Clinical Features

Leber hereditary optic neuropathy (LHON) affects at least 1 in 35,000 of the population with a much higher prevalence in men at about 1 in 14,000. Disease conversion in LHON is characterised by acute or subacute onset of visual loss in one eye, followed 2-4 months later by the fellow eye. There is an associated dense central or centrocaecal scotoma and colour vision is significantly impaired. Unilateral optic nerve involvement in LHON is exceptionally rare and another underlying pathological process should be actively excluded in those atypical cases. Bilateral simultaneous onset probably occurs in about 25% of patients although it can be difficult for some individuals to accurately report whether visual loss had been ongoing in one eye prior to the fellow eye being affected. The initial visual loss in LHON is severe and it usually plateaus over the next six months with most patients achieving visual acuities of 20/200 or worse. The peak age of onset is in the second and third decades of life and it is unusual for disease conversion to occur beyond the age of 50 years. LHON is typically a monosymptomatic disease, but additional features such as cardiac arrhythmias, peripheral neuropathy and dystonia have been reported as occurring more frequently in this disorder compared with the general population. There is also a well-reported association with a multiple sclerosis-like illness, especially among female LHON carriers (Harding's disease).

An intriguing feature of LHON is the fact that male carriers have about a 50% lifetime risk of developing visual loss compared with only about 10% for female carriers. Several hypotheses have been put forward to explain this marked incomplete penetrance and sex bias, in particular secondary mitochondrial and nuclear genetic factors. The identification of these secondary factors will be crucial both for more accurate genetic counselling and for the identification of pathological pathways that can be modulated to salvage retinal ganglion cells (RGCs). It has proven difficult to pin down specific environmental triggers, except for smoking, which shows a convincing association with an increased risk of visual failure. LHON carriers should therefore be strongly advised not to smoke to reduce this potentially modifiable risk factor.

Clinical Pearls

- LHON should be considered in all cases of bilateral simultaneous or sequential optic neuropathy, irrespective of age and sex, in particular when visual function is severely affected with little or no recovery.

- Relative preservation of the pupillary light reflex in the context of severe visual loss is a characteristic feature of LHON. This has been linked to the relative resistance of a special class of melanopsin RGCs to mitochondrial neurodegeneration.
- In about 20% of cases of LHON, the fundus looks entirely normal in the acute stage and those patients are not infrequently labelled as having functional visual loss.

Molecular Genetics

Three mitochondrial DNA (mtDNA) point mutations account for the majority (90%) of LHON cases: m.3460G>A (*MTND1*), m.11778G>A (*MTND4*), and m.14484T>C (*MTND6*), with m.11778G>A being the most common (70-90%) mutation worldwide. If those three primary LHON mutations are not detected and there is a high index of clinical suspicion, whole mitochondrial genome sequencing should be requested to identify other relatively rare pathogenic mtDNA variants. The visual prognosis is invariably poor in LHON and most patients will remain registered legally blind. The likelihood of visual recovery is greatest with the m.14484T>C mutation and most of the visual improvement, if it does occur, usually takes place within the first year of disease onset. Even without a marked increased in visual acuity, the appearance of small islands of vision within the patient's visual field (fenestrations) can greatly help with scanning vision, especially if the central scotoma becomes concurrently less dense.

Patient Management

Genetic counselling in LHON is complicated by the sex- and age-dependent penetrance of the underlying pathogenic mtDNA mutation. As a rule of thumb, the lifetime risk of disease conversion is about 50% and 10% in male and female LHON carriers, respectively. Furthermore, about 95% of carriers who experience visual loss will do so before the age of 50 years old. LHON carriers should be provided with practical advice as part of a healthy lifestyle and they should be strongly dissuaded not to smoke. It also seems sensible to avoid excessive alcohol intake and exposure to environmental triggers that have been linked to visual loss in LHON, in particular industrial toxins and drugs with mitochondrial-toxic effects, such as ethambutol.

Disease-modifying treatments remain limited in LHON. There is currently no prophylactic intervention that can prevent the onset of visual loss in at-risk LHON carriers or the involvement of the second unaffected eye after disease conversion. The only therapeutic option that is currently available for affected patients with LHON is idebenone, which is a short-chain analogue of ubiquinone that has been reported to improve mitochondrial ATP synthesis in addition to postulated antixoxidant properties. Most published studies, including a multicentre double-blind randomised controlled trial, support a consistent visual benefit in a proportion of patients treated with idebenone, especially when started early during the acute phase of the disease process. It must be stressed that idebenone will not completely reverse the significant damage already sustained to the optic nerve, but in those patients who do respond to the drug, there is an increased rate and likelihood of visual recovery compared with

the known natural history. A gene therapy approach for the m.11778G>A mtDNA mutation is currently being investigated based on allotopic gene expression and an intravitreal injection of a modified adeno-associated virus (AAV) vector to deliver the replacement *MTND4* subunit gene.

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MCQ answers page 29

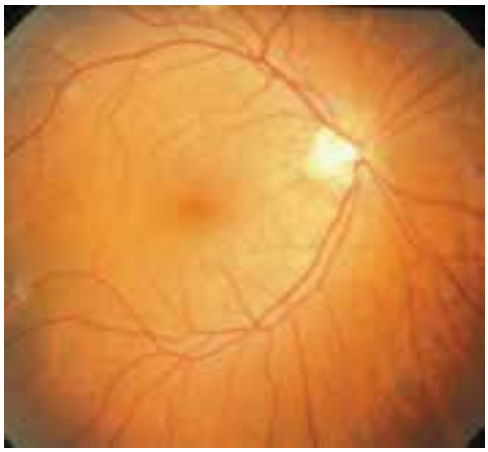
1. **Answer: c**

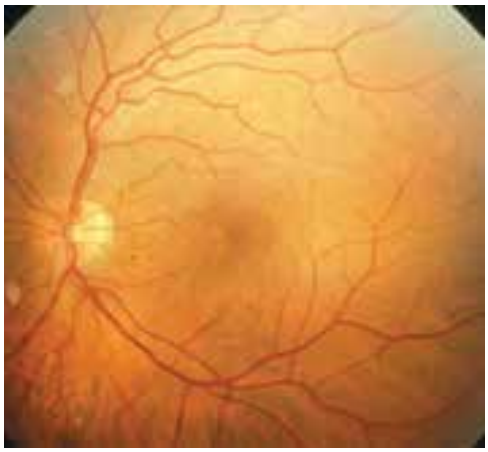
2. **Answer: c**

3. **Answer: e**

MCQ's

1. A 52 year-old patient presents with the acute onset of binocular vertical diplopia. Examination reveals a left hypertropia of 3 prism diopters and his head is tilted to the right. Fundus examination is the following





With these results, what is the most likely diagnosis in order to explain the diplopia?

a. Right IV nerve palsy
b. Left IV nerve palsy
c. Right skew deviation
d. Left skew deviation

2. A 32 year-old woman with a known and treated hypothyroidism complains of difficulty parking her car, when she needs to turn her head to her right side. Examination shows normal horizontal and vertical pursuit eye movements without limitation. Examination of saccades reveal a decreased speed of adducting saccades of her left eye. What is the most likely diagnosis ?

a. Partial left III nerve palsy
b. Myasthenia
c. Left internuclear ophthalmoplegia
d. Grave's (Basedow) ophthalmopathy

3. A 48 year-old man complains of binocular vertical diplopia. Examination reveals a slight hypertropia of the left eye but, during pursuit examination, the upgaze is globally limited.

Which test would be most useful to clinically establish a diagnosis?

a. Orthoptic examination with a Hess chart
b. Examination of pupils
c. Tensilon test
d. Ice cube test

Objectives

- Review of the various types of eye movements
- Internuclear ophthalmoplegia
- Skew deviation and ocular tilt reaction
- Parinaud's syndrome
- Oculomotor cerebellar syndrome

Eye movements and their examination

There are many informations that a physician canrapidly gather through a systematic examination of eye movements.

Fixation: initially, some time should be spent examining fixation, in order to determine whether it is stable or interrupted by either nystagmus or square-wave jerks.

Smooth pursuit: testing should be performed both horizontally and vertically, trying to adopt a regular and predictable movement of the object of fixation. The physician can determine whether there is some limitation of eye movement and whether the movement is smooth or saccadic (pathologic).

Convergence: testing for convergence requires a good cooperation of the patient. Performing small horizontal movements during convergence allows the examiner to be sure that the patient is following the command (by observing the corresponding small horizontal pursuit movements of the patient). Convergence can be normal or absent. Spasm of convergence can also be observed.

Saccades: it is important that both the object of fixation and the target are stable, in order to allow the patient to predict and calculate the trajectory of the saccade. Typically, the examiner's nose and one finger held at 20-30° of eccentricity will be used. Saccades are tested both horizontally and vertically. The examiner will determine whether the saccade initiation is immediate or delayed (pathologic), whether the saccades are rapid or slow (pathologic), and whether the saccades are precise, right on target, or dysmetric (pathologic), either hypo- or hypermetric.

Vestibulo-ocular reflex (VOR): this is a phylogenetically very ancient reflex, linking the vestibulum to the eyes, providing stability of eyes in space during head movement. Testing requires either a camera recording eye movements or a second examiner. The head impulse test is used: the patient's head is held with two hands and is rapidly rotated (20-30°) to one side (once the examiner is sure that the patient does not suffer from major neck problems!). When the gain of the vestibulum is normal (around 1.0), no eye

movement is visible upon reaching the eccentric position. In presence of a vestibulopathy, the gain is decreased and a repositioning eye movement can be observed.

Suppression of VOR by fixation: the act of fixation will induce a suppression of the normal VOR. This is very useful in daily life allowing us to read messages on our smartphone or to look at our watch while walking. Testing simply requires a swivel chair of any type (non medical). The patient is instructed to look at his thumb, with both arms extended. The chair is rotated to and fro to both sides and the examiner observes whether the eyes remain steady on the thumb or whether they lag behind necessitating catch-up saccades (pathologic). When the test is abnormal, the visual handicap can be quantified by asking the patient to read the near card during rotation. Normally, there is no decrease in visual performances while the chair is rotating.

Internuclear ophthalmoplegia (INO)

A normal horizontal gaze necessitates a perfect coordination of the internal rectus muscle (innervated by the III nerve) on one side and the contralateral external rectus muscle (innervated by the VI nerve). The center for horizontal gaze to one side is the ipsilateral VI nucleus, located in the pons. From the VI nucleus, efferent fibers go to both the ipsilateral VI nerve and the contralateral III nucleus via the internuclear neurons, travelling from the pons to the midbrain via the median longitudinal fasciculus (MLF). When a lesion is present within the MLF, adduction will be affected during voluntary gaze but will be preserved during convergence (as convergence input to the III nucleus is mediated through the rostral interstitial MLF (riMLF), located higher in the midbrain, unaffected by MLF lesions).

Initially, a complete INO will present with ipsilateral complete adduction deficit, dissociated nystagmus beating in the contralateral eye in abduction, and preserved adduction during convergence. Frequently, a recovered INO will still exhibit some abnormalities: the saccadic speed of the previously paretic adducting eye will be slower than the saccadic speed of the contralateral abducting eye. Partial INO will exhibit partial features of a complete INO.

Bilateral INO is not rare. In addition to the features of INO on both sides, patients will frequently exhibit a vertical jerk nystagmus, likely to be an upbeat nystagmus.

Etiologies include demyelinating, inflammatory, ischemic, traumatic, compressive etiologies. INO is particularly frequent in patients with multiple sclerosis.

Evolution is frequently spontaneously favorable and no long term treatment is needed.

Skew deviation, ocular tilt reaction (OTR)

Skew deviation describes a vertical imbalance of the eyes from supranuclear origin. Most frequently it is a comitant deviation, more rarely skew deviation can be incomitant or alternating. The side of a skew deviation is determined by the lower eye (hypotropic eye).

Ocular tilt reaction (OTR) is a triad consisting of a skew deviation, an ipsilateral head tilt and a conjugate ocular torsion, all ipsilateral (towards the lower eye). Also, a deviation of the subjective visual vertical can be present.

Vertical balance of the eyes is mediated through the graviceptive pathways, extending from the vestibulum on one side to the contralateral midbrain and thalamus, decussating at mid-pons. A lesion interrupting the graviceptive pathways will induce a vertical imbalance of the eyes (skew deviation), either ipsilateral to the lesion (in case of lesion before mid-pons decussation) or contralateral to the lesion (if the lesion is above the decussation). When a more complete lesion occurs, a full or partial OTR can be present. Ocular torsion is best appreciated during ophthalmoscopy, but fundus photography or macular OCT will provide images allowing to measure the torsion.

Etiologies include ischemic, compressive, post-operative, traumatic, demyelinating disorders.

Evolution is often favorable, 60-70% of patients requiring no further treatment. If diplopia persists, prisms or surgery can be performed.

Parinaud's syndrome, dorsal mesencephalic syndrome

Parinaud's syndrome consists of a triad of upgaze palsy, pupillary light-near dissociation and convergence spasms. It results from the dysfunction of the dorsal midbrain from either an intrinsic or extrinsic lesion. A complete Parinaud's syndrome is nowadays almost never present as modern neuroimaging will allow early detection of lesions in the region of the tectal midbrain.

Initially, the oculomotility dysfunction will be subtle. The **upgaze** can be completely normal by pursuit (slow eye movement) and the only eye movement abnormality might be slowed upgaze saccades (fast eye movement).

Pupillary light-near dissociation is an absence of pupillary reflex to light but a good response (miosis) to convergence. It reflects an interruption of the afferent pretectal pupillary fibers en route towards the Edinger-Westphal nuclei. As the afferent fibers

mediating convergence are located more ventrally in the midbrain, they are preserved. Patients are completely asymptomatic from a pupillary light-near dissociation. Hence, it is very important to test the pupils in any patient with a limitation of upgaze.

Convergence spasms are a rather late manifestation of Parinaud's syndrome. They can occur spontaneously in advanced cases, but are almost always provoked by an attempt to elevate the eyes, mostly through saccades. Convergence spasms are thought to result from a massive extraocular muscle recruitment in an attempt to elevate the eyes. The strongest internal rectus muscles will predominate. The late stage of convergence spasms is the exceptional presentation of **nystagmus retractorius**, when the eyes not only converge spontaneously but also become enophthalmic during convergence due to massive extraocular co-contraction.

Etiologies include compressive, infiltrating, ischemic, demyelinating disorders. Most frequently, it is an extrinsic compressive from a pineal tumor.

Oculomotor cerebellar syndrome

The cerebellum is the regulating balance of the body but plays also an important role in regulating eye movements. It interferes with the smooth pursuit, saccades, stabilization of the eyes in eccentric position of gaze, and the modulation of VOR.Abnormal eye movements encountered in cerebellar disorders include: saccadic pursuit, dysmetric saccades, gaze-evoked nystagmus, decreased suppression of VOR by fixation.

Saccadic pursuit and dysmetric saccades are asymptomatic. Gaze-evoked nystagmus can induce oscillopsia in various directions of gaze. Abnormal modulation of VOR can be responsible of decreased visual performances during motion which the patient usually report as visual disturbances when he is « outside »: visual blur, poor vision, impossibility to recognize friends, poor vision as a passenger in a car. Very rarely does the patient spontaneously mention that all the disturbances occur only during motion, which is characteristic of the abnormal VOR modulation.

Etiologies are various, including ischemic, degenerative, inflammatory, compressive/ infiltrative, toxic, traumatic.

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MCQ answers page 34 - 35

1. Answer: d

The left hypertropia could result from either a left IV palsy or a right skew deviation. Typically, a patient presenting with an acute left IV palsy will exhibit a right head tilt, in order to decrease the degree of diplopia. Fundus examination reveals a counterclockwise torsion (torsion to the right side of the patient), typical of a right ocular tilt reaction, in which a right skew deviation is present. A left IV palsy would have resulted in excyclotorsion of the left eye.

2. Answer: c

Partial III nerve palsy very exceptionally might affect only the internal rectus muscle, without any other features of III palsy, and adduction of that eye should be limited. Diplopia resulting from Grave's ophthalmopathy should be accompanied by limitation of eye movements. Myasthenia could present with temporarily normal excursion of eye movements, but the speed of adduction is typically not decreased. A VI nerve palsy is characterized by limitation of abduction. In presence of a subtle internuclear ophthalmoplegia (ION), adduction may not be limited during pursuit, nystagmus in the abducting eye may be absent, but saccade examination will reveal slow adducting saccades on the side of ION.

3. Answer: b

The presence of pupillary light-near dissociation in association with a limited upgaze is pathognomonic of the dysfunction of the dorsal mesencephalon (Parinaud's syndrome). Midbrain dysfunction can be accompanied by vertical diplopia, be it from a IV palsy, III palsy or skew deviation.

MCQ's

1. Downbeat nystagmus

a. Is a pendular form of nystagmus
b. Is often decreased in lateral gaze
c. Is explained by vestibulo-cerebellar dysfunction
d. Mostly results from brainstem stroke
e. Responds to gabapentin

2. Among the following sentence, which is the wrong one? A nystagmus changing beating direction according to the eye position in orbit

a. Can be peripheral vestibular
b. Can be central vestibular
c. Can be gaze evoked nystagmus
d. Can be due to Chiari malformation
e. Can be observed in alcoholic intoxication

3. Flutter-opsoclonus

a. Corresponds to high frequency nystagmus
b. Can reveal brainstem stroke
c. Follows basal ganglia dysfunction
d. Is often of auto-immune mechanism
e. Responds to baclofen

Objectives

- Understand the stabilizing oculomotor systems
- Examine and classify abnormal eye movements
- Understand how abnormal eye movement can help to orient the etiological or the topographic diagnosis
- Use pharmacological treatments in abnormal eye movements

Abnormal eye movements are more frequently corresponding to nystagmus and saccadic intrusions or oscillations, and less frequently to ocular drifts or paroxystic ocular tremor. Nystagmus and other abnormal eye movements have for a long time afraid both ophthalmologist and neurologist, probably because of the complexity of underlying ocular motor neurophysiological substrates and for most of them because of ununderstood pathophysiology. Furthermore, nystagmus was not recognised as an important and helpful clinical sign. Finally it was considered as resistant to pharmacological therapy. Thanks to the development of new and simplified models of eye movement control, to the improvement of brain imagery facilitating anatomo-clinical correlations and to the work of growing numbers of neuro-ophthalmological teams invested in eye movement disorders, a new look was given to nystagmus these last 10 years. Based on current knowledge of the neurobiology of eye movement, a modern classification of disorders of ocular stability emerged. Even in infantile forms of nystagmus, which is the unfortunate parent of nystagmus because of poorly understood mechanisms, some authors actually propose common mechanisms with those of acquired nystagmus. In either acquired or infantile forms, disorders of ocular stability are the consequence of disorders of the three mechanisms that normally help to maintain the gaze still: the visual fixation, the oculo-cephalic reflexes and the eccentric gaze holding mechanism. Abnormal eye movement must now be regarded as a valuable clinical finding and has to be interpreted in the context of general ophthalmological and neurological evaluation. It can sometimes specifically orient the etiological or the topographic diagnosis. Finally, based on the current concepts and models, new pharmacological treatments emerged that must deserve interest of clinicians.

Nystagmus may be defined as a repetitive, to and fro movement of the eyes, this involuntary eye movement being initiated by a slow phase. Two main waveforms exist: pendular nystagmus consists in oscillating to and fro slow phases; jerk nystagmus consists in alternation of slow phases with fast phase interrupting them. Even if the direction of jerk nystagmus is commonly described by the direction of the quick

phase, it is the slow phase that reflects the underlying disorder. This definition helps to differentiate nystagmus from other abnormal eye movements, like saccadic intrusions in which abnormal rapid eye movements reflect the underlying disorder.

Among the complete clinical (ophthalmological and neurological) evaluation that must be done in a patient with ocular instability, the following elements are fundamental to determine:

How is visual acuity of the patient? If the vision is poor, is it secondary to the abnormal eye movement or due to proper visual defect? Indeed, visual deficit, by altering possibilities of visual fixation control, is one of the mechanisms of nystagmus.

1. Does the patient complain of oscillopsia, an illusory to and fro motion of the visual world due to the eye movement? Oscillopsia is considered as a feature of acquired nystagmus and is not frequent in congenital forms of nystagmus.
2. Does the patient complain of vertigo? Vertigo orients the mechanisms toward vestibular disorders. In case of peripheral vestibular disorders, the patient mainly complains of vertigo but usually not of his nystagmus. In case of central vestibular disorders, vertigo may be absent and the predominant complain is nystagmus and resulting oscillopsia.
3. If the patient demonstrates jerk nystagmus during fixation, define the direction (horizontal, vertical, torsional or mixed) of eye movement, the beating direction (direction of quick phase), the effect of gaze direction and the effect of fixation. In case of acquired pendular nystagmus analyse the frequency, amplitude, conjugacy, direction and effect of convergence. Distinguish two main types of saccadic intrusions by the presence or absence of an intersaccadic interval.

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MCQ answers page 41

1. Answer: c

Downbeat nystagmus is a jerk nystagmus, often increased in lateral gaze, mostly resulting from degenerative involvement of the vestibulo-cerebellum. This nystagmus responds to clonazepam or 4 aminopyridine.

2. Answer: a

Peripheral vestibular nystagmus can be observed in only one lateral gaze position, but never change beating direction with eye position. Central vestibular can change beating direction, e.g. changing from horizontal to vertical with different eye position. Gaze evoked nystagmus is defined by its changing beating direction with gaze position: to the right in rightward gaze and to the left in leftward gaze, sometimes upbeating in upgaze. Chiari malformation can induce central vestibular nystagmus and gaze-evoked nystagmus. Gaze-evoked nystagmus is the most frequent nystagmus associated to alcoholic intoxication.

3. Answer: d

Flutter opsoclonus is not a nystagmus but corresponds to saccadic oscillations. It is observed in auto-immune disease, most often associated to cerebellar "myoclonus". It is not observed in brainstem stroke, neither basal ganglia dysfunction. It may respond to clonazepam.

MCQ's

1. Which of the following is MOST suggestive of a diagnosis of myasthenia gravis in a patient with ptosis?

a. After prolonged downgaze and saccade to primary gaze, the eyelid overshoots then becomes ptotic again
b. Significant weakness of the orbicularis oculi and jaw opening
c. Normalization of eyelid position after placing a bag of ice on the eye for 4 minutes
d. The eyelid opens quickly and returns to ptosis with lateral saccades

2. Which of the following test results is MOST consistent with a diagnosis of myasthenia gravis?

a. After resting, the esotropia improves from 8 PD to 4 PD
b. The jitter is significantly less than normal with single fiber EMG.
c. The action potentials decrease with repetitive stimulation EMG.
d. The acetylcholine receptor binding antibody is 0.4 (normal < 0.4 nmol/L)

3. Which of the following patients is MOST likely to have myasthenia gravis?

a. 25-year-old man
b. 35-year-old man
c. 55-year-old man
d. 75-year-old man

Objectives

- Describe the demographic profile of patients with myasthenia gravis
- Elaborate on the sensitivity of various diagnostic tests for myasthenia gravis
- Report the general principles of pharmocotherapy in myasthenia gravis

I. Pathophysiology

In the normal skeletal muscle neuromuscular junction, acetylcholine is released from the presynaptic nerve terminal and binds to postsynaptic receptors on the muscle cell to trigger contraction. In myasthenia gravis (MG), antibodies to acetylcholine receptors (AChRAb) inhibit this normal process. The 3 main subtypes (commercially available tests exist for these) of AChRAbs are the binding, blocking, and modulating antibodies. Other subtypes exist, for which we cannot easily test. This may partially explain seronegative MG, which is MG in the absence of the 3 main subtypes of AChRAbs.

II. Demographics

The annual incidence of MG is approximately 14-20/100,000 or 5 per million person-years. A bimodal distribution occurs with women in their 20's and 30's and men in their 60's and 70's. It is rarely familial.

III. Clinical findings

There are two clinical forms of the disease: 1) ocular myasthenia gravis (OMG) with involvement of only the extraocular muscles, levator palpebrae, and orbicularis oculi and 2) generalized myasthenia gravis (GMG) which affects the nonocular skeletal muscles. Approximately 50% of patients with MG present with eye involvement and 75-90% of all myasthenics eventually develop eye symptoms. Of those that present with OMG, approximately half will transition to GMG with most doing so in the first 2 years. It is unclear why the eye is so frequently involved. Theories suggest that it may relate to the fact that ocular and periocular muscles fire so frequently and thus much more apt to fatigue. Others suggest that only very mild weakness is necessary to cause diplopia, where as very mild weakness in proximal limb muscles would go unnoticed. Finally, it may be that the neuromuscular junction of the ocular muscles may somehow be more susceptible.

Ptosis in MG is typically variable. Most patients will say that it is much better in the morning or after a nap. Generally, ptosis from any cause worsens toward the end of the day, and this would not be a specific historical fact. If the patient describes complete ptosis at the end of the day, then that would raise greater suspicion. MG patients who look upward for 1 min, may induce worsening (fatigable) ptosis. The clinician may ask the patient to look down for several seconds and then quickly saccade to primary gaze. If the eyelid overshoots the target and then returns to the ptotic state, this is called Cogan lid twitch. This can be seen in MG but is not specific at all. Other nonspecific signs include lid hopping (the lid elevates quickly with lateral saccades) and curtaining (lifting the more ptotic eyelid causes the fellow eyelid to droop more). In patients with myasthenic ptosis, it is very common to find concomitant orbicularis oculi weakness.

Ocular motility can be affected in almost any fashion in MG. One may observe a pattern consistent with 3rd/4th/6th nerve palsy, internuclear ophthalmoplegia, omnidirectional ophthalmoplegia or almost any pattern. As a general rule, the eye motility will change with time, however in some cases the motility can appear stable for months. Strabismus that changes significantly within a single visit is highly suspicious for MG. Keep in mind that, normally, repeat strabismus measurements may change by as much as 5-6 PD in smaller deviations and 10-12 PD (< 20 PD) in larger deviations (> 20 PD). Rarely will the strabismus pattern appear comitant in MG, and if seen, one needs to place a decompensated phoria higher on the differential diagnosis. Myasthenia does not cause pain or numbness, and it does not affect the pupil. Myasthenia does not cause nystagmus or aberrant regeneration.

Patients may have unrecognized weakness of the proximal limb muscles or of the neck flexor and extensor muscles. Clinicians should also inquire about difficulty swallowing, going up stairs, keeping their arms above their head, voice fatigue, and shortness of breath. Patients may endorse jaw or tongue fatigue with prolonged chewing as well.

IV. Diagnostic approach

Placing a bag of ice on the eyes for 1-2 minutes can improve ptosis in MG (ice test) with a sensitivity and specificity of 94% and 97% respectively. My personal preference is that one not perform the ice test unless there is ptosis of at least 2-3 mm so that a significant improvement can be observed. If the patient has only 1 mm of ptosis, it may be challenging to determine if improvement occurs. One can also ask a patient to

rest in the office for 15-20 minutes (rest test). Substantial improvements in ptosis and strabismus are indicative of MG (sensitivity 90% and specificity of 91%).

After acetylcholine is released into the synaptic cleft, normally, acetylcholinesterase breaks it down to recycle back into the presynaptic nerve. Edrophonium is a short-acting acetylcholinesterase inhibitor, which prolongs the duration of acetylcholine effect within the neuromuscular junction. An edrophonium test consists of injecting edrophonium (up to 1 mg) intravenously and assessing the patient for significant improvement in ptosis or strabismus. Usually an effect is observed within 1-2 minutes of the injection and lasts only a few minutes. The sensitivity is only around 50% but the specificity is 97%. Rare adverse events include bradycardia, syncope, bronchospasm, and respiratory arrest. The test should be avoided in patients with arrhythmia, cardiac or pulmonary disease. Atropine (0.4 mg) should be available immediately to reverse these adverse events. Other common effects include sweating, lacrimation, abdominal cramping, nausea, vomiting, and salivation. Alternatively, intramuscular neostigmine, a longer-acting acetylcholinesterase inhibitor can also be tried. This is often given along with atropine. The severe adverse effects described above are not generally seen. The results of that test should be observed in 45 minutes.

Laboratory investigations include testing for AchRAbs. Usually the binding antibody is tested since the specificity is much higher. The sensitivity is approximately 90% in GMG and 50% in OMG. Blocking and modulating antibodies can also be tested. Anti- muscle specific kinase (MuSK) antibodies have been reported in patients with MG, but they almost always have bulbar symptoms. I do not typically order MuSK antibodies in the absence of dysphagia, dysphonia, or shortness of breath.

Electromyogram (EMG) using repetitive nerve stimulation may show a decrement. This can be performed on the extensor digitorum communis. In patients with OMG the sensitivity is only 50%. Single fiber EMG is another technique that isolates single nerve fibers and their corresponding muscle fibers. Jitter is the variability of measurements one gets from the action potential timing. With MG, the jitter increases and in some muscle pairs the action potential is blocked. The sfEMG can be done on a limb or on the face. The sensitivity of sfEMG for the diagnosis of OMG and GMG is 90%.

After a diagnosis of MG has been made, CT or MRI of the chest should be performed to evaluate for a thyoma. These are typically benign and occur in approximately 10% of patients with MG.

V. Management

Patients with OMG can begin pyridostigmine 30 mg four times daily for 4-5 days. If still symptomatic, the dose can be increased to 60 mg for 4-5 days and then 90 mg four times daily if required. Side effects include cramping, nausea, vomiting, and diarrhea. These can be mitigated with the use of anticholinergics such as propantheline. If pyridostigmine does not control symptoms or the patient cannot tolerate side effects, it is reasonable to consider oral prednisone. There is no clear consensus on how to manage the prednisone. Neurologists will often slowly increase the daily prednisone by 5mg weekly until the symptoms improve or they reach 50 mg. Then a slow taper ensues over months. Some neuro-ophthalmic literature endorses a more rapid escalation to daily prednisone 50 mg over 4 days and then a slow taper over months. There are a number of steroid sparing agents used to treat MG including azathioprine, mycophenolate mofetil, and methotrexate.

Patients with acute decompensation with severe bulbar or respiratory symptoms may require intravenous immunoglobulin or plasma exchange. Patients under the age of 45 with a positive AchRab should be considered for early thymectomy as this may be curative after several years. Patients with thymoma usually undergo thymectomy as well.

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MCQ answers page 45

1. Answer: c

This is a positive ice test, which has a very high specificity. Cogan's lid twitch (A), facial weakness (B), and lid hopping (D) are not specific to myasthenia.

2. Answer: c

Reduction in action potential on repetitive stimulation is the correct answer. Significant changes in small angle esotropia are > 5-6 PD. In A, you would like to see the ET resolve completely. Increased jitter, not reduced jitter, is consistent with myasthenia. The antibody levels are usually twice normal values. Many labs report a normal value as 0 – 0.4 nmol/L and most patients with true MG have levels > 1.0 nmol/L

3. Answer: d

There is a bimodal distribution. Women in their 20's and 30's and men in their 60's and 70's.

MCQ's

1. **Which of the following medications can cause bilateral optic disc edema with normal intracranial pressure:**

   a. linezolide
   b. chloramphenicol
   c. paclitaxel
   d. cyclosporine
   e. Accutane

2. **All of the following statements about ethambutol optic neuropathy are true EXCEPT:**

   a. The risk of toxicity increases with increasing dose
   b. Patients with renal insufficiency are at greater risk
   c. Visual loss usually reverses promptly upon discontinuation
   d. Visual field loss may have a bitemporal pattern
   e. Onset of visual loss is usually 2 – 5 months after starting the medication

3. **Which of the following has NOT been implicated as a cause of visual loss with optic disc edema:**

   a. ethambutol
   b. Alpha-interferon
   c. amiodarone
   d. infliximab
   e. PDE-5 inhibitors

Introduction

Medical treatments that sometimes produce neuro-ophthalmic complications include surgical procedures, radiation and medications. These manifestations can involve afferent visual pathways, higher cortical function, ocular motility or pupillary responses. In this review we will narrow our focus to include only the afferent visual system and limit to medication effects.

Optic Neuropathy

Medications may affect the optic nerves in several ways. Typically, there is bilateral visual loss without optic disc swelling (edema). Less commonly, a medication is associated with optic disc edema, with or without visual loss. In some of these cases disc edema is due to increased intracranial pressure (ICP) but in others the mechanism is more obscure. A few medications may cause disc edema both with and without elevated ICP.

Optic Neuropathy Without Disc Edema

The potential for certain medications to cause optic neuropathy is well known. The typical clinical profile consists of progressive central visual loss with dyschromatopsia and central or ceco-central scotomas. The predilection for central visual loss in toxic optic neuropathies has been attributed to the higher metabolic needs of the papillomacular bundle, rendering these fibers more vulnerable to deficiency of adenosine triphospate [Rizzo]. The clinical presentation of this form of toxic optic neuropathy is indistinguishable from that of nutritional optic neuropathy, for example that due to Vitamin B12 deficiency. Visual loss is painless, symmetric and typically subacute. In the early stages, the optic disc appearance is normal or hyperemic, progressing to optic atrophy (usually manifest as temporal pallor) in later stages. A number of drugs can produce this pattern of visual loss [see Table 1].

Ethambutol. The potential toxic effect of ethambutol on the optic nerve is dose dependent and is thus classified as a true toxicity rather than an idiosyncratic reaction. The incidence of optic neuropathy is reportedly <1% at doses of 15mg/kg/day, increasing to 5-6% at 25mg/kg/day and as high as 18% to 50% in patients receiving >35mg/kg/day [Menon; Fraunfelder 2006]. Conditions that increase the risk for ethambutol toxicity include renal or hepatic insufficiency, older age, diabetes, chronic alcohol or tobacco use, and the concomitant use of isoniazid. The mechanism

of optic neuropathy is not fully understood but evidence of copper chelation, zinc accumulation in lysosomes and decreased cytosolic calcium suggest compromised mitochondrial function in retinal ganglion cells.

Optic nerve dysfunction typically occurs 2 to 5 months after drug initiation though occasional patients experience visual loss much earlier, within weeks, even days of starting treatment. While central or cecocentral scotomas are the classic visual field defect associated with any toxic optic neuropathy, ethambutol occasionally produces a bitemporal hemianopia. This visual field pattern may be due to toxicity to the optic chiasm or, alternatively, to the nasal retina, as suggested by multi-focal electroretinographic findings [Liu]. Findings from electrophysiologic and other ancillary testing suggest a disturbingly high rate of subclinical optic nerve toxicity. A recent prospective study of 52 patients taking ethambutol at a dose of 15-20 mg/kg/day found abnormalities in almost 20%, consisting of delayed latency on pattern visual evoked potential (VEP) testing, loss of temporal retinal nerve fiber layer thickness and decreased contrast sensitivity [Menon].

Clinicians should be vigilant about ocular toxicity, particularly because of the potential reversibility of ethambutol-associated visual loss. Inquiring about visual symptoms at every medical visit is advised but monthly ophthalmic examination is recommded only for patients taking > 15 mg/kg/day or those at higher risk [seeTable 2]. Cases of severe and permanent visual loss from ethambutol-associated optic neuropathy have tempered the general assumption of reversibiltiy [Melamud]. In addition, visual loss may progress even after stopping the drug and there are no predictive factors to identify those in whom vision will recover. For these reasons, quantification of the nerve fiber layer using optical coherence tomography (OCT) or Heidelberg retinal tomography (HRT) is increasingly used to identify optic nerve damage, even before functional loss is evident [Zoumalan]. It is hoped that such early detection of subclinical toxicity will be able to prevent visual loss. In some cases recovery after stopping ethambutol is remarkably prolonged, with patients showing continued improvement up to 2 years after. The physiologic basis for such prolonged recovert course is unknown.

Disulfuram. Disulfiram (Antabuse) is a medication used to deter alcohol intake in individuals with alcohol addiction. Adverse events associated with disulfuran include hepatitis, encephalopathy, peripheral neuropathy and optic neuropathy. The latter typically appears after several months of daily treatment and presents as painless, progressive, bilateral visual loss with cecocentral scotomas and disc pallor [Bessero]. In malnourished chronic alcoholics, a nutritional deficiency may be an additional or

alternative source of progressive visual loss but it is important to remember that the pharmacologic treatment of chronic alcoholism might also be the cause.

Other medications. There are a number of other medications that can cause optic neuropathy without disc edema with clinical features similar to those of ethambutol [Table 1]. The diagnosis is suspected by recognition of the typical clinical profile of toxic optic neuropathy. In most cases, the mechanism of optic nerve damage is related to interference with mitochondrial protein synthesis, as is the case for linezolid and chloramphenical, two popularly used antibiotics which inhibit bacterial ribosomal protein synthesis [Javaheri]. As such, these and other medications are often associated with peripheral neuropathy as well as optic neuropathy. Because the toxic effects in most cases are cumulative, visual loss does not usually occur immediately after beginning treatment. The optic neuropathy of linezolid, for example, occurs after prolonged use, typically beyond 5 months at standard dosage. The prognosis for visual recovery is similar in toxic optic neuropathy, regardless of the responsible medication: recovery is possible but not guaranteed [Javaheri; Rucker].

Medications that Cause Optic Disc Edema

Certain medications can cause optic disc edema, with or without visual loss. The mechanisms by which they do so are varied. In some cases, the swollen disc represents true papilledema, i.e. increased intracranial pressure (ICP). Increased ICP due to medication may be caused by increased resistance to cerebrospinal fluid absorption at the Pacchonian granulations (e.g. Vitamin A excess) or to increased CSF production (e.g. exogenous growth hormone administration). In other cases, the mechanism is more indirect, such as occurs with drug-induced hypercoagulability causing venous sinus thrombosis which then leads to increased ICP (e.g. oral contraceptives or androgens). The list of medications commonly associated with increased ICP, regardless of mechanism, is given in Table 3.

Medication-induced increased ICP typically manifests as a pseudotumor cerebri syndrome (sometimes termed "secondary pseudotumor") with headache and papilledema. Treatment consists of stopping the inciting medication plus appropriate measures to decrease ICP, if needed. In the case of **tetracycline**, normalization of pressure takes from 2 to 5 weeks after drug discontinuation [Winn]. In patients with severe papilledema and decreased optic nerve function, acetazolamide can be initiated during this waiting period and discontinued when disc edema has resolved.

In some patients with medication induced bilateral disc edema the ICP is normal. In these cases, disc swelling is presumably due to local changes within the optic disc such as slowed axoplasmic transport and deposition of material within neurons or glial cells. **Tacrolimus** is an example of a drug that can cause optic disc edema without increased ICP [Avery; Venneti]. Biopsy in one case of tacrolimus optic neuropathy revealed demyelination with preservation of axons, suggesting oligodendroglial toxicity. In other cases, however, the findings have been more consistent with ischemia. In contrast to ethambutol toxic optic neuropathy, the optic neuropathy of tacrolimus occurs at non-toxic levels, is delayed by several months (and occasionally longer) after starting treatment and may show further progression even after discontinuing the drug. Cyclosporine can similarly cause optic disc edema without increased ICP. Both tacrolimus and cyclosporine are immunosuppressive agents, commonly used in patients undergoing organ transplantation [Venneti]. The differential for bilateral disc edema after organ transplantation is broad, including opportunistic infections of brain or retina, increased ICP, uncontrolled hypertension, malignancy, renal failure, and adverse drug effect. The evaluation is directed accordingly: the diagnosis of drug-induced optic nerve swelling should be one of exclusion. **Cyclosporine** can also can cause increased ICP and so defining the exact mechanism of disc edema in a patient on this medication may be difficult. *[Both Cyclosporine and Tacrolimus can also cause increased vascular endothelial permeability leading to vasogenic cerebral edema, with a predilection for the posterior cerebral hemispheres. This clinical picture, termed posterior leukoencephalopathy is discussed in a different section of this meeting.]*

Oprelvekin is a recombinant form of interleukin and a growth factor that increases platelet production. Bilateral disc edema without increased ICP occurs in 1% of adults and 16% of children who receive this medication. Optic nerve function is preserved and the disc edema is reversible with drug cessation [Passman].

Amiodarone. Optic neuropathy due to amiodarone has been described in a number of reports but remains a controversial diagnosis [Passman]. The exact mechanism for visual loss is not established. The clinical findings in reported cases of amiodarone optic neuropathy resemble those of non-arteritic anterior ischemic optic neuropathy (NAION) in some respects. In addition, similarities in the demographics and vascular risk factors in patients with cardiac arrhythmia and NAION have led to the argument that this apparent adverse drug effect is simply the chance occurrence of NAION in patients who happens to take amiodarone [Murphy].

However, several clinical features point to the existence of a true amiodarone-induced optic neuropathy. Bilateral simultaneous optic disc edema is the most common

presentation of amiodarone-associated optic neuropathy, accounting for two-thirds of cases, but is rare in NAION [Passman]. The disc edema associated with amiodarone is often asymptomatic and usually persists for months, even after drug discontinuation, due to the long half-life of amiodarone (21 to 107 days). In contrast, disc swelling in NAION is unilateral and typically resolves within one month. Regression of disc edema after discontinuation of the medication [Shinder] and two reports of optic neuropathy after a single intravenous dose of amiodarone [Ciechanowski; Bartolucci] lend further support for a causal relationship.

The average onset of visual symptoms in amiodarone-associated optic neuropathy is about 6 months from start of therapy but with a broad range (1 to 84 months). In general, optic nerve dysfunction is mild but varies from asymptomatic to severe visual loss. One way to make sense out of this variability in clinical expression is to consider that the degree of visual dysfunction is related to individual factors such as disc anatomy (crowded) and local arterioclerosis so that some discs tolerate disc edema better than others [Purvin].

In patients on amiodarone who develop acute unilateral visual loss with disc edema, have a crowded but non-swollen fellow disc and demonstrate prompt resolution of disc edema, a diagnosis of garden variety NAION is most likely. In those who have simultaneous bilateral optic disc edema, appropriate testing should first address possible increased ICP, compressive optic neuropathy and giant cell arteritis and if such testing is negative, a diagnosis of amiodarone optic neuropathy can be made.

Ideally, amiodarone can be discontinued upon diagnosis. In reported cases, visual acuity following discontinuation of amiodarone improved in 58%, was unchanged in 21%, and declined further in 21%. However, the potential visual benefit of stopping amiodarone has to be balanced with potentially serious cardiac consequences. In our series, of 16 patients in whom amiodarone was discontinued, one experienced a fatal stroke 2½ months later and 1 died of myocardial infarction 1 year later [Purvin]. Ultimately, the decision to continue or discontinue the drug should be made in conjunction with the patient's cardiologist.

Because of the controversy surrounding amiodarone and optic neuroathy, strict guidelines for management are difficult to establish. A baseline examination before or shortly after starting amiodarone is recommended but periodic screening exams are not considered routine. OCT is increasingly used to detect subclinical degrees of retinal nerve fiber layer thickening but whether action should be taken based on structural changes of the optic disc alone is unclear.

The development of dronedarone (Multaq), a related compound, is an alternative with a higher safety profile in regard to other adverse effects but with lesser efficacy. It is not clear whether this medication may similarly affect the optic nerve.

Alpha-interferon. Vascular retinopathy is a common finding in patients taking alpha interferon, found in 11% of patients at 2 weeks after starting -interferon therapy and increasing to 71% of patients at 6 months [Chuman]. The presumed mechanism is immune complex deposition, typically manifest as cotton-wool spots, areas of capillary non-perfusion, arteriolar occlusion and retinal hemorrhages [Guyer]. In most of these cases, accompanying visual loss is mild and reversible upon cessation of treatment.

Similar immune complex deposition within the posterior ciliary arteries may be the basis for the more uncommon occurrence of ischemic optic neuropathy in patients taking -interferon [Purvin]. Based on a review of 36 such cases [Fraunfelder 2011], onset of visual loss occurred on average 4-5 months after beginning treatment, though the range was wide (3 days to 4 years). Although the retinal vascular complications appear to be dose-related, this does not appear to be the case for AION [Fraunfelder 2011].

In 67% of patients, visual loss was bilateral, either simultaneous at onset or within a short interval, a feature that helps to distinguish this adverse event from the coincidental occurrence of "garden variety" NAION. Additionally, there are 3 reports of positive re-challenge cases, in which optic neuropathy recurred when the drug was restarted, providing support for a true causal association [Fraunfelder]. Diagnosis is based on characteristic clinical features and exclusion of other etiologies. In patients with an underlying malignancy, an MRI scan and lumbar puncture should be considered to rule out metastatic disease to optic nerve or meninges. Opportunistic infections, metabolic abnormalities such as anemia or renal failure and vascular derangements such as excessively high or low blood pressure should also be excluded.

Management of these patients is complex as many issues must be considered. For example, for some patients with interferon-associated visual loss there is no viable alternative for treating their underlying condition. Furthermore, stopping the medication is no guarantee of a favorable visual outcome. Vision may improve, remain stable, or even deteriorate further after discontinuing interferon [Gupta]. In occasional cases, second eye involvement has occurred after stopping treatment [Berg]. Overall, 50% of cases showed permanent visual loss despite discontinuation of the drug [Fraunfelder 2011]. Other factors that may compromise optic disc perfusion should be addressed, including relative systemic hypotension, anemia, hypoxia and sleep apnea. Such efforts are particularly important in patients for whom alternative treatment for the underlying condition is not available and the interferon must be continued.

In such instances, corticosteroids and brimonidine are sometimes prescribed, especially in patients with bilateral visual loss in which the pressure to not "just stand there but do something" is especially compelling.

Erectile Dysfunction Drugs. There are a number of case reports of NAION occurring shortly after the use of a phosphodiesterase (PDE)-5 inhibitor for erectile dysfunction (ED) [Pomeranz]. Because NAION is a common condition and the use of ED drugs is widespread, the likelihood of both occurring in the same individual is high, particularly given similarities in risk factors. Visual loss in NAION is often present upon awakening and drugs for ED are commonly taken at night, thus the temporal assocation furthers the impression of a causal relationship.

ED drugs administered to healthy individuals produce minimal effects on the cardiovascular system. However, in individuals with atherosclerosis, these medications, especially in conjunction with others drugs, may produce significant systemic hypotension. This consideration led an expert consensus panel to advise against the use of ED drugs in certain high-risk patients with cardiovascular disease. A mechanism for the production of NAION by ED drugs has not been established, however multiple cardiovascular changes may be involved. These include transient systemic hypotension, exacerbation of blood pressure swings by the simultaneous use of anti-hypertensives, increased plasma norepinephrine (NE) levels and diffusion of NE from the peri-papillary choroid into the optic disc disturbing local autoregulation [Hayreh].

Studies looking at a possible causal relationship include case reports, instances of re-challenge, observational and registry based studies, and investigations of possible mechanisms. Despite these efforts, both the FDA and WHO have concluded that there is, at present, a lack of conclusive evidence of a causal relationship [Danesh-Meyer]. Given the popularity of ED drugs, if they are in fact a cause of NAION, the incidence of this adverse event must be quite low.

The possibility that ED drugs may precipitate NAION is not a public health problem but largely a medico-legal issue. Are drug companies responsible for visual loss in affected individuals? After a patient has experienced an attack of NAION, what should he be advised regarding the future use of ED drugs? As with all treatment decisions, the relative risks and benefits of treatment must be weighed. Any patient with NAION should be informed that he is at some risk for an attack in the fellow eye and that it has been suggested, but not proven, that ED drug use might increase this risk. The subsequent use of these medications is the patient's choice. It seems unfair to over-emphasize this risk to protect ourselves at the expense of a medication that may significantly improve quality of life for the patient.

Anti-Tumor Necrosis Factor Alpha Drugs. Tumor necrosis factor alpha (TNF-) is a cytokine derived chiefly from macrophages and is an important mediator of tissue injury in a variety of autoimmune disorders. Agents that disrupt TNF-mediated inflammation have been found to be beneficial in the treatment of rheumatoid arthritis and inflammatory bowel disease, with a developing role in other autoimmune disorders. Although these drugs were developed to decrease the inflammatory process, there are a number of reports in which they appear instead to exacerbate inflammation, particularly involving the nervous system. The basis for this apparently paradoxic reaction may involve differences in genetic susceptibility in some individuals, decreased penetration into the CNS, and variable effects on different aspects of immune activation [Tristano].

Both central and peripheral demyelination have been reported, most commonly with **infliximab**, but also with **etanercept** and **adalimumab**. It is not clear if the drug has produced demyelination or has made manifest a latent primary demyelinating disorder. In most cases, optic neuropathy that develops during anti-TNF treatment resembles typical demyelinating optic neuritis including acute onset in one eye, pain with eye movement and a female predominance. The optic nerve is not edematous acutely but becomes pale later. MRI usually shows retrobulbar optic nerve enhancement. The interval between initiating treatment and onset of visual loss ranges from 2 to 18 months but the interval between the last dose and onset of optic neuritis is much shorter, often a few days to weeks. As in spontaneous demyelinating optic neuritis, excellent visual recovery is the rule, regardless of steroid treatment. If corticosteroids are given, the intravenous route is preferable [Simsek]. In some reported cases the patient later developed clinically definite multiple sclerosis.

There is a subset of patients using anti-TNFs who develop an optic neuropathy that more closely resembles the clinical picture of amiodarone-associated optic neuropathy [Chan]. In these cases visual loss is painless, bilateral sequential and accompanied by optic disc edema. In the majority of reported cases, visual loss is noticed in one eye but disc edema is present bilaterally at presentation. Neuroimaging is normal and visual recovery poor. The pathophysiologic basis for this uncommon syndrome is unclear.

When to Suspect Drug-Induced Optic Neuropathy

An adverse drug effect should be considered in any patient with unexplained bilateral painless visual loss associated with dyschromatopsia, central scotomas and normal or pale optic discs. Other diagnostic considerations in this setting include hereditary, nutritional, demyelinating and rarely compressive optic neuropathies and occult maculopathy. In occasional cases, visual loss may be due to a combination of an underlying genetic or metabolic vulnerability with the addition of a toxic effect of medication. An example of this interaction is optic neuropathy secondary to antiviral medication such as didanosine in an individual with a mitochondrial mutation that causes Leber's hereditary optic neuropathy [Shaikh].

Drug toxicity should also be considered in any patient with bilateral optic disc edema and is a diagnosis of exclusion. Other etiologies should be excluded with appropriate testing, usually including an MRI and lumbar puncture. If the clinical picture is consistent with pseudotumor cerebri syndrome, the patient's medication list should be checked for drugs that are known to produce this condition (see Table 3). In cases with normal ICP and spinal fluid constituents, the patient should be questioned about drugs that may cause disc edema secondary to local infiltration. Resolution of disc edema after drug withdrawal would constitute confirmatory evidence of drug toxicity in such cases. In many cases, the underlying condition for which the patient is under treatment is itself a potential cause of optic neuropathy. In such cases it is helpful to look for evidence, based on clinical findings and results of ancillary testing, that the disease is currently active.

The differential for drug-induced optic neuropathy includes retinal toxicity. For drugs that cause maculopathy (e.g. fingolimod, taxanes) the clinical picture is similar to toxic optic neuropathy, namely loss of acuity and color vision with bilateral central scotomas. Those that cause diffuse photoreceptor toxicity (e.g. hydroxychloroquine) produce photophobia, photopsias, altered color perception and difficulty seeing in dim illumination. In contrast, toxicity from vigabatrin involves the inner retina causing peripheral field loss.

Decreased near vision

In contrast to medications that cause decreased vision through retinal or optic nerve toxicity, some medications interfere with accommodation and therefore only disturb near vision. Patients typically complain that vision is blurry during reading or other close work but watching television or driving a car is unimpaired. Accommodation is

a delicate mechanism and is easily disrupted, particularly in individuals with incipient presbyopia. Any medication with central nervous system depressant activity can impair accommodation, most commonly **anti-convulsants**, **opiates**, **sleeping pills** and **muscle relaxants**. In addition to their effect on near focus, these medications can reduce fusional amplitudes. In patients with an underlying latent ocular misalignment (phoria), this loss of fusion causes decompensation of the phoria resulting in symptomatic diplopia. The clinician should be aware of this potential adverse effect of such medications because any new blurred or double vision in a patient with a recent neurologic event (e.g. a seizure or head injury) is often presumed to have a neurologic basis, prompting evaluation for a central lesion when in fact the symptom represents a medication side-effect.

Lowering the dose or discontinuing the responsible medication may alleviate symptoms but providing optical correction such as reading glasses or prisms is another option. In such cases it is important to explain to the patient that no permanent damage has occurred.

Induced Myopia

In contrast to the patient who has isolated impairment of near vision, certain medications may rarely cause the opposite pattern, that is, impaired vision at distance with normal near vision. In such cases of acute myopic shift, the mechanism is forward displacement of the lens-iris diaphragm caused by drug-induced ciliochoroidal effusion. The lens-iris shift may also progress to acute angle closure glaucoma which is a condition that requires urgent ophthalmologic attention.

This rare, idiosyncratic reaction has been linked to **sulfonamides**, most recently **topiramate**, a medication originally developed as an anti-convulsant but now commonly used for migraine [Boentert]. Onset of visual blur due to topiramate is acute, occurring from 3 to 21 days after starting treatment. Sudden onset of decreased vision in a patient with epilepsy or new headache suggests a lesion in the central visual pathways, sometimes leading to extensive neurodiagnostic studies. The correct diagonsis should be suspected from the disparity between distance and near vision. The diagnosis is confirmed with retinoscopy which shows a large degree of acquired myopia.

Discontinuing the medication typically brings prompt recovery of vision. If visual loss is accompanied by pain, red eye and halos, progression to angle closure glaucoma should be suspected and emergent ophthalmologic consultation should be obtained. Failure to treat promptly may result in permanent visual loss.

Illusions and hallucinations

Occasionally drugs cause positive visual phenomena such as illusions (misperception of a real object) and hallucinations (perception in the absence of a visual stimulus). Such visual distortion is a frequent accompaniment of delirium, including drug-induced forms (either toxic or withdrawal states). Sometimes such visual distortions are associated with drug use in the absence of a change in mental status.

Visual hallucinations occur in 8.8 to 44% of patients with Parkinson's disease (PD) [Barnes]. While high doses of anti-parkinsonian medications are often implicated as the cause of the hallucination, it is important to remember that they are in fact a feature of the disease itself. The visual hallucination in PD typically comprises a non-threatening complex image with people and animals and lasts only a few seconds. Such hallucinations often arise when the patient is alert in a dim illumination and may recur, similar to that seen with Charles Bonnet syndrome. Based on a large pathologic study, visual hallucinations strongly correlate with the presence of Lewy bodies, whether as part of idiopathic Parkinson's disease or as dementia with Lewy bodies.

Factors that have been associated with an increased risk of visual hallucinations include: greater age, severity of illness, cognitive impairment, depression and worse visual acuity. Clearly visual hallucination in Parkinson's disease is multi-factorial; the nature of the interplay among these factors and drug treatment has not been fully defined. Regardless of pathophysiology, hallucination in PD can often be managed by decreasing the dose of L-DOPA, treating depression and sleep disturbance, and adding non-phenothiazine anti-hallucinatory drugs, if needed.

Altered visual perception is a common feature of known hallucinogens such as lysergic acid diethylamide (LSD) and mescaline. Common manifestations include image distortion, intensification of colors, illusory movement and abnormal persistence of recently viewed images (palinopsia) [Kawasaki]. In some individuals these visual alterations may persist or may recur spontaneously and are termed hallucinogen persisting perception disorder (HPPD) or "flashbacks". **Flashbacks may be precipitated or exacerbated by certain medications, including phenothiazines, amphetamines, anti-histaminics and other cold remedies and serotonin reuptake inhibitor (SSRI) anti-depressants.**

Occasionally non-hallucinogenic medications can induce altered visual perception similar to HPPD, particularly prolongation of afterimages, termed palinopsia [See Table 4]. Cases related to the use of SSRI anti-depressants often involve the concomitant use of other psychotropic medications (particularly **tricyclic anti-depressants**) or drugs

with anti-cholinergic effects. Hallucinations typically resolve after discontinuation of the inciting medication. **Clomiphene citrate**, a non-steroidal agent used for the treatment of infertility, has been associated with a constellation of visual symptoms that includes palinopsia [Purvin]. In addition to prolonged after-images, affected individuals describe shimmering of the peripheral field and increased sensitivity to light. When these visual symptoms occur during brief, low dose treatment, they are reversible. However, prolonged high dose administration may produce persistent, apparently permanent, visual changes. Psychophysical and electrophysiologic tests in affected individuals are normal and thus the basis for this distinctive visual disturbance is unknown.

Tables

Table 1. Medications that Cause Optic Neuropathy Without Disc Edema

Adalimumab
Carbon disulfide
Chloramphenicol
Chloroquine
Dapsone
Deferoxamine
Diiodohydroxyquinolone
Disulfuram
Emetine
Etanercept
Ethambutol
Gentamicin
Hexachlorophene
Infliximab
Isoniazid
Isonicotinic acid hydrazide
Linezolid
Streptomycin

Table 2. Suggestions for monitoring visual status in patients taking ethambutol
(From Fraufelder et al. Expert Opin. Drug Saf. 2006;5:615-618.)

1. Baseline examination to include acuity testing, visual field, color vision and funduscopy.
2. Consideration of contrast sensitivity testing and/or pattern VEP and/or OCT for retinal nerve fiber layer thickness (quadrant and total) in addition to baseline examination.
3. Monthly examination for patients with pre-existing ocular disorders, e.g. glaucoma, patients taking more than 15mg/kg/day, patients at increased risk for toxicity, and patients who are unable to complain of visual loss, e.g. young children, demented patients.
4. Consider discontinuation of drug for any visual symptoms or change in baseline visual status.

Table 3. Medications Associated with Increased Intracranial Pressure

Tetracyclines (minocycline, doxycycline)
Nalidixic acid
Nitrofurantoin
Vitamin A and its analogues (isotretinoin [Accutane], all-trans-retinoic acid)
Androgens (danazol, leuprorelin))
Growth hormone
Oral contraceptives (levonorgestrel)
Lithium
Cyclosporine
Amiodarone
Adrenal corticosteroids (withdrawal)

Table 4. Medications That Cause Palinopsia

trazodone
nefazodone
risperidone
maprotiline
olanzapine
topiramate
clomiphene citrate

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MCQ answers page 51

1. **Answer: d**

2. **Answer: c**

3. **Answer: a**

Acquired autoimmune retinopathies

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09

Electrophysiological examination can be instrumental in resolving some of the diagnostic issues in neuro-ophthalmic practice, particularly in defining the type and severity of the abnormality in a patient with optic nerve disease, and the site and nature of the defect in the patient with medically unexplained visual loss. The latter patient may have disease behind the globe of the eye without physical signs on ophthalmoscopy; a covert retinopathy; or non-organic visual loss. In addition, it can be difficult on clinical grounds to distinguish between macular and optic nerve dysfunction and that process is facilitated by electrophysiology.

Electrophysiological recordings depend upon stimulus and recording parameters and the adaptive state of the eye, and standardisation is therefore mandatory for meaningful scientific and clinical communication between laboratories. The International Society for Clinical Electrophysiology of Vision (ISCEV) has published Standards for all of the routinely used tests. There are also Guidelines for Visual System Testing published by the International Federation for Clinical Neurophysiology, which include test strategies for the investigation of different visual symptoms. A brief review of the main tests follows.

The electroretinogram (ERG)

The ERG is the mass electrical response of the retina to luminance stimulation. It is recorded using corneal electrodes with stimuli delivered by a Ganzfeld bowl, ensuring uniform whole field illumination. Reference electrodes should be positioned at the ipsilateral outer canthi. Scotopic ERGs are obtained following a 25-minute period of dark-adaptation; photopic ERGs after >10 minutes light adaptation using a background luminance in the Ganzfeld of 30 cd/m2.

ISCEV ERGs are named using terminology that incorporates the adaptive state of the eye and the strength and nature of the stimulus. Thus, DA 0.01 refers to a dark-adapted ERG elicited using a stimulus of 0.01 cd.s/m2, whereas LA 3.0 refers to a light adapted ERG elicited using a stimulus of 3.0 cd.s/m2. The main ISCEV ERGs are the DA 0.01 and DA 10.0 (or DA 30.0) scotopic responses, and the LA 30Hz and LA 3.0 photopic responses. The DA 0.01 or rod-specific response consists of a b-wave generated in the rod On- bipolar cells (BPCs). This response acts as a measure of the sensitivity of the rod system but cannot localise dysfunction either to inner retina or the retinal photoreceptors. Such localisation is enabled by the DA 10.0 response, which consists of an a-wave, largely arising in relation to photoreceptor hyperpolarisation, followed by a larger b-wave arising in the BPCs.

Cone system ERGs are obtained using both single flash (LA 3.0) and 30Hz flicker stimulation (LA 30Hz) superimposed upon a photopic, rod-suppressing background luminance within the Ganzfeld bowl. At 30Hz, the poor temporal resolution of the rod system, in addition to the presence of the rod-suppressing background, enables a cone-specific waveform to be recorded. This response is the more sensitive measure of cone dysfunction, but is generated at an inner retinal level. Localisation within the retina may be obtained with the single flash cone response (LA 3.0). Then, the a-wave arises in cone photoreceptors shaped by Off- BPCs while the cone b- wave reflects post-phototransduction activity from both On- and Off- BPCs in the cone system. There is no significant retinal ganglion cell contribution to the clinical (flash) ERG. As a mass response, the ERG is normal when dysfunction is confined to small retinal areas, and, despite the high photoreceptor density, this also applies to macular dysfunction; an eye with disease confined to the macula has normal ERGs.

The Pattern Electroretinogram (PERG)

The PERG is the response of central retina to an iso-luminant stimulus, usually a reversing black and white checkerboard. It has origins in the retinal ganglion cells, but is "driven" by the macular photoreceptors and thus allows both a measure of central retinal function and an evaluation of retinal ganglion cell function. It facilitates the electrophysiological differentiation between optic nerve and macular dysfunction. The PERG is recorded using non-contact lens electrodes in contact with the cornea or bulbar conjunctiva to preserve the optics of the eye, and without mydriasis. Ipsilateral outer canthus reference electrodes are necessary to avoid the contamination from the cortically generated VEP that results if forehead or ear reference electrodes are used.

The transient PERG has 2 main components: P50 at approx. 50msec and a larger N95 at 95msec. Measurement concentrates on the amplitude of P50, from the trough of the early negative N35 component; the latency of P50 measured to peak; and the amplitude of N95, measured to trough from the peak of P50. N95 is a contrast-related component generated in the retinal ganglion cells. Approximately 70% of P50 also appears to be generated in the ganglion cells, but P50 is driven by the macular photoreceptors and reflects macular function.

The Visual Evoked Potential (VEP)

The VEP is mostly generated in relation to cortical function. The responses are recorded to monocular stimulation using occipitally placed electrodes, and are used to assess the intracranial visual pathways, particularly the optic nerves and optic chiasm. The responses to patterned stimuli are most sensitive to visual pathway dysfunction. A reversing black and white checkerboard is usually adopted as a routine stimulus. Pattern onset/offset is particularly effective in certain conditions (see below), and diffuse flash stimulation may also be useful.

The transient (<2/sec recommended) checkerboard pattern reversal VEP (PVEP) contains a prominent positive component at approximately 100msec (P100). Stimulus parameters such as contrast, luminance, check size, field size etc., are important determinants of the waveform, and it is essential for each laboratory to establish their own normal controls. A single midline recording channel is not suitable for chiasmal disease. Assessment of chiasmal function is highly complex, with stimulus and recording parameters requiring particular attention; these issues are discussed in the IFCN Guidelines. The pattern appearance (onset/offset) VEP is most often used for the assessment of visual acuity and in the detection of the intracranial misrouting associated with albinism. It is also less affected than the reversal VEP in a patient with nystagmus in the primary position of gaze; under such circumstances pattern reversal VEP results must be treated with considerable caution.

Clinical applications:

ERG

Although reduction in the rod specific ERG b-wave is a sensitive indicator of rod system dysfunction, it is the DA 10.0 response a-wave that directly reflects activity of the photoreceptors, the b- wave being generated in the inner nuclear layer. Genetically determined retinal degenerations, such as rod-cone (retinitis pigmentosa) and cone-rod dystrophies, thus give overall ERG reduction consequent upon photoreceptor degeneration. RP initially may only affect the rod-derived ERGs. True sector (restricted) disease may give amplitude reduction with no implicit time change; diffuse or generalised disease is usually also associated with abnormal peak time. The fundal appearance may not reflect the severity or nature of the disorder; the ERG enables accurate diagnosis and may provide prognostic information.

Cone dystrophies have normal rod responses, but abnormal cone responses, with the LA 30Hz flicker ERG usually showing both amplitude reduction and peak-time delay. Delay is also a feature of inflammatory disorders such as birdshot chorioretinopathy, but then there may be amplitude preservation. Indeed, the 30Hz flicker in birdshot chorioretinopathy, as a sensitive objective indicator of generalised retinal dysfunction, can also be used to guide management decisions. There is a known association between uveitis and multiple sclerosis (MS), and 30Hz flicker ERG delay can occur in such cases. Delay in the flicker ERG is also anticipated in AZOOR.

A "negative" ERG, where the a-wave is spared and there is selective b-wave reduction, indicates dysfunction post-phototransduction, and probably post-receptoral. The "negative" ERG in central retinal artery occlusion (CRAO) reflects the duality of the retinal blood supply with RPE/photoreceptors supplied via choroidal circulation, but bipolar cells supplied via central retinal artery. Other causes of negative ERG include X-linked congenital stationary night blindness, X-linked retinoschisis, quinine toxicity, melanoma associated retinopathy (MAR), Batten disease etc. The causes of negative ERG have recently been extensively reviewed.

PERG

The PERG has two roles; the identification and assessment of disorders of macular function via the P50 component, an objective index of macular function, and the primary assessment of the central retinal ganglion cells with the N95 component. In maculopathy, the P50 component of the PERG is abnormal, often with preservation of the N95:P50 ratio. P50 amplitude is usually affected, with peak-time delay only occasionally being seen, particularly in macular oedema, serous macular detachment, and some inherited disorders. In clinical practice, the PERG is best combined with the (full-field) ERG. The ERG assesses the degree of peripheral retinal involvement, and the PERG the degree of central involvement. Even in a patient with normal macular anatomy the PERG may reveal macular dysfunction. The ERG is normal in disease confined to the macula and, when abnormal, facilitates the distinction between macular dystrophy, cone dystrophy and cone-rod dystrophy in a patient with an abnormal macular appearance. In patients with rod-cone dystrophy, but normal central retinal function, the PERG may be normal even when the ERG is almost undetectable.

It is the ganglion cell generated N95 component that is usually selectively affected if the PERG is abnormal in optic nerve disease, but the PERG will often be normal. P50 latency may shorten in severe ganglion cell dysfunction, but not in macular disease. Equally,

PERG extinction is a feature of macular disease, but not optic neuropathy. Primary ganglion cell dysfunction is associated with marked N95 component loss, particularly Leber hereditary optic atrophy, with dominant optic atrophy (DOA) showing similar findings in advanced disease. Very severe optic nerve disease will affect P50 amplitude, and the associated shortening of P50 latency becomes important. Extinction of the PERG rarely if ever occurs in optic nerve disease, providing at least one eye has enough vision to maintain fixation for binocular PERG recording; the PERG may still readily be detectable in an eye with no light perception. Patients with primary optic nerve dysfunction can show PERG N95 abnormalities consequent on retrograde degeneration to the RGCs.

VEP

The PVEP is a sensitive indicator of optic nerve function. Halliday showed in the early 1970's that the PVEP is usually delayed in optic nerve demyelination and that the delay may occur with no signs or symptoms of optic nerve involvement, significantly affecting management in a patient with spinal cord disease and possible multiple sclerosis (MS). The VEP is almost invariably delayed following symptomatic optic nerve involvement in MS, even when vision has returned to normal. Toxic optic neuropathy (e.g. ethambutol) is also associated with delay, but non-arteritic anterior ischaemic optic neuropathy gives mainly amplitude reduction with minimal latency change. The VEP changes in swelling of the optic disc are consequent upon the nature of the underlying pathology, but papilloedema per se does usually not result in a VEP abnormality unless secondary optic atrophy has occurred. Chiasmal lesions, such as pituitary tumours, give a "crossed asymmetry" where there is an abnormal distribution over the two hemispheres, which is in an opposite direction for the two eyes. Stimulus parameters are crucial for accurate localisation.

The diagnosis of the intra-cranial misrouting of albinism, where the majority of optic nerve fibres from each eye decussate to the contralateral hemisphere, may be established by the VEP. Pattern appearance is used rather than the usual pattern reversal stimulus. The flash VEP is more effective in infants and the appearance VEP in adults. FVEP may also be useful in non-cooperative patients (infants, coma etc.), and where there is no PVEP; FVEP and PVEP may be complementary.

Electrophysiology is crucial to the diagnosis of nonorganic visual loss by demonstrating normal function in the presence of symptoms that suggest otherwise. Great care is needed in such patients to ensure that any attempts voluntarily to affect the results, by

poor fixation, defocusing etc., are unsuccessful. Objective VA assessment is performed with pattern appearance stimulation using a very brief appearance time in order to minimise the possibility of voluntary defocusing.

Delayed pattern VEPs can occur both in macular dysfunction and optic nerve disease, and a delayed PVEP must never be assumed to indicate optic nerve dysfunction; that differentiation is enabled by the PERG. A delayed or absent pattern VEP with a normal PERG or an abnormality confined to the N95 component indicates suggests optic nerve/ganglion cell dysfunction, whereas pronounced P50 reduction usually indicates macular dysfunction. Furthermore, a normal PVEP should not be assumed to indicate normal macular function as mild macular dysfunction may give a PVEP within the normal range but a pathological PERG.

Autoimmune retinopathy (AIR)

This describes a group of rare disorders usually affecting outer retinal function but inner retinal disease can occur. The dysfunction may be caused by circulating anti-retinal antibodies in relation to a tumour, but can occur in the absence of malignancy. They can be divided into carcinoma associated retinopathy (CAR), melanoma associated retinopathy (MAR), and non-paraneoplastic retinopathy (npAIR). AIR is the umbrella term. CAR usually presents with rapid, painless, progressive visual loss, usually bilateral but which may be unilateral or asymmetric in onset and severity. Predominant cone system dysfunction manifests with photophobia, reduced visual acuity and impaired colour vision. Rod system dysfunction results in night blindness. Positive phenomena such as photopsias or shimmering are common. The symptoms usually rapidly progress but may stabilise. MAR usually presents with a sudden onset of acquired night blindness accompanied by shimmering photopsias. There is no or slow progression. The presentation of npAIR is variable, with acuity loss, field loss, positive phenomena or night blindness, often with a normal fundus appearance. The fundus in CAR may initially be normal, later developing retinal pigment epithelium (RPE) atrophy and mottling and vessel attenuation. The fundus is usually normal in MAR but vessel attenuation and optic disc pallor have been reported. Vitreous cells may be present. Patients with npAIR may a have normal fundus appearance. Some develop subtle, granular pigment changes at the fovea; some show more marked retinal disturbance.

Vision loss in CAR precedes diagnosis of an underlying malignancy in approximately 50% of cases. CAR is most frequently associated with small-cell lung carcinoma, followed by gynaecological and breast malignancies. Less frequently, CAR is associated with solid

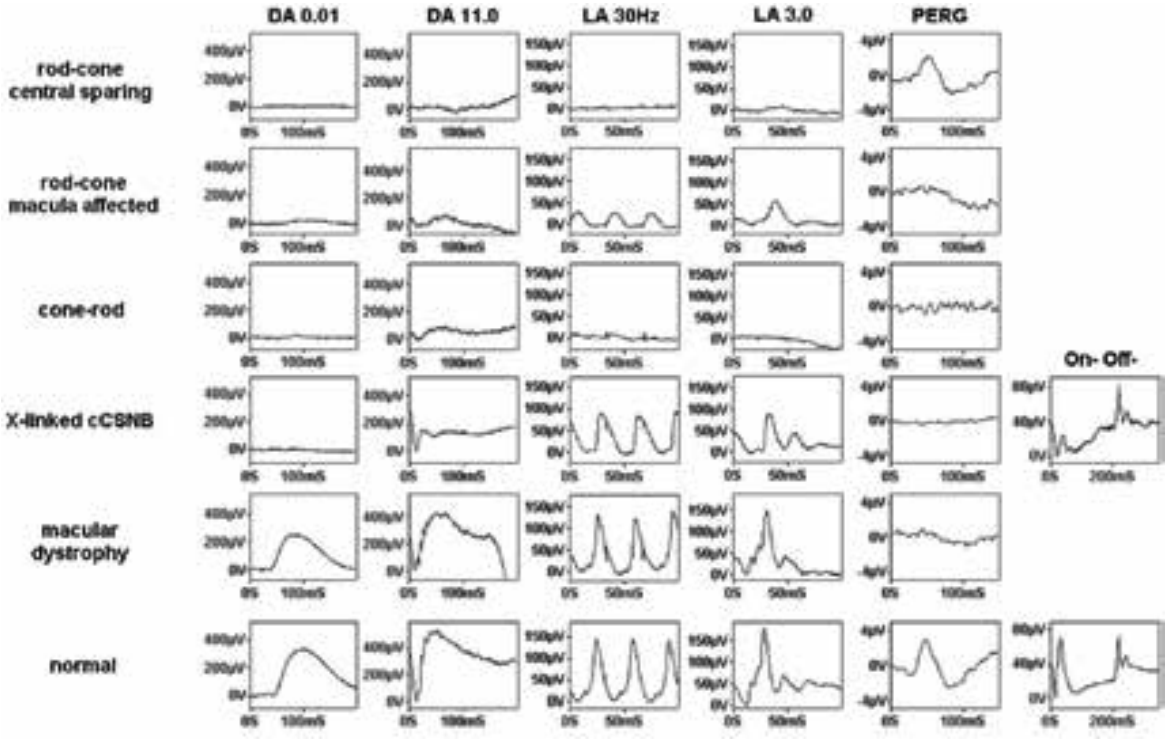
tumours and haematological malignancies. The interval between cancer diagnosis and CAR ranges from weeks to years, with a shorter interval often associated with rapidly progressive visual loss. Patients with MAR usually have a history of cutaneous malignant melanoma, although uveal and rarely mucosal melanomas have been described. NpAIR is associated with autoimmune disease (eczema, psoriasis, thyroiditis etc.) in approximately 50% patients. A diagnosis of presumed npAIR should only be made following full systemic review to exclude occult malignancy.

The electroretinogram is vital in the diagnosis of AIR. CAR predominantly affects the photoreceptors, with the rod system commonly involved, giving a-wave reduction in the DA 10.0 response, which can be severely abnormal even shortly after presentation. There is usually peak-time delay and amplitude reduction in the 30 Hz flicker ERG. Pattern ERG abnormalities reflect macular involvement. When there is a rod > cone abnormality pattern, early macular involvement in CAR may assist the differentiation from an inherited rod–cone dystrophy, but visual acuity reduction in CAR can also relate to cystoid changes. The anti-recoverin CAR phenotype has been associated with severe loss of rod and cone function, whereas anti-enolase retinopathy typically has mainly cone dysfunction. Inner retinal dysfunction, evidenced by a negative ERG, can also occur in CAR in the absence of photoreceptor involvement but is uncommon. The findings in MAR are far more consistent, with loss of On-bipolar cell (BPC) function in rods and all 3 cone types but preserved Off-BPC function. This results in electronegative waveforms that are indistinguishable from those of "complete" congenital stationary night blindness (cCSNB), with a negative waveform DA 10.0 ERG and a distinctive appearance in the LA 3.0 response. NpAIR is highly variable and can affect photoreceptors or inner retinal function. Anti-transducin- associated npAIR is reported to show reduced scotopic and photopic responses, with increased peak times; anti-enolase retinopathy is associated with cone dysfunction.

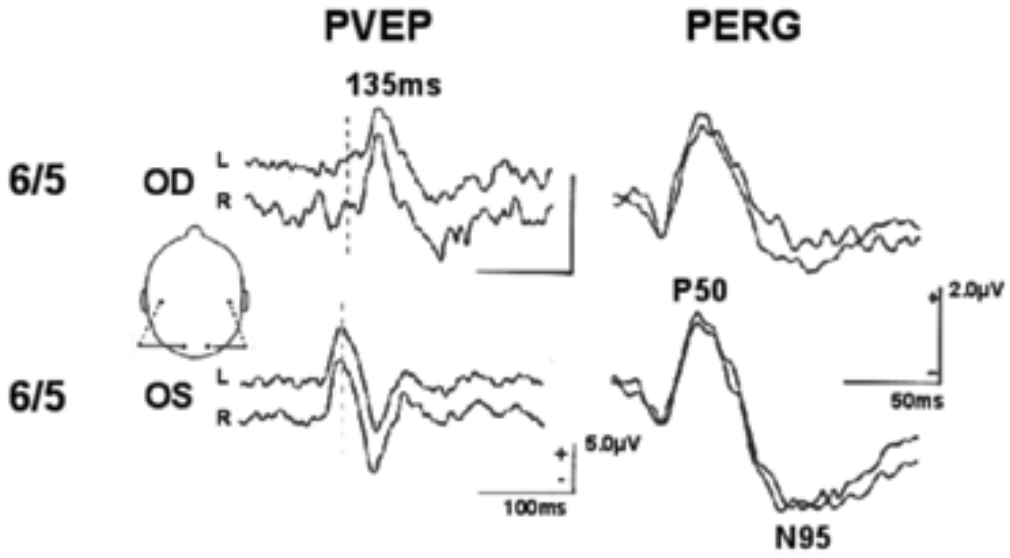
The presence of serum autoantibodies can be established by a variety of methods, including immunohistochemistry, Western Blotting, ELISA etc., and has a frequency of approximately 65% in CAR and MAR patients, somewhat lower in npAIR. CAR-associated antibody targets include recoverin (23 kDa) in 10%, -enolase (46 kDa) in 30%, and rod transducin- (40 kDa) in 17%. There is overlap between NpAIR associated antibody targets and those of CAR, with the exception of recoverin, which has not yet been reported in npAIR. MAR-associated antibody targets include enolase, transducin- , rhodopsin, arrestin (48 kDa), the TRPM1 transduction channel in On-BPCs and others. The electronegative ERG in MAR may relate to the effect of autoantibodies to TRPM1; mutation in the gene encoding TRPM1 is associated with recessively inherited cCSNB in humans.

Nonetheless, caution must be exercised in the interpretation of the autoantibodies identified in association with AIR; their presence may be causative and play a direct pathogenic role, but may simply be an epiphenomenon. For example, anti-recoverin antibodies have been reported in patients with retinitis pigmentosa, and other anti-retinal antibodies can be found in other disorders that include cystoid macular oedema, diabetic retinopathy, idiopathic uveitis etc.

Typical patterns of ERG abnormality



Right optic nerve conduction delay following recovered optic neuritis.
OS findings normal. Note right eye PERG N95 component reduction.



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Posterior reversible encephalopathy syndrome (PRES)

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10

MCQ's

1. The most common location of brain lesions associated with PRES is:

a. brainstem
b. parietal and occipital lobes
c. cerebellum
d. medulla
e. pituiary

2. Visual loss associated with PRES is most commonly due to:

a. retinal detachment
b. cortical visual loss
c. chiasmal compression
d. cataract
e. optic neuropathy

3. The most common category of drugs associated with PRES is:

a. nonsteroidal anti-inflammatory agents
b. calcineurin inhibitors
c. beta blockers
d. vinca alkaloids
e. GABA antagonists

Objectives

- To recognize the clinical syndrome of PRES
- To know the conditions and drugs associated with PRES
- To know the prognosis of visual loss due to PRES

Previously termed reversible posterior leukoencephalopathy syndrome, the more current name for this particular clinico-radiological entity is Posterior Reversible Encephalopathy Syndrome, or PRES. Clinically, PRES is characterized by an acute or subacute neurologic syndrome that develops over hours to days. Seizure is often a heralding event, occuring in 60-75% of patients. Other presenting manifestations are headache, encephalopathy (ranging from mild confusion to stupor) and visual disturbance. The visual disturbances associated with PRES include cortical blindness (most commonly), homonymous hemianopia, visual neglect, blurred vision and visual hallucations. It is very rare for visual disturbance to be the sole manifestation of PRES. However, the patient may have altered mental status or new headache which may so mild as to be overlooked. Focal neurologic deficits, such as hemiparesis or aphasia, are unusual, noted in 5–15% of patients, and when they occur associated with an acute homonymous hemianopsia, the overall clinical picture resembles an acute ischemic stroke syndrome.

The radiologic findings associated with PRES are best seen on T2 weighted MR imaging, especially with fluid attenuated inversion recovery (FLAIR) acquisition. Hyperintense (bright) lesions representing patchy edema are seen in both cerebral hemispheres, particularly in the parietal-occipital region, and involving subcortical white matter. PRES lesions are bilateral and while the brain lesions may be asymmetric, a strictly unilateral lesion on neuroimaging should raise suspicion of another diagnosis. In addition to cerebral hemispheric lesions in the gray and white matter, PRES can cause similar lesions throughout the cerebellum, brainstem, thalamus, and basal ganglia.

T2 –weighted imaging and FLAIR acquisition are indispensable for identifying the distribution of the PRES lesions. However, these sequences cannot distinguish vasogenic oedema (reversible) from cytotoxic edema (irreversible). It is helpful to request diffusion-weighted imaging (DWI) when ordering the brain MRI in patients with suspected PRES. DWI can differentiate the vasogenic (reversible) edema that is characgeristic of PRES. Specifically, the lesion of PRES will appear iso-intense or hyperintense on DWI and show hyperintensity on apparent diffusion coefficient (ADC) mapping. Signal abnormality can be detected within 24-48 hours of the acute event and then can be followed until the disappearance of clinical features.

The most common conditions associated with PRES are hypertension, pre-eclampsia/eclampsia, renal failure, immunosuppressive therapy, chemotherapy, autoimmune disease, and infections. Previously considered rare, autoimmune disease is increasingly recognized as a condition associated with PRED. Specific disorders include systemic lupus erythematosus, thrombotic thrombocytopenic purpura, hypothyroidism, scleroderma, Crohn's disease, ulcerative colitis, primary sclerosing cholangitis, rheumatoid arthritis, Sjogren syndrome, polyarteritis nodosa, granulomatosis with polyangiitis, and neuromyelitis optica. A large number of other diseases and toxic agents have been also been reported as causes of PRES. In post-transplantation patients, the use of calcineurin inhibitors such as cyclosporine and tacrolimus is a major risk factor for the development of PRES. The onset of post-transplantation PRES varies from 1 week to several months after transplantation. Other drugs implicated with PRES are the antiangiogenic drugs that antagonise the action of vascular endothelial growth factor, such as bevacizumab, sunitinib, and sorafenib.

Pathophysiology

The critical event leading to PRES is endothelial injury which leads to breakdown of the blood– brain barrier and subsequent brain edema. Normally, the cerebral perfusion pressure is held relatively constant by autoregulatory mechanisms mediated largely via changes in sympathetic tone. Rapidly developing hypertension may exceed the upper limit of autoregulation, leading to failure of compensatory vasoconstriction and vasodilation with hyperperfusion Endothelial injury and breakdown of blood–brain barrier ensues, allowing the interstitial extravasation of plasma and macromolecules. The posterior brain regions are particularly susceptible to hyperperfusion-related injury because little sympathetic innervation exists in the posterior fossa.

Indeed acute hypertension frequently accompanies PRES and careful treatment of acute hypertension results in clinical and radiological resolution of abnormalities. Yet 15–20% of patients with PRES are normotensive or hypotensive at the time of blood pressure reading. In such cases, 24 hour pressure monitoring may be helpful to identify sudden but nonsustained peaks of hypertension.

The vasodilation-hyperperfulsion is the popularly quoted pathophysiologic basis of PRES. An alternate theory, however, exists. The alternative theory purports that inappropriate vasoconstriction is the mechanism leading to brain edema. This is based on the notion that placental hypoperfusion and ischemia in eclampsia/pre-eclampsia lead to the upregulation of cytokines and release of vasoconstrictive agents into the bloodstream, inducing widespread vasoconstriction and ischemia. Support for this alternate theory

comes from neuroimaging studies of patients with PRES that demonstrate decreased cerebral blood flow in the affected areas of the brain. Additionally, it is curious to note that occasional PRES patients demonstrate serous retinal detachment and choroidal hypoperfusion due to breakdown of the retinal pigment epithelial barrier.

Management

Management of PRES begins with early diagnosis and search for causative agents, in particular certain drugs. Seizures, if present, are treated immediately. If a causative drug is found, its withdrawal or dose reduction can initiate recovery. If blood pressure is determined to be elevated, careful reduction of pressure is important while avoiding sudden dips in the blood pressure. Vasodilators such as nitroglycerin are excluded because they can worsen clinical manifestations.

Prognosis is generally favorable with resolution of clinical and radiological abnormalities in several weeks but reversibility is not uniformly guaranteed. Prolonged elevation of blood pressure has been associated with incomplete resolution. Reduction in the ADC on diffusion-weighted imaging suggests development of cytotoxic edema and has been associated with persistent focal deficits, gliosis and atrophy.

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MCQ answers page 79

1. Answer: b

The "P" in PRES stands for "Posterior" and this refers to posterior cortex and most clinical manifestations, including visual loss, are due to cortical dysfunction. PRES lesions can occasionally be found in cerebellum, brainstem , thalamus, and basal ganglia but these are not the most common sites of involvement.

2. Answer: b

PRES is not known to cause ocular, optic nerve or retinal lesions.

3. Answer: b

Keep in mind that when PRES occurs in post-transplant patients, the cause is likely due to Cyclosporin or Tacrolimus (calcineurin inhibitors) .

Neuromyelitis optica (NMO) and spectrum disorders

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11

MCQ's

1. Which of the following ophthalmic presentations is not consistent with a diagnosis of NMO?

a. Optic neuritis
b. Optic chiasmitis
c. Internuclear ophthalmoplegia
d. Papilloedema
e. Nystagmus

2. When compared with MS, which of the following statements about NMO is false?

a. May present at an older age
b. Commoner in men
c. May have other autoimmune diseases
d. Less likely to show periventricular white matter lesions
e. More likely to show CSF pleocytosis

3. Which of the following is not a recognised treatment for NMO?

a. Cyclosporine
b. Mycophenolate mofetil
c. Rituximab
d. Prednisolone
e. Azathioprine

Neuromyelitis optica (NMO) is a rare neuro-inflammatory disease which has assumed particular importance in the last decade for two reasons: (a) it was the first demyelinating condition proved to be autoimmune and associated with a pathological antibody; and (b) its treatment is different from other causes of demyelination and so it is important that the diagnosis is made early in the course of this disease.

Historical

From the early 19th century there have been many anecdotal case reports of patients presenting with acute optic neuritis and transverse myelitis. In 1894 Eugene Devic presented a case at the Congres Francais de Medicine in Lyon, and later that year his PhD student, Fernand Gault, submitted his thesis on what he called 'Neuromyelite optique' based on this and other cases. The condition was subsequently known as NMO or Devic's disease, and initially assumed to be a variant of multiple sclerosis (MS). However, throughout the 20th century further analysis revealed important differences between these conditions in terms of the clinical features, the pathology, CSF analysis and neuroimaging, response to treatment and outcomes. The discovery in 2004 of an NMO-specific antibody directed against the aquaporin 4 water channel (AQP4) provided final proof that NMO is an auto-immune antibody-mediated channelopathy which is entirely different from MS both in its pathogenesis and in its management.

Pathology & Epidemiology

AQP4 is one of a number of water channels that are distributed in areas of the body where water levels and transport are of paramount importance, eg kidneys, lungs, brain etc. In the central nervous system, AQP4 channels are located on the end feet of the astrocytes, and distributed mainly in the optic nerves, spinal cord and floor of the 4th ventricle. In patients with NMO, antibodies directed against these AQP4 channels cross the blood-brain barrier and bind with AQP4 to activate complement causing recruitment and activation of inflammatory cells; the primary injury appears to be a cell-dependent cytotoxicity causing death of these astrocytes, but that leads to subsequent damage to the oligodendrocytes with demyelination and eventually loss of neurons. NMO is rarer than MS, with a prevalence of <5 per 100,000 and an annual incidence of 0.05-0.4 per 100,000 person-years. Women are more commonly affected than men (9:1), with a slightly older median age of presentation (39) compared with MS – importantly, the NMO age range is much wider than MS and patients as young as 5 or as old as 85 have been known to develop this disease.

NMO is also seen quite commonly in ethnic groups at low risk of MS, eg people of Afro-Caribbean origin. Patients with NMO often have other autoimmune diseases, eg Sjogrens, myasthenia, SLE, coeliac disease.

Clinical

The commonest presentation to ophthalmologists is with optic neuritis (ON). In general there is a large degree of overlap between MS-associated and NMO-associated optic neuritis, and it is not always easy to distinguish these diagnoses; features favouring NMO include severity of visual loss, simultaneous bilateral involvement and poor outcome. NMO can also affect the optic chiasm or tract, giving rise to hemianopic visual field defects. Much less commonly, NMO may present with brainstem symptoms and signs such as nystagmus, opsoclonus and wall-eyed bilateral internuclear ophthalmoplegia (WEBINO). NMO most commonly presents to the neurologists with acute transverse myelitis (TM), but occasionally patients may be referred with hiccups or 'central' vomiting due to lesions in the floor of the 4th ventricle. NMO may initially present with ON alone, TM alone, or both – but in most cases, the natural history of NMO is relapsing-remitting, and the severity of each relapse and the degree of recovery determine the final level of disability.

Investigations

The MRI findings in ON are similar for MS and NMO, but in the cord the lesions are more likely in NMO to extend to 3 or more segments – sometimes associated with cavitation. NMO lesions may sometimes be seen in the brain, but their distribution (brainstem, especially the floor of the 4th ventricle) is different from the typical periventricular lesions seen in MS. CSF analysis often shows a marked pleocytosis and oligoclonal bands are uncommon, in contrast with MS. Serology for the specific AQP4 antibody causing NMO (NMO-IgG) is positive in over 75% cases, with a false-positive rate of less than 0.1%; however it should be noted that the serology results may not be available for several weeks (i.e. after the point at which decision about treatment need to be made), and that some patients who are initially sero-negative may convert to being sero-positive during subsequent relapses. It is still not clear whether NMO-IgG serology should be tested in all cases of ON, or just those with 'atypical' features.

Treatment & Prognosis

In the acute setting, most patients with NMO will be initially managed with pulsed intravenous methylprednisolone (1g/day*5), but NMO is not particularly responsive to steroids and so it is increasingly common to go on to plasma exchange (PEX) or intravenous immunoglobulin (IVIg). Subsequent therapies aimed at preventing relapses include oral agents such as azathioprine, mycophenolate mofetil, methotrexate and cyclophosphamide; good results are also increasingly being reported with rituximab, which needs to be given as infusions every six months. Unfortunately we do not yet have any Grade 1 evidence (randomised clinical trials) to guide treatment in this rare condition. Patients with NMO do not go on to a secondary-progressive phase (in contrast with MS), but the morbidity is higher from each relapse; at 5 years after diagnosis, half of NMO patients will have a visual acuity less than 6/60 in at least one eye, and recurrent TM may leave the patient wheelchair-bound.

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MCQ answers page 85

1. **Answer: d**

2. **Answer: b**

3. **Answer: a**

Transient monocular visual loss: carotid embolus vs giant cell arteritis

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12

MCQ's

1. **75-year-old man with ischemic heart disease and hypertension experiences a single 10-minute episode of painless visual loss in his right eye. He describes the episode as a "black window shade" pulling down and then releasing. Which is the most likely etiology of this visual loss?**

   a. Migraine
   b. Vertebra basilar circulation insufficiency
   c. Uhthoff phenomenon
   d. Retinal artery embolus
   e. Ischemic optic neuropathy

2. **In a 76-year-old woman with sudden monocular loss of vision for 6 minutes and a history of headache and weight loss, which of the following is the MOST APPROPRIATE next step:**

   a. CT scan of the brain and orbits
   b. MRI of the brain
   c. Evaluation of the sedimentation rate and the C Reactive Protein
   d. Immediate referral to a neurologist
   e. Electrocardiogram

3. **A 30-year-old man without past medical history except for a myopia of minus 6 OU, consults in emergency for a transient right monocular visual loss for 6 minutes, described as a grey shadow pulling down and then releasing. He complains about mild right periocular pain; Medical examination reveals a right ptosis and a right myosis. Which of the following is the MOST APPROPRIATE next step:**

   a. Evaluation of the sedimentation rate and the C Reactive Protein
   b. Electrocardiogram
   c. MRA or CTA of the brain and the neck
   d. Monitoring of the blood pressure for 24 hours
   e. Migraine management

Objectives

- Review the different steps in evaluating a patient with TMVL
- The different mechanisms and causes of TMVL with their clinical and biological characteristics

Introduction

The annual incidence of transient monocular visual loss or transient monocular visual field loss (TMVL) rises from 1.5/100,000 in the third decade of life to 32/100,000 in the seventh decade of life. Except before 44 years, the incidence is higher in men than in women. The differential diagnosis of TMVL is broad and assessment is challenging. As most patients are no observed during the attack, the examination is frequently normal. Vascular TMVL is an emergency and requires urgent assessment. The description of the trouble must be very detailed to help with the differential diagnosis especially between embolic vs non embolic (and mostly Giant Cell Arteritis or GCA) etiologies.

1/ Description of the TMVL

1.a. Onset and pattern

The first question is always asking whether the trouble is truly **monocular**, because some patients are more aware of the temporal than the nasal visual field. If the patient didn't close one eye and after the other, during the trouble, reading impairment and the respect with the vertical meridian suggest vertebro basilar pattern and will require investigations for a possible occipital stroke.

Sudden and painless TMVL with an altitudinal pattern, resembling a curtain or shade, ascending or descending instantly or over seconds, is strongly suggestive of vascular etiology. Other patients experience dimming, complete constricting or black lacunae with progressive extension to complete monocular visual loss. The concentric pattern of VFL may be caused by generalized ocular hypoperfusion. Blobs may coalesce to produce complete VFL. Such patterns of VFL are unlikely to be from an embolus and more likely relate to hypoperfusion or vasospasm.

The pattern of VFL can be characterized by the presence of positive phenomena (scintillations or photopsias) that patients describe as sparkles, flashing lights, flickering, or colors. Most of time, these positive phenomena are also not associated with an embolic etiology.

Slowly spreading VFL associated with positive symptoms that move across the VF and are also visible to the patient with the eyes closed, are suggestive of central pathology—most frequently migraine

1.b. Duration

The duration of attack is usually comprised between 5 minutes and one hour. Even if there is no strict parallelism between the duration of the TMVL and the mechanism, the answers can help determine the cause. Very brief episodes are likely to represent transient visual obscuration associated with disk swelling; retinal emboli produce a very sudden TMVL lasting from 1 to 4 minutes; the result of ocular hypoperfusion would be progressive at least 5 to 10 minutes and associated with standing up or bright lights. Venous congestion causes a progressive loss, lasting 10 to 20 minutes or more and precipitated by bending over or Valsalva maneuvers. Migrainous visual aura has a progressive installation (migrainous march), lasts typically 20 to 30 minutes and is followed in most cases by the headache.

1.c. Associated features

- Headaches are frequently associated with transient visual loss. In young patients, and especially if there are positive visual phenomena and if symptoms like photophobia, phonophobia, and autonomic dysfunction are present, migraine needs to be considered in the differential diagnosis.
- In older patients, headaches, scalp tenderness, weight loss, malaise, anorexia, fever, neck and proximal muscle pain and jaw and tongue claudication are closely associated with GCA.
- Eye or brow pain associated with TMVL in young a myopic people suggest pigmentary glaucoma, especially if the pain is triggered by exercise; in older and / or hyperopic patients, it may be associated with an intermittent angle closure glaucoma. But this eye or brow pain is not specific as it may be associated with ciliary ischemia secondary to GCA or ipsilateral ICA stenosis
- If simultaneous contralateral hemisensory or motor findings are associated with TMVL, a carotid workup must be performed emergently in a stroke Unit

1.d. TRIGGER FACTORS

- Gaze evoked TMVL with recovery after the eye returned in primary position suggest an orbital disease, most commonly an optic nerve sheath meningioma
- TMVL triggered by bright light suggest ipsilateral internal carotid artery (ICA) occlusion
- TVML triggered by postural change (when getting up) and associated with malaise or syncope may be associated with postural arterial hypotension

2/ Diagnostic approach (fig 1)

After the description of the TMVL and the evaluation of the past medical history, especially the vascular risk factors, the clinical examination, although often normal, may be helpful in the differential diagnosis of embolic vs non-embolic TMVL.

2.a. General examination

The blood pressure has to be measured in seated and up position
An electrocardiogram could reveal atrial fibrillation or signs of recent or cardiac ischemia
Temporal pulse should be determined in older patients
If the TMVL is associated with an ipsilateral Horner syndrome, a carotid disease such as a dissection must be ruled out.

2.b. Ophthalmic examination

It is a critical step to rule out ocular causes of TMVL (dry eyes, hyphema, angle closure glaucoma, pigmentary dispersion, optic nerve disorders), orbital disease with proptosis, and to detect retinal emboli, retinal ischemia, cotton wool spots, venous stasis retinopathy or optic nerve abnormality. Retinal emboli are transient and can be missed if the ocular examination is delayed.

If there is a suspicion of GCA, a fluorescein angiogram must be performed and may show a delay in choroidal filling

In case of suspicion of a transient arterial retinal occlusion, an OCT may reveal increasing of the thickness and disorganization of the internal retina.

2.c. Ancillary studies

- In older patients, complete blood count, erythrocyte sedimentation rate and C Reactive Protein should be obtained emergently to rule out GCA. These markers may be elevated secondary to GCA, infection, malignancy, or autoimmune disorders such as rheumatoid arthritis. If a patient has a normal ESR and CRP, it is less likely that he has GCA. In approximately 20% of cases, patients with GCA can have a normal ESR or no systemic symptoms of GCA.
- If an ocular transient ischemic event is suspected, head and vascular carotid imaging is requested in emergency using Computed Tomography angiogram or Magnetic Resonance Image / Angiography and the evaluation of the intracranial circulation by transcranial Doppler is helpful to predict the risk of stroke in patients with severe carotid stenosis
- In patients with a preliminary negative work up, a trans-esophageal echocardiogram should be performed to look for cardiac sources of emboli and aortic arch atheroma
- In selected patients whose vascular and cardiac evaluations are negative, and especially in young patients who lack arteriosclerotic risk factors, other causes of TMVL as hypercoagulable state and autoimmune disease should be ruled out.

3. Vascular TMVL

The mechanism of vascular TMVL are emboli, hypoperfusion of the eye, vasculitis (often GCA), arterial vasospasm and venous congestion

- Retinal emboli most often result from lesions of the interval carotid artery that embolize material to the retinal circulation. Most commonly the symptom is a black or dark shade, spreading across the visual field of the affected eye and disappearing after few minutes. Emboli may be observed as they pass through the retinal arteries
- Hypoperfusion of the eye is seen in severe carotid stenosis and may be induced by situations that decrease perfusion pressure (postural change) or increase oxygen demand (exposure to bright light) or when blood flow is shunted elsewhere (exercise). It may be associated with longer and progressive TMVL with positive visual phenomena
- GCA is a cause of recurrent TMVL in subject older than 50 years old. Choroïdal hypoperfusion or less frequently ischemic anterior optic neuropathy may be diagnosed on fluorescein angiogram.

- Vasospasm of the central retinal artery is a diagnosis of elimination and most often affects young and healthy people with negative work up
- Central retinal vein occlusion may be preceded by episodes of TMVL, most often with only blurry vision. The episodes last longer than those with arterial ischemia.

4. Natural History

The natural history of TMVL varies depending on the age and the etiology, but there are 3 potentials risks after a vascular atheromatous TVML:

- Among patients with vascular TMVL resulting from severe internal carotid stenosis, the risk of irreversible visual loss (by central retinal artery occlusion) is estimated to be about 1% per year.
- The rate of cerebral infarction in patients with ICA stenosis of 50% or more is 10% at 3 years (vs 20.3% after cerebral transient ischemic attack). This risk increases with the degree if stenosis.
- The risk of vascular death (myocardial infarction) is about 4% per year.

4.- Treatment

- In vascular non arteritic TMVL, treatment addresses secondary prevention of ocular and cerebral infarction with treatment of vascular risk factors (high blood pressure, hyperlipidemia, and antiplatelet agents).
- Long term anticoagulation should be used for the prevention of stroke with patients with atrial fibrillation, other high risk cardiac sources of embolism and hypercoagulable states.
- Carotid endarterectomy should be considered in selected high risk patients with an ipsilateral ICA stenosis of 70 to 99%
- Giant cell arteritis is a therapeutic emergency to prevent irreversible visual loss and patients need immediate steroids treatment associated with antiplatelet agents

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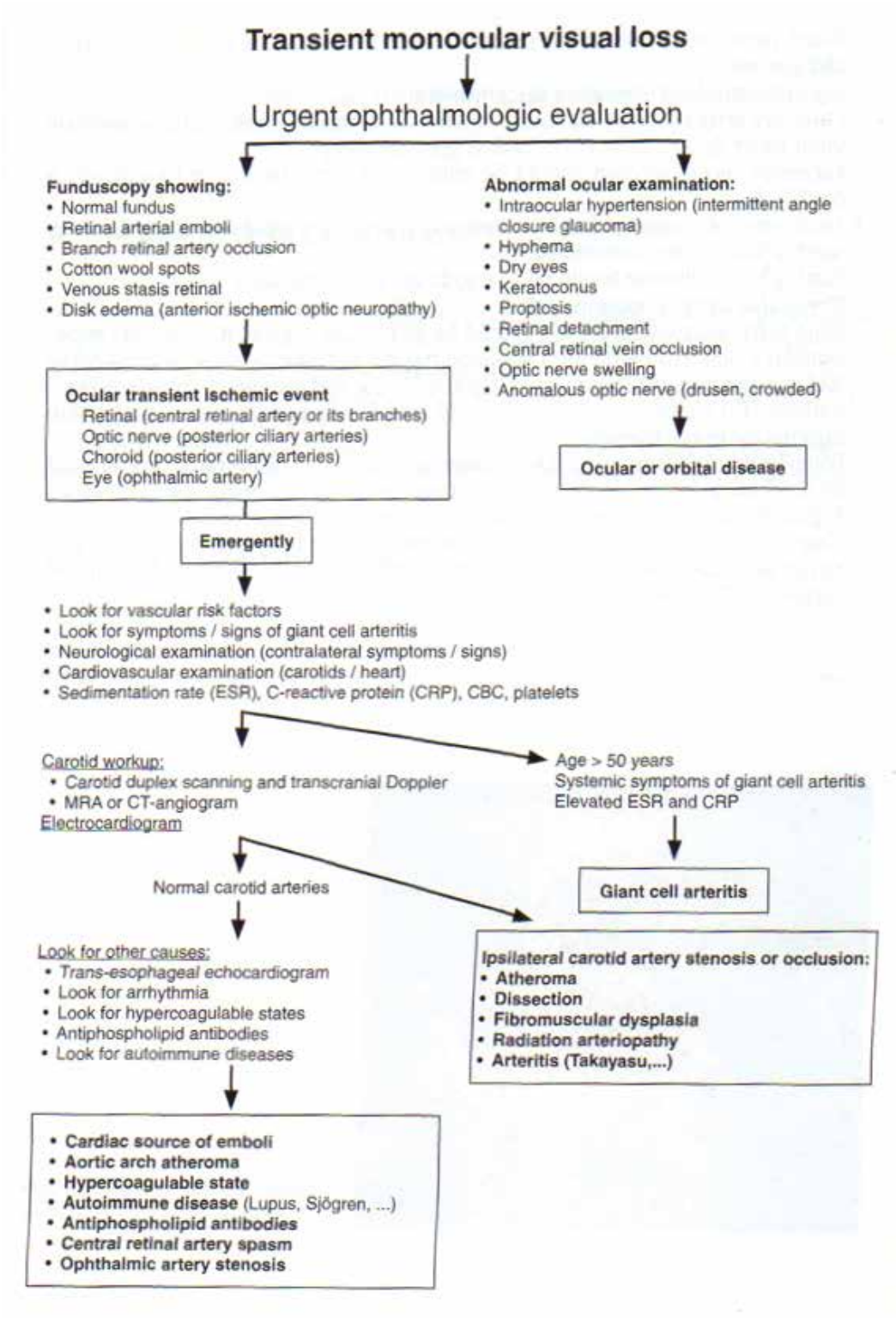

Figure 1

From V Biousse, NJ Newman. Neuro Ophthalmology illustrated Thieme 2009

MCQ answers page 90

1. Answer: d

The migraine typically progresses to a maximal deficit, usually affects both eyes and is accompanied by positive visual phenomena. Vertebro basilar insufficiency causes a transient homonymous hemianopia and Uhthoff phenomenon, often associated with increased body temperature is an unlikely disorder for a 75-year-old man. Retinal artery embolus produces acute, painless monocular visual loss that usually lasts for less than 5 minutes and has an altitudinal pattern

2. Answer: c

This 76-year-old woman has an history suggestive of GCA. Evaluation of the sedimentation rate and the C Reactive protein will support the diagnosis, which will be confirmed by a biopsy of the temporal artery The treatment with steroids is an emergency and should be initiated immediately

3. Answer: c

The association of a TMVL and a Horner syndrome in this young man supports the diagnosis of a carotid dissection with stenosis of the lumen and ocular hypoperfusion. Imaging of the carotid by CTA or MRA will confirm the diagnosis? The treatment by anticoagulation drugs must be initiated in emergency

MCQ's

1. Which of the following patients with AION is MOST likely to have GCA?

a. 51-year-old man with ESR of 35 mm/hr and pain when he opens his mouth
b. 64-year-old woman with CRP of 4 mg/L and a cup-to-disc ratio of 0.3
c. 66-year-old woman with a cotton wool spot near the temporal arcades
d. 72-year-old man with malaise, headache, and recent 10-lb weight loss
e. 51-year old man who had a recent flu shot

2. A 70-year-old woman experiences transient diplopia lasting seconds occurring several times over a week. She then notes sudden darkening of the vision OS and pain to move her left eye. Her visual acuities are 20/20 OD and 20/100 OS. She has an afferent pupillary defect OS. Her fundus examination looks completely normal. Which of the following is the MOST APPROPRIATE next step?

a. MRI orbit with gadolinium and fat suppression
b. Admit for high-dose intravenous corticosteroids
c. CT of the pituitary gland with gadolinium
d. Check serum NMO, ANA, ACE, RPR, TSI
e. Rule out syphilis

3. Which of the following findings is MOST suggestive of GCA in a patient with AION?

a. The choroid shows areas of nonfilling for 15 seconds
b. The cup-to-disc ratio is 0.4 in the fellow eye (some argue that 0.4 is clearly a non-crowded disc and is highly suggestive..maybe make the C/D smaller?
c. The visual acuity is Count Fingers in the affected eye
d. The patient is a 75-year-old white woman and proximal muscle pain
e. The optic disc edema is associated with hemorrhages and a macular star

Objectives

- Describe jaw claudication in great detail
- Identify patients at increased risk of GCA based on clinical signs and symptoms
- Recognize the diagnostic pitfalls in GCA

I. Demographics

Giant cell arteritis (GCA) is an inflammatory vasculitis affecting large and medium vessels. It affects older individuals (minimum age = 50 years) and the incidence (2 to 45 per 100,000) increases with age (average = 70 years). Women are affected more often than men (2:1) and Caucasians are much more likely to have GCA than pigmented individuals (30:1).

II. Clinical findings

Nonspecific symptoms of GCA include headache, scalp tenderness, weight loss, malaise, anorexia, fever, neck pain, and proximal muscle pain. Headache is the most common and often initial symptom. Additionally, it is unusual for the elderly to experience headache and this should raise suspicion. Jaw and tongue claudication are highly specific when present, but it is important that the clinician obtain an accurate history. The pain of claudication develops after prolonged chewing or talking and worsens as the patient continues. After stopping, the pain slowly resolves over minutes. The pain likely results from poor blood flow to the muscles of mastication. Pain that begins with jaw opening or biting down is not consistent with jaw claudication and may reflect TMJ or tooth issues.

Neuro-ophthalmic symptoms can include transient or persistent visual loss in one or both eyes, binocular diplopia, ptosis, and eye pain/headache. The most common presentation is visual loss. Permanent visual loss occurs in 20-50% of patients with GCA making prompt diagnosis and early intervention paramount. The most common cause of visual loss is anterior ischemic optic neuropathy (AION). Therefore, when making the diagnosis of AION in patients over the age of 50, the clinician must determine if this is non-arteritic (NAION) or arteritic (AAION) in etiology. About 5% of AION is due to AAION. Eyes with NAION and AAION can have any visual acuity, but eyes with AAION tend to have worse visual acuities (20/200 or worse at presentation in 60%). Rapidly progressive, severe, or bilateral visual loss are concerning for GCA. Eyes with NAION may have a cotton wool spot in the peripapillary area. However, cotton wool spots away from the optic nerve suggest retinal ischemia and raise strong

suspicion for AAION. Concomitant BRAO with AION requires investigation for GCA since this indicates involvement of the ophthalmic artery. Most eyes with NAION have a small cup-to-disc ratio in the fellow eye. Fellow eyes with a large cup should prompt an evaluation for GCA. Finally, when the optic disc edema is chalky white in color, this may indicate an arteritic cause.

About 5% of central retinal artery occlusions occur from GCA. Other causes of visual loss include posterior ischemic optic neuropathy, choroidal ischemia, and cortical stroke. Transient diplopia or amaurosis prior to visual loss should raise strong concern for GCA in the elderly patient. These transient deficits often occur hours to days before permanent visual loss.

GCA can also cause persistent binocular diplopia. The most common cause is ocular motor cranial nerve palsies. Brainstem ischemia may lead to a skew deviation or internuclear ophthalmoplegia. Orbital ischemia may damage individual or multiple extraocular muscles.

III. Diagnostic approach

The ophthalmologist should consider the patient's demographics and review of systems when evaluating whether a neuro-ophthalmic deficit results from GCA. There is no clear cut "formula" to make this determination. As a general rule, Caucasian patients with double vision or vision loss, who are older than 55-60 **with** symptoms suggestive of GCA, warrant closer evaluation. If the patient is over 65, then screening should be considered even in the absence of systemic symptoms.

Nonspecific markers of systemic inflammation include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count. These markers may be elevated secondary to GCA, infection, malignancy, or autoimmune disorders such as rheumatoid arthritis. Some normal individuals have elevated ESR and CRP as well. Many labs indicate a normal ESR as < 20 mm/hr but this may be an overly sensitive threshold. Most neuro-ophthalmologists use the general rule of thumb of a top normal ESR of age divided by 2 in men and (age + 10) divided by 2 in women. For example, the upper limit of normal for ESR is 35 mm/hr in men and 45 mm/hr in women. Normal values for C-reactive protein vary by laboratory as well, however many papers cite 0.5 mg/dL. It is important to keep in mind that some labs report CRP as mg/L (e.g. 0.5 mg/dL = 5 mg/L). There are less clear cutoffs for upper limit of normal in GCA. Some studies use 2x the normative value by the individual laboratory. Using the formula for ESR and a cutoff of 0.5 mg/dL, the sensitivity of ESR and CRP is

97%. Therefore, if a patient has a normal ESR and CRP, it is less likely that they have GCA. In approximately 20% of cases, patients with GCA can have a normal ESR or no systemic symptoms of GCA (labeled "occult GCA"). Thrombocytosis (platelet count > 400,000) can occur with inflammation. It is reasonable to include a CBC to assess platelets. Anemia can occur in GCA. It can also result in an artificially elevated ESR.

A fluorescein angiogram in patients with AION may show a delay in choroidal filling. Normally, the choroid fills completely within 3-5 seconds after choroidal filing begins. A significant delay is nearly pathognomonic for AAION.

Clinicians should consider temporal artery biopsy in patients suspicious for GCA. The biopsy specimen should be at least 2 cm in length to avoid missing the diagnosis, since the inflammation can "skip" areas of temporal artery. A small specimen that includes only the normal area of artery may show false negative results. A positive temporal artery biopsy is the gold standard for the diagnosis, but the sensitivity is approximately 87%. If the biopsy is negative and the suspicion for GCA remains high, then contralateral temporal artery biopsy may be considered. The increased diagnostic yield is approximately 5%. Some clinicians choose to forgo the second biopsy and treat based on clinical suspicion. Treatment with corticosteroids (discussed below) should not be delayed while the biopsy is being arranged. This will reduce the risk of further vision loss and will not confound results of the biopsy for 10-14 days.

IV. Acute Management

Nearly all agree that corticosteroids are the treatment of choice. However, there are no clear data on dosage. Many rheumatologists may use prednisone 20 mg daily while neuro-ophthalmologists use up to 1 mg/kg daily prednisone. GCA patients without visual loss may start with lower doses such as 40 mg/day. As a general rule, patients with visual loss suspicious for GCA should receive high doses of corticosteroids. Many neuro-ophthalmologists favor starting with intravenous solumedrol 250 mg four times daily. Some studies have shown benefit to intravenous vs. high dose oral corticosteroids while others have not. In the absence of clear data, oral prednisone 80-120 mg can be considered as well.

The systemic symptoms of GCA resolve fairly quickly over a few days. Visual improvement is less likely and is predicated on initiating steroids within 24 hours (58% improve vs. 6% after 24 hours) of symptom onset. Patients who begin steroids can suffer from worsening vision in either eye for the first 5 days. After this time period, visual loss is unusual in the acute stages of GCA.

V. Chronic management

Patients are often on at least 1 mg/kg/day of prednisone for the first month and slowly tapered over the course of one to several years. Prednisone is tapered in the absence of systemic symptoms and consistently normal ESR and CRP. Long-term side effects should be reviewed with patients, and an internist should manage these complications.

Steroid sparing agents have been studied extensively. The best-studied agent is methotrexate. There have been three randomized, placebo controlled, multicentered clinical trials comparing methotrexate/prednisone to placebo/prednisone. One study showed a significant reduction in cumulative steroid dose and relapse rate in the methotrexate group compared to placebo and two studies did not. Many rheumatologists continue to use methotrexate as an adjunctive medication to prednisone. There is no clear data on the benefit of other steroid sparing agents such as cyclosporine, dapsone, cyclophosphamide, etancercept, infliximab or rituximab.

Ischemic complications can result despite treatment with prednisone. A few retrospective studies have shown that antiplatelet agents reduce the risk of ischemic complications in patients with GCA. They did not appear to increase bleeding risk. It is reasonable to add aspirin to prednisone therapy for the long term treatment of GCA.

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MCQ answers page 98

1. Answer: c

The patients in A and E is quite young to have GCA. Although ESR is higher than his age divided by 2, it is a nonspecific marker. While jaw claudication is highly suggestive of GCA, the pain occurs with prolonged chewing rather than jaw opening. The patient in B has a normal CRP. Recall that the units vary with CRP and that normal for most labs is 5 mg/L or 0.5 mg/dL. Patients with AION and a cotton wool spot off the disc is concerning for two areas of ischemia from involvement of the ophthalmic artery. This should raise strong concern for GCA. The patient is female and in her mid-60s. The systemic symptoms of the patient in D are nonspecific for GCA. While they should prompt a workup, the patient in C is the most concerning for GCA.

2. Answer: b

The greatest concern here is that the patient has posterior ischemic optic neuropathy and that she will lose vision from giant cell arteritis. Older patients with PION who experience antecedent diplopia are very concerning for GCA. Other considerations on the differential diagnosis would include pituitary apoplexy and atypical optic neuritis. However, these entities can be managed initially with corticosteroids as well. The patient can be admitted for steroids and evaluated for GCA with ESR, CRP, and temporal artery biopsy. If these are negative, then an MRI of the orbit and chiasm, would be reasonable. A laboratory workup for atypical optic neuritis may be warranted if the MRI shows enhancement of the optic nerve.

3. Answer: a

On fluorescein angiography, the choroid typically fills completely within 3-5 seconds. A significant delay in choroidal filling is nearly pathognomonic for GCA. Most patients with NAION have a small cup-to-disc ratio and this should raise some suspicion but this is not as concerning as the patient in A. Nearly any visual acuity can be seen with NAION. Patients who are LP or NLP should be very concerning for GCA. Although patients with GCA are twice as likely to be women and overwhelmingly white, this is a nonspecific demographic.

Acute diplopia: third nerve palsy

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14

MCQ's

1. Third nerve palsy may be associated with each of the following EXCEPT:

a. Tremor
b. Fever
c. Hemiparesis
d. Headache
e. Nystagmus

2. The pupil in third nerve palsy may have each of the following characteristics EXCEPT:

a. May be large and unreactive
b. May be small and unreactive
c. May be used to determine whether a patient needs a scan
d. May constrict on attempted adduction
e. May be normal

3. Which of the following investigations is not relevant in a suspected case of third nerve palsy?

a. Urea and electrolytes
b. Erythrocyte sedimentation rate and CRP
c. Cerebrospinal fluid analysis
d. CT angiogram
e. Acetylcholine receptor antibodies

Newly-presenting acute third cranial nerve palsies (3NP) are usually easy to diagnose, but require careful clinical evaluation and investigation so as not to miss important causes that are potentially dangerous.

Anatomy

The third cranial nerve is one of the largest cranial nerves and is traditionally divided into five regions. (1) *Nuclear:* the cell bodies lie in a complex of sub-nuclei in the upper midbrain ventral to the aqueduct at the level of the superior colliculi. (2) *Fascicular:* their axons travel ventrally through the tegmentum of the midbrain passing through the red nucleus and the corticospinal tracts. (3) *Subarachnoid:* as the nerve passes anteriorly in the subarachnoid space it lies in close proximity to several arteries. (4) *Cavernous:* the third nerve passes forwards in the wall of the cavernous sinus where it lies close to cranial nerves 4, 5 and 6, the sympathetic nerves and the internal carotid artery. *(5) SOF/orbital:* the third nerve enters the orbit within the common tendinous ring and immediately divides into a superior division (supplying the levator palpebrae superioris and superior rectus muscles) and inferior division (supplying the medial and inferior rectus muscles, the inferior oblique muscle, and preganglionic parasympathetic fibres that terminate in the ciliary ganglion and convey motor signals destined for the ciliary and iris sphincter muscles within the eye).

Diagnosing 3NP

A complete 3NP is easily recognised, comprising a complete ptosis, an eye that is exotropic ('down and out') and only able to abduct, and a large unreactive pupil. However, in many cases the 3NP is *incomplete*: for example, there may be only partial ptosis, or the pupil may be 'spared'. If the 3NP is longstanding and associated with a compressive lesion then there may also be signs of *aberrant regeneration*, eg lid elevation on attempted downgaze (pseudo-von Graefe's sign). It is important to determine whether the 3NP is an 'isolated' sign or associated with other neurological deficits; easily missed examples of '*3NP Plus*' syndromes include contralateral hemitremor (Benedikt's syndrome), ipsilateral Horner syndrome (HS) or trigeminal neuropathy (5NP), and fever (suggesting an infective aetiology). Careful clinical evaluation enables detection of these additional signs and directs the investigations towards the likely site and nature of the underlying pathology. The differential diagnoses that need to be considered for external ophthalmoplegia and ptosis include myasthenia, carotid-cavernous fistula, giant cell arteritis and CPEO; and for internal ophthalmoplegia include exposure to antimuscarinic drugs and acute Holmes-Adie syndrome.

Causes of 3NP

Intrinsic brainstem pathology such as CVA, MS or gliomas may cause nuclear or fascicular 3NP – but usually present to neurologists rather than ophthalmologists and there will be other deficits/signs. In the subarachnoid space, 3NP are often isolated, pupil-involving, and may present initially to ophthalmologists; importantly, these cases may be associated with aneurysms or other structural/compressive lesions and need careful imaging studies. An acute subarachnoid 3NP may also be an important early sign of uncal herniation, and neuro-obs therefore routinely include monitoring of pupil size/reactivity, but these patients are usually moribund and under the care of neurosurgeons so ophthalmologists are not involved in this aspect of their care. In the cavernous sinus, 3NP are often caused by compressive lesions such as aneurysms or tumours and usually there are additional 'localising' deficits such as HS or 5NP. SOF or orbital 3NP may have an inflammatory, infective, vasculitic or neoplastic aetiology and is usually associated with proptosis or other signs of orbitopathy. In the paediatric population 3NP may be an isolated relapsing-remitting condition and associated with severe headache; the cause is still debated, but it is usually self-limiting and rarely persists into adulthood. In older adults, an isolated 3NP may be caused by ischaemia; traditionally these 3NP were said to be pupil-sparing due to the close proximity of the superficially-located parasympathetic fibres to the pial vessels, but in practice this sign is unreliable and cannot be used to exclude a more dangerous aetiology such as an aneurysm.

Investigating 3NP

The most dangerous condition likely to present to ophthalmologists with isolated 3NP is an aneurysm – often of the posterior communicating artery, although other arteries may be involved – and because there are no symptoms or signs that allow this possibility to be excluded with absolute confidence, all patients with an acute 3NP need emergency admission to hospital, neuro-obs and targeted imaging studies (each hospital will have its own protocols for detection of aneurysms). Most 'surgical' causes of 3NP will be detected by appropriate imaging, and 'medical' causes by careful examination and systemic work-up. Cases of isolated 3NP with normal imaging/pathology results in patients over 50 years old are most commonly ischaemic/microvascular in aetiology and are likely to resolve spontaneously within 8-10 weeks, often with full recovery.

Useful References

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MCQ answers page 104

1. **Answer: e**

2. **Answer: c**

3. **Answer: a**

Acute anisocoria: aneurysm vs Horner syndrome

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15

MCQ's

1. **The most likely diagnosis of a large dilated pupil that does not constrict to 1% pilocarpine is:**

   a. tonic pupil
   b. Horner syndrome
   c. oculomotor nerve palsy
   d. atropinized pupil
   e. migraine

2. **Which clinical finding is not consistent with oculomotor nerve palsy?**

   a. ptosis
   b. sectoral palsy of the iris sphincter
   c. poor pupil light reflex
   d. limitation of infraduction
   e. limitation of adduction

3. **The most constant feature of Horner syndrome is**

   a. hemianhidrosis
   b. anisocoria greater in darkness
   c. cholinergic denervation supersensitivity
   d. ptosis
   e. red eye

Objectives

- To recognize and distinguish pupil disorders due to parasympathetic vs sympathetic defects.
- To recognize and distinguish the clinical syndrome of preganglionnic and postganglionnic parasympathetic defects.
- To recognize anisocoria due to pharmacologic manipulation.

The pupil size is determined by the sum of active sympathetic and parasympathetic input to two iris muscles, the radial dilator and the sphincter. Thus unequal pupil size implies an asymmetry in the neuromuscular forces of the iris. Anisocoria is never due to visual loss.

A mechanical anisocoria is due to ocular pathology such as trauma, infection, intraocular surgery, laser treatment or pseudoexfoliation. These conditions can damage one or both iris muscles (radial dilator and iris sphincter). Thus, structural iris defects can lead to a small pupil that does not dilate well or a large pupil that does not constrict well. A slit lamp examination should be adequate for identifying most causes of mechanical anisocoria. Clues that iris damage is the cause of anisocoria include distortion of the pupillary shape, iris transillumination defects, synechiae, intraocular inflammation and pigment dispersion.

A Large, Poorly Reactive Pupil

When testing the light reflex, if the larger pupil reacts poorly to light (indicating sphincter impairment) compared to the smaller pupil, then the larger pupil is the abnormal pupil, i.e. the iris sphincter dysfunction. In this situation, the magnitude of anisocoria will be greater in bright room lighting compared to dim light. The 3 most common conditions of a large, poorly reactive pupil are an oculomotor nerve palsy, a tonic pupil or a pharmacologically dilated pupil.

The neurologic basis for a large, poorly reactive pupil is interruption of pupilloconstrictor impulses to the iris sphincter. The oculo-parasympathetic pathway that mediates pupilloconstriction is a 2-neuron pathway. The pre-ganglionic neurons lie in the Edinger-Westphal subnuclei of the oculomotor nuclear complex in the dorsal midbrain. Their axons (the pre-ganglionic parasympathetic fibers) join the motor fibers to form the oculomotor nerve and exit into the subarachnoid space. Passing through the anterior cavernous sinus into the orbit, these parasympathetic fibers follow the

inferior division of the 3rd nerve before they synapse in the ciliary ganglion located just behind the globe. From the ciliary ganglion, post-ganglionic parasympathetic fibers are carried in the short ciliary nerves to innervate the iris sphincter and ciliary muscle. The neurotransmitter at the iris sphincter muscle is acetylcholine.

1/ Oculomotor nerve palsy

Interruption of parasympathetic innervation of the sphincter can occur at any point from midbrain to orbit. Lesions of the pre-ganglionic segment, in addition to pupillary fiber damage, almost always involve one or more motor fibers of the oculomotor nerve. Thus when a large, poorly reactive pupil is found, it is important to look very closely for lid or motility deficits. Testing ocular ductions alone is not sufficient; cross-cover testing, particularly in upgaze and in adduction, or formal orthoptic testing with Hess Weiss screen is mandatory to reveal any subtle motility deficits. Formal measurements of lid position and levator function should be noted. With rare exception, anisocoria NOT accompanied by ptosis or ocular motility disturbance is NOT an oculomotor nerve palsy.

The features of an oculomotor nerve palsy are summarized below:

- The pupil is large and responds poorly to light and near stimulation. There is no light-near dissociation.
- The pupil constricts vigorously to full-strength (1% to 4%) pilocarpine. It may also constrict well to dilute 0.125% pilocarpine due to denervation supersensitivity.
- An ipsilateral ptosis is usually present.
- An ocular motility disturbance (infraduction, supraduction and/or adduction deficit) is present on the side of the large pupil.
- Sometimes only 1 or 2 motor functions are disturbed, for example, an oculomotor nerve palsy with only ptosis and supraduction deficit.

An acute oculomotor palsy represents a neurologic emergency because it may be the initial sign of an expanding or ruptured intracranial aneurysm. Pain is a common symptom and a large, poorly reactive pupil on the side of the aneurysm is seen in 90% of patients. Impairment of levator palpebrae or ocular motor function is nearly always present as well. Such patients are often evaluated initially in the ophthalmologist's office because of headache, anisocoria and diplopia. Appropriate imaging studies are advised without delay. In contrast, acute unilateral pupillary dilation as a sign of cerebral herniation does not occur as an isolated clinical finding. Such patients are typically comatose with multiple neurologic deficits.

2/ Tonic pupil

A tonic pupil represents a lesion in the post-ganglionic parasympathetic pathway, i.e. in the orbit. The initial injury occurs either at the ciliary ganglion or the short ciliary nerves, resulting in acute denervation of the iris sphincter and ciliary muscle. Acutely, patients complain of a dilated pupil, photophobia and blurring of near vision. As the denervation injury is typically incomplete, sectoral (focal) palsy of the iris sphincter is detectable by observing each clock-hour segment of the iris sphincter under high magnification at the slit-lamp. In the absence of structural iris damage, the presence of sectoral sphincter palsy is diagnostic of post-ganglionic oculo-parasympathetic damage. Denervation supersensitivity to cholinergic agonists develops within several days to weeks.

Following acute denervation injury, the short ciliary nerves tend to re-sprout and re-connect. However the short ciliary nerves contain many more accommodative fibers than pupilloconstrictor fibers and so, the sphincter becomes re-innervated mostly by accommodative fibers, i.e. aberrant re-innervation. This leads to recovery of the pupillary near response while the light reflex remains poor, a finding called light-near dissociation. Furthermore the recovered pupillary movement, during constriction and re-dilation, is slow and tonic. Most cases of unilateral tonic pupil are idiopathic, called Adie's pupil, occur in women aged 20 and 50 years, and do not require neuroimaging.

The features of a tonic pupil are summarized below:

- A "freshly denervated" pupil (acute tonic pupil) is very large and poorly responsive to both light and near stimulation.
- The pupil light reflex may appear to be completely absent. However even in the acute stage of denervation, under careful slit-lamp examination, sectoral sphincter palsy alternating with segments of preserved contraction is present.
- After several days to weeks, the denervated pupil demonstrates pharmacologic hypersensitivity to a dilute cholinergic agonist (denervation supersensitivity).
- After several weeks to months, light-near dissociation develops as the pupillary near reflex recovers to a greater extent than the pupil light reflex.
- The velocity of pupilloconstriction to a near stimulus is now slow and sustained, called "tonic". The re-dilation after near constriction is also tonic.
- After several months to years, a chronic tonic pupil often becomes smaller than the normal pupil due to tonic firing in the accommodative fibers innervating the sphincter. It still demonstrates a poor light response, sectoral palsy, light-near dissociation and tonicity.

Dilute pilocarpine (0.125% or less) is the most popular pharmacologic agent used to test for cholinergic denervation supersensitivity of the sphincter. Cholinergic supersensitivity is not specific for tonic pupil (it can be present in a dilated pupil due to oculomotor nerve palsy) and its absence does not rule out tonic pupil (about 80% sensitivity). A pharmacologically-dilated pupil never shows cholinergic supersensitivity.

3/ Pharmacologic mydriasis

Topical mydriatic agents can be divided in to two categories: parasympathetic inhibitors (anticholinergic substances) and sympathomimetics. Products containing atropine-like, anticholinergic substances include scopolamine patch, certain insecticides, plant-based belladonna alkaloids such as Jimson weed, and anticholinergic inhalants used to treat respiratory disease. A pupil dilated by an anticholinergic substance, e.g. an atropinized pupil, is enormously large (8-9 mm) and non-reactive to light and near stimulation. It is distinguished from an acutely denervated pupil by the absence of sectoral palsy and unresponsiveness to full-strength pilocarpine eyedrops.

Sympathomimetics are adrenergic-like substances that cause pupillary dilation by excessively stimulating the dilator muscle but they do not paralyze the sphincter muscle. Thus, the pupil retains a light reflex though it has less amplitude compared to the normal pupil AND may constrict rather well to full-strength pilocarpine. Mydriasis from a sympathomimetic agent can be suspected from conjunctival blanching and lid retraction in the eye with the larger pupil. Examples include epinephrine, phenylephrine, ephedrine, hydroxyamphetamine, cocaine, ocular decongestants and adrenergic inhalants. Even in patients using eyedrops in both eyes, asymmetric absorption can lead to anisocoria.

Normal Pupillary Light Reflex and Anisocoria Greater in Darkness

If the patient with anisocoria has a normal pupillary light reflex in both eyes, then the oculo-parasympathetic system is intact. In such a case, anisocoria is often more noticeable in dim lighting than in roomlight. The 2 most common conditions of this scenario is Horner syndrome and physiologic anisocoria.

1/ Horner syndrome

Horner syndrome is due to interruption of sympathetic innervation to the head and eye and results in miosis, ptosis and facial anhidrosis on the side of the lesion. The ptosis is typically mild and involves both the upper and lower lid, due to superior and inferior tarsal muscle weakness. However, absence of ptosis occurs in 12-13% of patients with Horner syndrome. Facial anhidrosis is seldom reported by patients. Thus an anisocoria may be the only complaint or sign of an oculo-sympathetic defect. The sign that differentiates the anisocoria from Horner syndrome from physiologic anisocoria is dilation lag of the smaller pupil in darkness. When the roomlight is abruptly turned off, the pupil with an oculosympathetic defect shows slow and delayed dilation over 15-20 seconds compared to the normal pupil which promptly re-dilates back to baseline within 3-5 seconds. This finding is diagnostic for Horner syndrome but is demonstrable in only about 50% of patients. Therefore, practical diagnosis of Horner syndrome usually requires a pharmacologic test. Currently, two agents are used for this purpose: cocaine and apraclonidine. Note: apraclonidine is not used in children due to potential cardiorespiratory depression.

Occasionally, a patient with a mechanical anisocoria is confused with a Horner syndrome because the restricted pupil also exhibits impaired dilation in darkness and dilates poorly to cocaine. Slit lamp examination should reveal iris abnormalities like synechiae, pigment dispersion or traumatic changes that are limiting the extent of pupillodilation. Pharmacologic testing with 10% epinephrine is helpful because a Horner pupil will dilate the same or more as the normal pupil but a mechanically restricted pupil cannot dilate.

It is beyond the scope of this handout to discuss pharmacologic localization and investigation of Horner syndrome but 2 points must be emphasized. First, an acute and painful Horner syndrome is a neurologic emergency as it may be the first sign of acute carotid dissection. Immediate imaging is advised. The risk of embolization to the eye or brain is highest in the first 2 weeks of dissection and early anticoagulation is often recommended. The second point is that any new ptosis or anisocoria in a child must be thoroughly investigated. A Horner syndrome may be the initial manifestation of a neuroblastoma.

2/ Physiologic anisocoria

Both pupils dilate equally in darkness. No other related ocular or neurologic abnormalities are present. The anisocoria is usually about the same in bright light and in darkness, though sometimes it is more notable in darkness, creating confusion with Horner syndrome. This is even more confusing if the patient with physiologic anisocoria has levator dehiscence causing ptosis on the same side as the smaller pupil. Pharmacologic testing will differentiate physiologic anisocoria from Horner syndrome.

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MCQ answers page 109

1. Answer: d

1% (or higher) concentration of pilocarpine is a powerful direct stimulant to the iris sphincter muscle. Denervated or not, the sphincter will contract (pupil constricts) to 1% pilocarpine UNLESS the muscle receptors are blocked pharmacologically or the muscle itself is damaged.

2. Answer: b

Sectoral palsy of the iris sphincter is a sign of either postganglionic parasympathetic denervation or direct sphincter muscle damage.

3. Answer: b

A Horner syndrome is an interruption in the sympathetic pathway to the head and eye. The postganglionic receptors assessed for denervation supersensitivity in Horner syndrome are adrenergic in, not cholinergic.

Acquired cranial nerve palsies
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16

MCQ's

1. Which of the following statements for acquired eye muscle paresis is true?

a. In children the most important therapeutic goal is to restore binocular vision.
b. The diagnostic work-up in an eye muscle paresis include MRI and CT-Angiography
c. An eye muscle paresis always manifests with diplopia
d. Diplopic complaints always point to an eye muscle palsy
e. A prism shpuld only be used in elderly patients

2. In an congenital fourth nerve palsy, a typical finding is

a. a head tilt to the shoulder of the involved side
b. torsional nystagmus
c. torsional diplopia
d. vertical diplopia
e. an associated RAPD

3. Which of the following clinical signs/symptoms is not typical for an acute acquired palsy

a. incomitance of deviation
b. diplopia
c. head tilt
d. restriction of eye motility opposite to the field of action of the paretic muscle
e. confusion

Clinical signs and symptoms

Clinical signs and symptoms of an eye muscle paresis depend on the type of paresis, the underlying cause the letter one being responsible for addtional signs and symptoms, the age of the patient and whether the paresis is acquired or congenital.
When evaluationg an eye muscle paresis, one must always perform a complete neuroophthalmological exam the result of which is crucial for the diagnostic work-up and management.
An acute deviation from eye alignment usually causes **binocular dipopia**, which is the most prominent symptom of an acquired eye-muscle paresis and **visual confusion**. The diplopia increases in the field of action oft he paretic muscle. Visual confusion is usually not reported as such, but may subjectively be experienced as ‚*vertigo*', and difficulties of orientation especially in acquired IVth nerve palsies. If in the setting of a misalignment of the eyes the two perceived images are close together, the patient rather reports ‚**blurred vision**' instead of having ‚diplopic complaints'.

A **head turn or tilt** in order to compensate for a misalignment may be present.

The ocular misalignment oft he eyes is greatest in the field oft he paretic muscle and smallest or even absent in the contralateral field of action. This difference of misalignment is called incomitancy, which is a hallmark of an eye muscle paresis.

One must be aware, that in children, oculomotor palsy related symptoms can be of very short duration or completely lacking due to the **child's ability to suppress** the perceived image of the devitaed, non-fixating eye. In children a short lasting blinking on one side could be the only symptom.of an acute eye muscle palsy.

Acquired VIth nerve palsy

Symptoms and signs

- horizontal diplopia at far > at near.
- Limitation of abduction oft he involved eye
- head turn in the direction oft he involved eye
- esodeviation is greatest at far and in the direction of the affected eye (far-near incomitancy and right left incomitancy).In bilateral symmetric VIth nerve palsy there is a hughe far-near incomitancy and a bilateral abduction deficit without right-left incomitancy.
- Slowing of abducting saccades as compared to adducting saccades oft he affected eye

Additional clinical signs and symptoms depend on the location of the palsy and the involvement of neighbouring structures.
Pons lesions (Neoplasms, inflammatory, demyelinating,vascular etiologies, other):
Lesions of the abducens nerve fascicle often coexist with a lesion oft he VIth nucleus (which manifests as a horizontal gaze palsy)
-ventral pontine lesion *Millard-Gubler-Syndrome*): VIth nerve palsy, ipsilateral peripheral facial palsy, contralateral hemiplegia (tractus corticospinalis)
Dorsal pontine lesion (*Foville syndrome*): ipsilateral N.V, N.VI N.VII-palsy with additional loss of taste, ipsilateral Horner syndrome, and contralateral weakness is called

Lesions in subarachnoid space (Trauma, infection, inflamamtory conditions, Neoplasm, Aneurysm, Subarachnoid henorrhage).

The abducens nerve exit the brainstem at the ponto-medullary junction entering the subarachnoid space at the cerebellopontine angle. It ascends the clivus, enters the Dorello canal, runs over the petrosus apex before entering the cavernos sinus, It is attached to the pons by the anterior inferior cerebbellar artery. and to the skull base at the level oft he Dorello canal. Therefore is is vulnrable to any stretching e.g. caused by a downward displacement oft he brainstem (Supratentorial mass, hydrocephalus, Chiari-malformation) increased intracranial pressure.

Lesions at the cavernos sinus: Thrombosis, parasellar tumors, Neoplasms, Fistulas, Granunolmatous processes

Diagnostic work-up:

Every patient with a VIth nerve palsy needs a neurological evaluation including the first eight cranial nerves and the oculosympathetic pathway
In patients over 60 or patients over 50 with known vasculopathic risk factors and acute onset oft he VIth nerve palsy without any other abnormality,: clinical exam and blood test (CRP, BSR to rule out possible vasculitis. Patients should be reexamined and reassesed every two weeks. If the paresis worsens or if there are any additional symptoms and if the paresis persists after three months: MRI oft the brain and the orbit with MRA or CT-Angiography should be performed.
Every patient without vasculopathic risk factors or younger than 50 years of age: Complete Neurologic exam and Neuroimaging as stated above.

Congenital VIth nerve palsy

An isolated congenital VIth nerve palsy is extremely rare. Usually a Duane Syndrome or an infantile esotropia with bilateral abduction deficit are the underlying causes of an esotropia with abduction deficit. The underlying cause of a congenital VITh nerve palsy may be a birth trauma. The prognosis in terms of regeneration is usually good.

IVth nerve palsy

A IVth nerve palsy may be acquired or congenital. It is the most frequent cause of vertical diplopia in adulthood.
An acute acquired IVth nerve palsy manifests with vertical and sometimes torsional diplopia which increses in downgaze. The vertical diplopia may be worse in adduction and downgaze of the affected eye. In contrast to this patients with a congenital IVth nerve palsy never have torsional diplopia. Their diplopic complaints worsen in adduction oft he involved eye.
In the acquired condition a trauma as the underlying cause is much more frequent than neoplasms, inflammations and other causes due to the long intracranial cause of the nerve.
In patients over 60 years of age with a monosymptomatic fourth nerve palsy who belong the the ,'vasculopathic risk group' short term follow-up combined with a complete reassessment oft he neurologic condition at every appointment is mandatory. Neuroimaging including lumbar puncture are warranted if there is any additional symptom or clinical sign or if the paresis does not improve after 3 months. Clinical signs that point to the midbrain as location of an aquired IVth nerve palsy is a relative afferent pupillary deficit without optic nerve dysfunxtion and a central Horner-Syndrome.
The clinical picture of both, the acquired and the congenital condition have some similarities, however, it is usually possible to distinguish between both conditions on clinical grounds.
This distinction is important since neuroimaging is required in an acquired IVth nerve palsy whereas it is not mandatory in patients with a congenital IVth nerve palsy.
In addition one must wait at least one year before surgery in an acquired paresis wheras surgery could be performed right away in a congenital fourth nerve palsy

Differential diagnosis of acquired and congenital IVth nerve palsy on clinical grounds

	aquired	**congenital**
diplopia:	always present vertical and torsional	may be present if present always vertical
onset of symptoms :	sudden	gradual
complaints:	vertigo, difficulties in orientation	asthenopic complaints
ocular deviation:	hardly visible	always obvious
head tilt:	conciously made to avoid diplopia	patients usually not aware of a head-tilt
Bielschowsky manouver:	positive in downgaze	positive in down-and upgaze
vertical deviation:	incomitant, VD in adduction.: 5-10°	concomitant VD in adduction: 10-15°
excyclotropia:	upgaze 1 -5-°, downgaze 5 - 10°	concomitant, 3-5°
field of binocular fusion and field of diplopia	horizontal	vertical
seperated by	line	line

It has been shown that a congenital abesence of the fourth nerve in association with a hypoplasia oft he suprior oblique muscle may be the underlying cause in many cases of a congenital fourth neve palsy. In addition a abnormal insertion of the superior oblique tendon with or without lacking fourth nerve is found in some patients with congenital fourth nerve palsy. Children with more or less symmetrical bilateral congenital IVth nerve palsy do not have a head tilt. They have subnormal binocular

vision and an abnormal retinal correspondance with an excclorotation of both eyes that may be obvious on funduscopy.
The clinical picture of a fourth nerve palsy is found in patients with abnormality of the anatomy oft he orbits like in M. Crouzon.

Therapeutic management of acquired and congenital palsies include therapy/ prevention of diplopia by patching or a vertical prism. Sometimes the head tilt suffices to avoid diplopia in the principal gaze directions. Surgery is beneficial in many cases and could be performed when no regeneration of the (aquired) paresis may be expected, e.g. after 12 months.
Congenital fourth nerve palsies could be treated right away without neuroimaging or further investigation.

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MCQ answers page 117

1. **Answer: b**

2. **Answer: d**

3. **Answer: d**

Congenital cranial dysinnervation disorders

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17

MCQ's

1. Duane syndrome

a. Affects more frequently the right eye
b. Is characterized by retraction of the globe in abduction
c. Up- or downshoots can occur in abduction
d. Is more frequent in women
e. Is caused by absence or hypoplasia of the IIIrd cranial nerve

2. Surgical treatment of Duane syndrome

a. Is mandatory in most patients
b. Is contra-indicated in patients with strabismus in primary position
c. Consists mostly in muscle resections
d. Allows restoration of normal eye movements
e. Is indicated if a large face turn is present

3. Congenital Brown syndrome

a. Is always caused by embryonic remnants impairing tendon movements through trochlea
b. Is characterized by an elevation deficit which is maximal in adduction
c. Should be operated as early as possible because spontaneous improvement is very rare
d. Is much rarer than inferior oblique muscle palsy
e. Is often associated with divergence in downgaze producing an "A pattern" strabismus

Objectives

- Overview of the various types of congenital cranial dysinnervation disorders
- Duane syndrome
- Brown syndrome

Congenital cranial dysinnervation disorders (CCDDs) result from abnormal neuronal development, and share common features of dysinnervation to the ocular and facial musculature.

In most of these disorders, absent or deficient innervation results in extraocular muscle hypoplasia and fibrosis causing limitation and restriction of ocular rotations. In addition, neuronal misinnervation frequently develops and induces distinctive combinations of synkinetic eye movements (table 1).

Duane retraction syndrome

Duane retraction syndrome (DRS), **the most common** CCDD, is a congenital ocular motility disorder that arises from deficient VIth cranial nerve (CN) innervation to the lateral rectus (LR) muscle causing anomalous innervation from the medial rectus (MR) muscle (branch of IIIrd CN).

DRS accounts for 1 %–4 % of strabismus cases. It is mostly **sporadic** (90%), more common in **females** (60%), and preferentially affects the **left eye** (60%); 20% of cases are bilateral.

Clinical features

The anomalous innervation produces co-contraction of both horizontal rectus muscles and a striking retraction of the globe on attempted adduction (causing narrowing of the palpebral fissure), as well as possible up- or downshoot in adduction due to "retraction escape". Palpebral fissure can widen during attempted abduction.

Most patients achieve binocular vision through compensatory head turn. Amblyopia is uncommon.

Huber's classification defines three main groups depending on eye motility (table 2).

Differential diagnosis

• VIth CN palsy:

- no globe retraction in adduction
- no up- / downshoot in adduction
- larger esotropia in primary position, concordant with limitation of abduction (DRS: small esotropia despite large abduction impairment)

Associated anomalies (15-33%): some frequent associations:

- ocular: heterochromia, coloboma, nystagmus, epibulbar dermoid, ptosis
- systemic: deafness, Goldenhar syndrom, heart / vertebral abnormalities

Etiology

Compensatory innervation to a paretic lateral rectus muscle (LR) by an extra branch of the IIIrd CN, causing co-contraction of both horizontal rectus muscles (Hoyt and Nachtigael 1956).

- electromyography: paradoxical innervation of the LR.
- histopathology: absence of the VIth CN, hypoplasia of the corresponding portion of the VIth CN nucleus, and misinnervation of the LR from fibers of the IIIrd CN.
- orbital magnetic resonance imaging (MRI): normal size of the LR (= trophic effects of anomalous innervation by IIIrd CN), absence of VIth CN, misinnervation of the LR by fibers of IIIrd CN.
- dynamic orbital MRI: diameter of LR remains constant in adduction and abduction (= does not relax during adduction as it should).

Cause of DRS is unknown, and could be various:

- genetics *(only 10% of cases are familial)*: CHN-1 (encodes alpha2-chimaerin = signaling protein implicated in neuronal development), SALL4, HOXA1
- teratogens: thalidomide
- thromboembolism within the carotid territory occurring in utero

Management

- Surgery does not correct the underlying innervation abnormality, thus does not normalize eye motility!
- Most patients do not require surgery because they can compensate well with a mild degree of head positioning

- Surgical indications:
    - **large face turn**
    - strabismus in primary position
    - marked globe retraction
    - large up- / downshoots
- Main surgical strategies: prefer recession to avoid increased retraction!
    - convergent strabismus in primary position, compensatory face turn in ADduction of the involved eye → **MR recession**
    - divergent strabismus in primary position, compensatory face turn in ABduction of the involved eye → LR **recession**
    - very large globe retraction, very large up-/ downhoot → MR + LR **recession**

Brown syndrome

Brown syndrome is characterized by restriction of active and passive elevation in adduction. It can be congenital or acquired, constant or intermittent, and results from multiple pathologies affecting the tendon, trochlea, or innervation of the superior oblique (SO) muscle.

Brown syndrome is estimated to represent 1/450 strabismus. When congenital, it is more frequent in **women** (55%), and preferentially affects the **right eye** (53%; left eye 38%; bilateral 9%).

Clinical Findings

(1-6 must be present for definitive diagnosis) *(Wilson et al. 1989)*

1. Deficient elevation in adduction
2. Less elevation deficiency in midline
3. Minimal or no elevation deficit in abduction
4 Minimal or no superior oblique overaction
5. Divergence in upgaze producing a "V" pattern
6. Positive forced duction testing
7. Downshoot in adduction
8. Widened palpebral fissure on adduction
9. Anomalous head posture
10. Primary position hypotropia

Differential diagnosis

- Double elevator palsy (monocular elevation deficiency): same deficient elevation in adduction, primary position, and abduction; ± ptosis; ± hypotropia in primary position (PP)
- Inferior oblique muscle palsy: much rarer than Brown syndrome; look for other signs of IIIrd CN palsy, namely pupillary involvment; incyclorotation, A pattern, ± hypotropia in PP, ± SO overaction, normal forced duction test
- Primary SO overaction: downshoot in adduction, A pattern, incyclotorsion, normal forced duction test
- Congenital fibrosis of the extraocular muscle (namely inferior rectus): frequent ptosis, frequent A pattern
- Orbital blow-out fracture with muscle entrapment
- Thyroid orbitopathy
- Myasthenia gravis

Etiology

1. Congenital Brown syndrome

The same clinical pattern of "congenital Brown syndrome" can probably result from various abnormalities (Figure 1):

A. SO tendon anomalies between trochlea and the eye
B. Embryonic remnants impairing tendon movements through trochlea
C. SO muscle/tendon anomaly posterior to the trochlea
D. SO misinnervation (CCDD): absence of the IVth CN → misinnervation of the SO muscle by IIIrd CN fibers → co-contraction of SO and inferior oblique and/or medial rectus muscle.

Figure 1. Causes of congenital Brown syndrome (see text).

Spontaneous resolution of congenital Brown syndrome has been reported in 21-75% of cases, probably due to either growth of involved structures, or repetitive elevation of the eye caused by superior rectus muscle contraction.

2. Acquired Brown syndrome

- Can result from any lesion of the tendon, muscle or trochlea of the superior oblique: inflammation, trauma, SO muscle surgery.
- Often intermittent, can be transient (resolving spontaneously or after medical treatment)
- Inflammatory forms can present as a "click" syndrome, in which the tendon is intermittently prevented from passing through the trochlea, causing an alternation between superior oblique palsy, Brown syndrome, and normal motility.

Management

- Congenital cases should be observed because possibility of spontaneous improvement.
- Acquired cases in which an inflammatory cause is suspected should be treated by systemic anti-inflammatory therapy or steroid injections into trochlear area.
- Main surgical indications:
    - o large compensatory head position
    - o strabismus in primary position
    - o diplopia in primary position or downgaze.
- Surgery:
    - o often involves SO weakening procedures
    - o with or without silicone spacer to lengthen the tendon
    - o has often disappointing results, probably reflecting the variety of causes of the same clinical pattern.

Congenital Cranial dysinnervation disorders (CCDDs)		
Involved CN	Eye motility limitation **with** lack of innervation	
	without synkinetic eye movement	**with** synkinetic eye movement
VI	• Congenital VIth nerve palsy • Horizontal gaze palsy with progressive scoliosis (HGPPS) • Möbius sequence	• Duane retraction syndrome
III	• Congenital IIIth nerve palsy • Double elevator palsy • Congenital ptosis	• Marcus Gunn jaw winking • Congenital fibrosis of the extraocular muscles (CFEOM) • Congenital IIIth nerve palsy with ocular motor synkinesis • Vertical retraction syndrome
IV	• Congenital IVth nerve palsy	• Congenital Brown syndrome
	Ocular motor synkinesis **without** lack of innervation	
	• Co-innervations between III, IV, VI • Co-innervations between III, IV, VI and V, VII, IX, XII	

Table 1. Congenital Cranial dysinnervation disorders (CCDDs)

Duane retraction syndrome	**Type I**	**Type II**	**Type III**	**(Type IV)** ***synergistic divergence***
% of DRS	**78%**	7%	15%	very rare
VIth CN innervation to LR	-	(+)	-	-
IIIrd CN innervation to LR	+	+	++	++
IIIrd CN innervation to MR	++	++	++	+
Retraction of the globe in (attempted) adduction	present	present	present	absent
Abduction	**impaired**	normal / slightly impaired	**impaired**	normal; **excessive abduction** when attempted adduction
Adduction	normal	**impaired**	**impaired**	**absent**
Strabismus in primary position with head straight	often **convergent** (moderate)	**divergent**	variable	**divergent** (large angle)

Table 2. Classification of Duane syndrome.

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MCQ answers page 124

1. Answer: d

Duane syndrome is caused by **absence or hypoplasia of the VIth cranial nerve**, with anomalous innervation of the lateral rectus muscle from the IIIrd cranial nerve causing co-contraction of the medial and lateral rectus muscles, responsible for **retraction of the globe** as well as **up- or dowshoots** in **adduction**. It is more frequent in **women**, and affects more frequently the **left** eye.

2. Answer: e

Surgical treatment is **unnecessary in most patients** because they can compensate well with a mild degree of head positioning. Surgical indications include presence of a **large face turn** and **strabismus in primary position**. Muscle **recessions** are preferred to avoid increased retraction. Because it does not correct the underlying innervation abnormality, surgery **does not normalize eye movements**.

3. Answer: b

Brown syndrome is characterized by an **elevation deficit which is maximal in adduction**. Congenital Brown syndrome can result from **various abnormalities** of superior oblique tendon, muscle, trochlea or innervation. It can be associated with divergence in upgaze causing a **"V" pattern**, and is **more frequent than inferior oblique muscle palsy** (which causes a "A" pattern). Because **spontaneous improvement is frequent**, early surgery should be avoided.

Surgical indications and management of paralytic strabismus

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18

MCQ's

1. Surgery in paretic strabismus …

a. can be performed 6 months after trauma
b. most often needs transposition surgery
c. may include surgery of the non-paretic eye
d. is similar to surgery in restrictive strabismus
e. cannot resolve abnormal head position

2. Transposition surgery of the vertical recti muscles …

a. often causes transient vertical and torsional deviation
b. can be used as a counterparesis – procedure
c. can be used in mild 6th nerve palsy
d. can be used in complete 3rd nerve palsy
e. must be combined with a medial rectus recession in 6th nerve palsy

3. In 4th nerve palsy …

a. strengthening of the anterior part of the superior oblique muscle is mandatory
b. symmetric bilateral cases have a large vertical deviation in downgaze
c. combined oblique muscle surgery is a standard procedure
d. Harada-Ito procedure has a high risk of post-op Brown's syndrome
e. prismatic correction is a good temporary treatment option

Introduction

Surgery in paretic strabismus faces two extra challenges: the criterion for success is functional and more demanding because most patients experience diplopia. Second, the incomitance of deviation has to be taken into account in the surgical plan. Its management differs significantly from incomitant strabismus due to restriction (e.g. Graves orbitopathy, entrapment of muscle) where loosening the tight muscle by recessions only is mandatory. Treatment of congenital eye motility disorders esp. CCDDs also differs significantly from the treatment of acquired paresis and is covered in the chapter by Kaeser.

Non-surgical treatment

As with any strabismus surgery, accommodative influence on the horizontal deviation has to be eliminated by full hyperopic correction of glasses and avoidance of myopic overcorrection. In small horizontal or vertical deviations (≤ 5°) a permanent prismatic correction with glasses can be considered. It should be placed in front of the paretic eye to avoid larger secondary deviation. In large deviations or changing deviations while waiting for recovery of the nerve, prismatic correction with Fresnel prism foils can be helpful. Cyclodeviations cannot be treated with prisms.

Principles of treatment

Aim of treatment

Reasons for surgery can be:

- diplopia	Because most patients with acquired paresis did not learn to suppress the image of the deviated eye (as in childhood strabismus) diplopia can be present in some direction of gaze, primary position or all directions of gaze. The patient will adopt a head position, close one eye or wear occlusive patch or contact lens.
- abnormal head position	In cases of mild paresis the deviation decreases when looking away from the paresis to the extent that the patient may fuse it and use a head position in the direction of the paresis.

- psycho-social: Large deviations will cause psycho-social stress to the patient

Timing

Obviously any known cause of paresis must be treated first. Surgery is only a reasonable treatment option in stable cases. In general we should wait one year for spontaneous recovery e.g. after trauma or tumour resection. Even in cases without any recovery during 6-9 months it may happen at 10-12 months. In progressive cases surgery may provide only temporary relieve for the patient.

Surgical strategies

Combined surgery

In cases with only slightly limited motility combined surgery is a good option. Dosage by deviation should be slightly increased compared to non-paretic strabismus.

Augmented combined surgery

Large recess-resect procedures are a good option in cases where motility is more limited but reaches primary position. Muscle elongation with interponate (e.g. bovine pericardium, Tutopatch®) should be used instead of very large recessions or hang-back recessions because it gives less motility deficit and more predictable results.

Transposition

Even in complete paralysis of a muscle some residual motility will be possible because of elastic properties of connective tissues and relaxation – activation of the antagonist. Clinical paralysis is defined as motility not reaching midline. In these cases even augmented combined surgery gives unsatisfying results, esp. in long follow-up. Replacing the missing active muscle force by transposing one or two muscles (more often: parts of neighbouring muscles) to the insertion of the paralytic muscle is a good option. There will be no change of innervation but elastic forces help to improve position and motility of the eye. Transposition surgery can be combined with recession of the antagonist as a simultaneous procedure or as a second intervention. However it bears the risk of ischaemia if more than two recti muscles are operated on one eye.

Counterparesis

In cases of small deviation and only slightly limited motility of the paretic eye, weakening of the contralateral agonist/yoke muscle is a good option, esp. when further surgery on the paretic eye is not possible, e.g. because of risk of ischaemia after surgery of at least two other rectus muscles. Prae-op monocular fixation with the paretic eye must be possible without abnormal head position. Weakening can be done by recessions, retroequatorial myopexia (Faden-surgery) or Y-splitting.

6th nerve palsy

Depending on the amount of residual motility in abducens paresis, any of the above mentioned surgical procedures can be performed. Recession of the medial rectus muscle can be augmented to 10mm and resection of the paretic lateral muscle up to 12mm,

4th nerve palsy

Major obstacle to fusion and cause of diplopia in trochlear palsies is cyclodeviation which increases with downgaze. Especially in bilateral cases there is very little or no vertical deviation but excyclodeviation > 15°. Therefor prismatic correction is no option.

Weakening of the inferior oblique muscle is less effective and the standard surgical procedure is enforcing the superior oblique muscle. The anterior part of the muscle is especially helpful in correcting cyclodeviation whereas the posterior part is more active for vertical deviation. Because excyclodeviation is the main factor causing diplopia in these patients, tightening the anterior part is the preferred surgical procedure. This can be done by tucking this part of the muscle or even more effectively by anterior transposition of the anterior half of the muscle 3-7mm lateral of the superior rectus insertion. In cases of significant VD the posterior part can be tucked (risk of post-op elevation limitation, "Brown's syndrome"). Residual vertical deviation with little excyclo-deviation can be corrected with a contralateral inferior rectus recession as second surgery.

3rd nerve palsy

This is the most complex situation in paralytic strabismus because vertical and horizontal deviation as well as ptosis must be treated. Often surgery cannot be limited to the affected eye because surgery on more than 2 recti muscle (which is often needed to correct horizontal and vertical deviations) bears the risk of anterior segment

ischaemia. The stronger deviation or motility disorder (either horizontal or vertical) should first be corrected on the paretic eye. Then second surgery on the contralateral eye should correct the other, lesser deviation. In cases of large exodeviation recess-resect horizontal surgery can be combined with vertical displacement of both muscles to correct small vertical deviation (<5-6°).

Transposition surgery of superior and vertical recti muscles to the medial rectus muscle in adduction paralysis is often not possible because both vertical recti muscles are also paretic. In these cases, when large exodeviation causes severe psycho-social stress, transposition of the lateral rectus muscle (with or without splitting) to the nasal side can be an option. However this only achieves good eye position in primary gaze but no motility and no useful field of binocular single vision. To avoid diplopia occlusive contact lenses are helpful.

In cases with ptosis three further options must be considered: 1) some patients show regeneration of the 3rd nerve with dysinnervation of the levator muscle. The lid may open in a) adduction or b) downgaze. If motility of the paretic eye is not too limited, ptosis and strabismus can be corrected simultaneously by correcting exotropia (a) or rarely hypertropia (b) by operating the contralateral eye. 2) Ptosis surgery must be corrected only after all corrections of eye position because this may affect lid position. 3) In cases where eye alignment cannot be achieved ptosis should be used as a "natural' protection against diplopia and not be operated. If permanent ptosis is not acceptable to the patient (e.g. dominant eye or psychologically) occlusive contact lenses can be used.

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MCQ answers page 134

1. Answer: c

After trauma we should wait 1 year for spontaneous recovery. Transposition surgery is needed only in severe paralysis. Yes, counterparesis is a useful surgical option when motility of the paretic eye is only mildly limited. In restrictive strabismus only weakening procedures are usefull. Surgery DOES help with head position.

2. Answer: a

Yes, due to slight asymmetry of the superior and inferior branc vertical and torsional diplopia may occur - in most cases it resolvs after weeks. Counterparesis is a weakening procedure unlike transposition. Transposition should be used only in severe paralysis. In complete 3rd nerve palsy the muscles you would like to transpose to correct exotropia (superior and inferior rectus muscle to the nasal side) are also paretic. Because of the risk of anterior segment iscaemia medial rectus recession should be done when needed and as a second procedure.

3. Answer: a

Yes, because cyclotrosional diplopia is the main complaint of the patient. Largest deviation is in downgaze but in symmetrical cases depression deficit is balanced and no VD is present (excyclodeviation add to each other). Inferior oblique muscle recession is rarely needed. Because the posterior fibers (which are responsible for vertical motility) are not touched there is no significant elevation deficit in anterior fiber strengthening procedurers (Harada-Ito). Because of torsional diplopia prisms are no option in most cases of IVth nerve palsy.

Amblyopia: physiologic basis and management

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19

MCQ's

1. Amblyopia:

a. Should be divided into three distinct types: deprivation amblyopia, strabismic amblyopia, and refractive amblyopia.
b. Each of these forms of amblyopia has a different effect on brain structure or metabolism.
c. Each form of amblyopia has a different period of plasticity.
d. Loss of visual function may differ greatly for each form.
e. All of the above.

2. Amblyopia:

a. Different recommendations exist for the optimal number of hours of contralateral eye occlusion necessary to reverse depending on the country and even depending on different regions within a country.
b. These differences are not due to genetic differences between populations.
c. The improvement in vision that is reported in the literature from these different countries or regions appears to be comparable.
d. It is possible that there may be more than one "correct" way to treat each distinct form of amblyopia, whether by occlusion or via penalization.
e. All of the above

3. Changes in the striate cortex due to amblyopia:

a. Were discovered by David Hubel and Torsten Wiesel following work performed on kittens in the 1960s for which the two investigators received the Nobel Prize in Physiology in 1981. In the 1970s, Gunter von Noorden verified similar changes to take place in primates.
b. Subsequent work beginning in the 1990s by Jonathan Horton, one of Hubel's students, found the above findings to be true only for the deprivation amblyopia. No anatomical changes within cerebral cortex have been found in either strabismic or in refractive amblyopia. Subtle changes in neural metabolism are now only suspected for these two other forms of amblyopia.

c. Shrinkage of cells in the lateral geniculate body first noted by von Noorden in some instances of strabismic amblyopia, appears to be due to reduced signal afferents received from the morphologically still intact striate cortex that go to the lateral geniculate body.
d. Approximately only 20% of the nerve afferents to the lateral geniculate body come from the optic nerve.
e. All of the above.

Amblyopia designates monocular or binocular visual loss associated with impediment of a light stimulus, strabismus, or uncorrected refractive error. Nobel prize-winning neuroscientific studies on kittens in the 1960s by Hubel and Wiesel identified a critical period early in life in which the visual system is vulnerable to amblyopia and the site of pathology as the primary visual cortex. These investigators received the Nobel Prize in Physiology for their work in 1981. In the 1970s, Gunter von Noorden had verified similar effects to take place in primates. However, subsequent work beginning in the 1990s by Jonathan Horton, one of Hubel's students, has found the above findings to be true only for amblyopia due to visual deprivation such as by eyelids being sewn shut or due to congenital cataracts. No anatomical changes within cerebral cortex have been found with either strabismic or with refractive amblyopia. Shrinkage of cells in the lateral geniculate body noted by von Noorden only in some instances of strabismic amblyopia in primates, appears to be due to reduced signal afferents received from the morphologically still intact striate cortex that go back to the lateral geniculate body (only 20% of the nerve afferents to the lateral geniculate body come from the optic nerve).

Subtle changes in neural metabolism only are now suspected for causing strabismic and refractive forms of amblyopia. Recent observations have greatly refined these concepts, permitting a better correlation with various clinical presentations and greatly affecting management. A broader understanding of the differing pathophysiology for various forms of amblyopia will be critical to refining and providing optimized therapy for afflicted patients.

Differing neuro-anatomical correlates of deprivational amblyopia (D-amblyopia), strabismic amblyopia (S-amblyopia) and refractive amblyopia (R-amblyopia) with experimental effects of visual form deprivation on anatomical striate cortex, lateral geniculate body and on neural metabolism will be discussed and highlighted.

Neural plasticity will be discussed in the context of critical periods for these various forms of amblyopia, with direct implications for amblyopia therapy.

Different recommendations exist for the optimal number of occlusion hours necessary to reverse amblyopia depending on the country and depending even on different regions within a country. These differences cannot be attributed to differences in genetics. Improvements in visual acuity reported from these different regions or countries, nonetheless, appear comparable. Management will be discussed,

harmonizing recommendations from various schools of thought and country/regional practices and related to recent scientific literature for each distinct form of amblyopia. There may be more than one "correct" way to treat various forms of amblyopia, whether by occlusion or via penalization. Indications for, as well disadvantages of, occlusion and penalization therapy in routine patient care will be briefly touched upon.

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MCQ answers page 140-141

1. **Answer: e**

2. **Answer: e**

3. **Answer: e**

Screening strategies for amblyopia
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20

MCQ's

1. In children what is the correct proposition?

a. Amblyopia is more less among children from low socioeconomic backgrounds
b. 20% of the children under 6 years-old present ocular anomalies
c. Refractive errors, amblyopia and strabismus are equal in premature infants and term infants
d. Amblyopia is more common in myopic children
e. Amblyopia is preventable with visual screening and re-education therapy

2. Concerning amblyopia what is the correct proposition?

a. Amblyopia results from an abnormal visual system development
b. Prevalence of amblyopia varies from 5 to 10% of the population
c. Refractive errors, amblyopia and congenital glaucoma are the more common pathologies in children under 6 years old
d. Preschool screening is the best strategy to pick up amblyopia and congenital cataract in children
e. Visual acuity measurement is the only test screening visual impairment

3. Concerning refraction in children what is the correct proposition?

a. Children under 6 years-old present a high possibility of accommodation
b. Photoscreeners measurements allow to prescribe optical correction
c. Automatic photorefracter measurements allow to prescribe optical correction
d. Mydriaticum drops has cycloplegic effect allowing prescription of optical correction
e. Atropine drops prescribed during 3 days at the optimal dosage allow a reliable measure of refraction

Objectives

- To understand the definition of amblyopia
- Review of the aetiologies of amblyopia
- To understand normal visual development and visual deprivation
- Refraction in children

Introduction

In the paediatric population of children of 6 years or less, INSERM study had identified 20% of ocular anomalies. These anomalies are predominantly refractive errors but also amblyopia and strabismus. Rare ocular diseases as congenital cataract or congenital glaucoma can also be found in the general population but prevalence is low. Standard screening techniques are primarily at detecting the presence of amblyopia or high refractive errors. The methods are based on recognition visual acuity measurements however they are usually ineffective in children under 3 years-old. The requirements of the screening need to integrate appropriate methods for children younger than verbal age. Thereby, the screening strategies must be adapted to the age of the child.

Clinical examination

Clinical examination is the key point of the screening of visual anomalies in children. History of the child and his family must be described. So prematurity, refractive errors, anisometropia, amblyopia, strabismus and neurologic impairment represent major risk factors. A complete clinical examination includes binocular, monocular far and near visual acuity, ocular alignment with corneal reflects, ocular motility, ocular pursuit, cover test and red retinal reflects. For preverbal children objective visual acuity measurements can be used as preferential looking testing. Slit lamp and fundus must complete the clinical examination.

Refraction

The refraction of the children has to be evaluated or measured precisely. Nowadays we have different possibilities using different groups of devices.

- Photoscreeners

They are based on a photographic technique that estimates the refractive error without cycloplegia, based on the reflected image. The major limitation is the failure to detect small refractive errors but also the lack of reliable measurements in some cases with as important as 4 diopters difference with automatic photorefracter measurements under cycloplegia.

- Automatic Photorefracter

Children has a very high potential of accommodation. Objective technique of refraction remains the gold standard for detecting significant refractive errors in children. The measurements must be performed with an automatic photorefracter under cycloplegia. The cycloplegia is obtained with atropine or cyclopentolate eyedrops with the adapted dosage following the age of the child. Tropicamide eyedrops has a very little cycloplegia effect. This method allows the evaluation of hyperopia, myopia and astigmatism. The correction is not applied to all refractive errors and should be decided with the overall clinical evaluation.

Conclusion

The screening strategy of visual anomalies requires history of children and family, a careful clinical examination and refraction under cycloplegia. The screening remains difficult at preverbal age which is the optimal age for screening amblyopia. The methods used are adapted to the age of the children. An early detection of amblyopia allows prescription of optical correction and re-education in order to avoid visual handicap of the adult.

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MCQ answers page 145

1. Answer: e

2. Answer: a

Amblyopia is a visual developmental anomaly and is evaluated to less than 5% in the general population. Congenital glaucoma is a rare disease even if it can causes amblyopia. Preschool screening is the best strategy for congenital cataract but not for amblyopia.

3. Answer: a

Children have a strong possibility of accommodation so only an examination under cycloplegia allows the prescription of the refraction errors. For cycloplegia 3 days of atropine is not sufficient to get an acceptable accommodation blockage.

Infantile nystagmus

Pierre-François KAESER, Switzerland

21

MCQ's

1. Infantile nystagmus

a. Is usually present at birth
b. Can be associated with underlying visual abnormality
c. Always presents with head nodding
d. Can be horizontal, vertical or torsional
e. Increases with convergence

2. In children with nystagmus, cerebral MRI should be performed

a. In every patient
b. If nystagmus is associated with foveal hypoplasia
c. If history reveals the presence of severe photophobia
d. If the nystagmus is monocular or asymmetrical
e. If the nystagmus decreases with convergence

3. A child with infantile nystagmus should have an electroretinogram (ERG) examination

a. Always
b. If optic atrophy is present
c. If severe photophobia is reported
d. If pupils dilate in darkness
e. If spasmus nutans is suspected

Objectives

- Review of the more frequent types of congenital nystagmus in children
- Infantile nystagmus
- Latent nystagmus
- Spasmus nutans
- Voluntary nystagmus

Infantile nystagmus

Onset

2-3 months (rarely present at birth)

Clinical features

- horizontal pendular or jerk nystagmus
- increased intensity on side gaze
- right-beating in right gaze and left beating in left gaze
- remains horizontal in upgaze
- null zone (region of gaze with minimal intensity of the nystagmus), often with associated head turn
- decreases during convergence
- increases with fixation and visual effort
- no oscillopsia
- reversed horizontal optokinetic responses
- With-the-rule astigmatism
- Head nodding in 10%

Types

- **Idiopathic** = motor = isolated
- **Sensory** = underlying sensory visual disorder
    - o 50% of patients with infantile nystagmus
    - o Look for suggestive history or signs of ocular abnormality, namely:
        - albinism
        - cataract
        - macular hypoplasia
        - retinal dystrophy
        - optic nerve hypoplasia / atrophy

Type of waveforms (pendular versus jerk) or age of onset cannot predict the presence or absence of underlying visual deficit!

Investigations

Electroretinogram (ERG) if symptoms / signs of congenital retinal dystrophy:

- History:
    - o photophobia (*achromatopsia, blue cone monochromatism?*)
    - o night blindness (*congenital stationary night blindness – CSNB?*)
    - o family history of poor vision
- Signs:
    - o photophobia (*achromatopsia, blue cone monochromatism?*)
    - o paradoxical pupillary phenomenon (initial miosis in darkness) (*CSNB, achromatopsia?*)
    - o high myopia (*CSNB?*)
    - o high hypermetropia (*certain forms of Leber congenital amaurosis?*)
    - o oculodigital reflex (*Leber congenital amaurosis?*)

Cerebral MRI if:

- Nystagmus + **ON hypoplasia**: *pituitary infundibulum, cerebral hemispheres or midline structures abnormalities?*
- Nystagmus + **optic atrophy**: *congenital suprasellar tumor, hydrocephalus?*
- **Dissociated nystagmus, spasmus nutans**: *suprasellar tumors (chiasmal glioma)?*
- Infantile nystagmus + **seesaw nystagmus**: *achiasma?*

Neurological evaluation (± cerebral MRI) if:

- Late-onset of nystagmus (> age 4 months)
- oscillopsia
- disconjugate nystagmus (both eye moving in opposite direction)
- normal horizontal opto-kinetic nystagmus
- pathological neuro-ophthalmological findings (e.g. relative afferent pupillary defect, papilledema)
- neurological symptoms (e.g. vertigo, nausea)

Management

- Allow the child to use its null zone /compensatory torticollis
- Prescribe full optical correction
- Contact lenses trial
- Surgery:
  - **Lateralized null zone**: Kestenbaum surgery (surgery of all 4 horizontal muscles to "move the eyes towards the direction of the head turn (away from the null zone)") → shift of the null zone from lateral to straight gaze position
  - **Nystagmus damps during convergence; near VA > far VA**: artificial divergence surgery (iatrogenic exophoria) → fusional convergence reduces nystagmus. Binocular union is mandatory.
  - Other: weakening all 4 horizontal muscles by large recessions or botulinum toxin injection (often disappointing results).

Latent nystagmus

Onset

+++ in infantile esotropia

Clinical features

- bilateral conjugate horizontal (+/- torsional) jerk nystagmus
- occurs with monocular occlusion
- present with both eyes open if only 1 eye used for vision (amblyopia / suppression) ("*manifest* latent" nystagmus)
- beats towards fixing eye: direction changes with change of fixing eye:
    - o right-beating ***(fast phase to the right)*** with right eye fixing
    - o left-beating with left eye fixing
- intensity
    - o increases in abduction of the fixing eye
    - o decreases in adduction of the fixing eye
    - → head turn to fixate in adduction with the fixing eye

Spasmus nutans

Onset

6-12 months

Spontaneous resolution after 1-2 years

Clinical features

- dissociated: monocular or asymmetrical
- can be intermittent
- horizontal (rarely vertical, oblique or torsional)
- small amplitude, high frequency "ocular shiver"
- head nodding (vertical + horizontal)
- torticolis in 50%
- visual acuity ± normal

Investigations

Cerebral MRI to exclude congenital suprasellar tumor!

Voluntary nystagmus

- 5% in normal population, can be familial
- generally brought on by a strong convergence effort
- fine-amplitude, rapid, conjugate, horizontal oscillations (not a true nystagmus)
- duration 20-30 seconds
- clue = inability to sustain the oscillation

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MCQ answers page 150

1. Answer: b

Onset of infantile nystagmus is at **age 2-3 months**, rarely at birth. It is associated with an **underlying sensory visual disorder in about 50%** of patients. Infantile nystagmus is typically **horizontal, decreases during convergence**, and is associated with **head nodding in only 10% of cases**.

2. Answer: d

Cerebral MRI should be performed if the nystagmus is **dissociated** (monocular or asymmetrical) to look for suprasellar tumor. It is indicated neither in case of **foveal hypoplasia**, nor if **severe photophobia** is present, which can be a sign of **retinal dystrophy**. Infantile nystagmus typically **decreases** during convergence.

3. Answer: c

Severe **photophobia** is suggestive of **congenital retinal dystrophy**, which should be excluded by **ERG**. Paradoxical pupillary phenomenon (initial **miosis** in darkness – instead of initial mydriasis!) can be a sign of CSNB or achromatopsia). When nystagmus is associated with **optic atrophy,** is **dissociated** or when **spasmus nutans** cannot be excluded, **MRI** should be performed to look for suprasellar tumor.

Secondary and iatrogenic strabismus

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22

MCQ's

1. Which surgery can cause iatrogenic strabismus:

a. Endoscopic sinus surgery
b. Cranofacial surgery
c. Glaucoma surgery
d. Retina detachment surgery
e. All of the above

2. Which statement is true?

a. Secondary strabismus is a surgical mistake
b. Adjustable sutures can always prevent overcorrection
c. Adjustable sutures can always prevent undercorrection
d. A patient should be aware of the risk of secondary strabismus
e. Secondary strabismus occurs only in children

3. The heavy eye phenomenon is due to

a. The heavy weight of the myopic eye
b. The large volume of the posterior bulbus
c. The herniation of the posterior bulbus between the superior and lateral rectus muscle
d. The large anterior chamber which pulls the eye down and in
e. The progressive weight gain of the lens due to cataract progression

Secondary Strabismus:

Consecutive strabismus can be the result of over or undercorrection of preoperative strabismus about 10-25% over strabismus surgeries can lead to secondary strabismus. It is important to warn patients and parents about the possibility of secondary strabismus, which might need another surgical intervention.

Iatrogenic strabismus is caused by any treatment leading to misalignment of the eyes. Several causes can be addressed and will be shown in this presentation.

- Adhesions: conjunctival adhesions can cause gaze limitations due to constriction.
- Adherence syndrome is caused by damage during surgery of orbital septae and orbital fat. Typically this occurs in inferior oblique surgery when anatomic structures are damaged (chicken soup). This will cause limitation of elevation in adduction mimicking a Brown syndrome.
- Pterygium surgery can cause strabismus when extraocular muscles are compromised either by direct damage or adhesions secondary to tenons or conjunctiva.
- Retinal surgery with buckles and explants can cause adhesions limiting versions and ductions. Typically adhesions between superior oblique and inferior oblique with the neighboring rectus muscles limit normal ductions and induce cyclovertical and horizontal strabismus. Due to the encircling band the distal part of the 4 rectus muscles can show fibrotic changes. Removing the encircling band will only in a few cases repair normal eye movements. Miragel explants in the early 80-ies of the last century were notorious troublemakers. The soft implant would swell over time and harden causing strabismus and restrictions of eye movements.
- Glaucoma tubes like Baerveldt, Molteno and Ahmed explants. Due to the increased size of the filteringcyst, which resides under the rectus muscles even in freefloating (not sutered to the sclera) implants. This will increase the volume of the orbit contents limiting ductions. Secondary fibrosis with the eye muscles is a late complication of these glaucoma- shunting implants.
- Orbital surgery can cause strabismus either due to fibrosis of the eye muscles or by damage to the orbital septae. Orbital fat can adhere to the globe and EOM causing restrictions. After orbital decompression for ophthalmic Graves disease strabismus can occur or worsen, needing surgical correction.

- Cranio facial surgery: Orbital blowout correction by CF surgery can result in restrictive strabismus with limitation of elevation. In the acute fase the inferior rectus muscle can get entrapped in the orbital floor fracture.
- ENT endoscopic surgery (FESS); A dreaded complication of endoscopic sinus surgery is direct damage to the medial rectus and superior oblique nuscle. In these cases the muscle can be severed or damaged. Secondary adhesions will further limit eye motility. If the medial rectus muscle is cut in two pieces one can try to suture both part end to end. However if the distal part is lost and not to be retrieved one must perform a transposition surgery using part of the superior and inferior rectus muscles.
- Strabismus in High myopia (Heavy eye phenomenon): In high myopic eyes a progressive esotropia with hypotropia can develop. This is due to the herniation of the posterior pole of the enlarged bulbus between the superior and lateral rectus muscle. This can occur because the intermuscular septum and band between these 2 muscles gets floppy and can break. On MRI imaging one can see an enlargement of the angle between the superior and lateral rectus muscles. This can progress to an strabismus fixus in which the eye cannot be moved and stays in esotropic and hypotropic position. The solution is a Yokoyama non-absorbing suture between the muscle belly of the superior and lateral rectus at the position 15mm posterior of the insertion. This will close the opening between the two muscles and prevent the herniation of the posterior bulbus. In cases with a tight medial rectus muscle a recession of this tight muscle in addition to the Yokoyama suture is needed.
- Conjunctival inclusion cysts: These can occur after any eye surgery. In many cases it is more disfiguring than limiting function. Sometimes these cysts can become very large and will limit normal eye motility. Total removal is needed in order to prevent recurrence.

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MCQ answers page 157

1. **Answer: e**

2. **Answer: d**

3. **Answer: c**

Esotropia: Considerations in Infants and Adults

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23

MCQ's

1. Infantile esotropia shows typical sensorimotor abnormalities. Which abnormality is not typical for infantile esotropia?

a. Latent Nystagmus
b. Deficit of fusional vergence
c. Naso-temporal asymmetry of the vestibulo-ocular reflex
d. Dissociated Vertical Divergence
e. Crossed fixation

2. Which observation will allow differentiation between manifest latent nystagmus and congenital nystagmus?

a. Nystagmus during fixation at near
b. Nystagmus during a change of fixation between eyes
c. Nystagmus during lateral gaze
d. Nystagmus change during a change in gaze directions
e. Nystagmus change over time

3. Which observation allows differentiation between a fourth nerve palsy and an upshoot in adduction?

a. Vertical deviation comitance in adduction
b. Torsional deviation comitance in adduction
c. Vertical deviation comitance in abduction
d. Torsional deviation comitance in abduction
e. Cyclovertical deviation in primary position

Objectives

- vergence mechanisms
- microtropia
- infantile esotropia
- patterns

Incidence:

Caucasians: 1.1% age 11 months, 1.9% 36 m., 2.9% at 72 months; esotropia/ exotropia = 5/1

Asian: Exotropia> Esotropia

Prevalence of approximately 2 - 3% of all children younger than 6 years

- fully accommodative: 10 - 35%
- partially accommodative: 10 - 40%
- acquired non accommodative: 15 - 30%
- esotropia associated with an abnormal central nervous system: 10%
- infantile esotropia: 8%

Cause of esotropia is largely unknown. The anatomical position of rest is a divergent alignment of 20°.

So, convergence is necessary in order to align the eyes. Tonic vergence, proximal vergence and accommodative vergence all serve to this end. Finally fusional vergence will correct the error of these forces. Without the feedback from disparity, e.g. when one eye is occluded, a phoria shows this error. However, in the presence of binocular fixation, so with disparity feedback, there may still be a small error in convergence: fixation disparity. The larger the phoria, the larger will be the fixation disparity. Fusional vergence needs this disparity signal to overcome the phoria, because disparity vergence is rapid but lacks durability. Esophoria, fixation disparity, microtropia and esotropia together illustrate the spectrum of esodeviations.

Genetic factors seem to play a role. Twin studies show concordance of 54% in monozygotic twins and 14% in dizygotic twins.

Accommodation appears to be another causative factor. Population studies show an average hyperopia in newborn infants of 1.5 D which diminishes in the first ten years of life. In strabismus, hyperopia increases at first, till the age of four years and decreases after that time. Hyperopia more than or equal to 3.5 D at the age of 7-9 months occurs in 5-6% of children. These children have a 13 times higher chance of strabismus at the age of 4. Partial hyperopic correction reduces this a 4 times higher chance.

Infantile esotropia is associated with typical sensorimotor abnormalities like a defect of ocular pursuit: an impairment of temporally directed pursuit when viewing a moving target monocularly. The pursuit defect was not found in subjects with non-infantile strabismus. Infantile strabismus may either be caused by a defect in the fusion faculty within the brain or result from abnormal visual experience.

Types of esotropia:

Infantile esotropia

Strabismus before the age of 6 months is called infantile strabismus. It used to be named congenital strabismus but foveal fixation is unstable at birth also in normal children. At birth the visual system is immature: the optic nerve is myelinated around birth, fixation is at first eccentric (nasal retina) and unstable, binocular disparity sensitivity and fusion are absent in neonates and fusional vergence is also immature with over-convergence and errors, while stereopsis emerges suddenly at the age of 3 to 5 months.

This immaturity likely is responsible for the typical sensorimotor abnormalities of infantile strabismus, i.e.

- Deficit of stereopsis and fusional vergence
- Dissociated vertical Divergence (DVD): 90%
- Latent nystagmus (LN) 55%
- Nasotemporal asymmetry of optokinetic tracking, smooth pursuit and motion VEP´s,

LN: A latent bilateral jurk nystagmus with the fast phase beating in the direction of the fixating eye. It is called latent because nystagmus is absent during unobstructed bilateral fixation. After occlusion of the left eye, both eyes show a slow drift towards the left corrected by a saccades to the right. Occlusion of the right eye causes a slow drift to the right and corrective saccades to the left. Latent nystagmus may become manifest with partial visual loss or amblyopia of one eye. LN likely is caused by dominance of the evolutionary older crossed retinal ganglion cell pathway in the cortical pursuit pathways.

DVD: Dissociated vertical divergence with torsional version. Occlusion of the left eye causes slow elevation of the left eye. The left eye will excyclorotate and the right eye will incyclorotate during elevation of the left eye. Dissociation seems determined by the balance of fixation between both eyes. If the left eye is up and a filter is placed before the right eye, the left eye will come down. If occlusion is changed towards the right eye, the right eye will elevate and excyclorotate while the left eye will take on fixation and incyclorotate. DVD likely is caused by dominance of the evolutionary older crossed retinal ganglion cell pathway in the cortical vergence pathways.

Accommodative esotropia

A patient with uncorrected hyperopia uses accommodation to focus a retinal image. Accommodation will stimulate convergence and strain fusional divergence. When fusional divergence is overcome, the eyes cross. The patient with uncorrected hyperopia can see either a single blurred image or a double image in which one image is clear and one image is suppressed.

Acquired esotropia

Esotropia that does not show an influence of accommodation occuring in patients aged between 1 and 8 years, is called acquired esotropia. More usually it develops in patients aged 2-5 years. With acquired esotropia, the angle of deviation is relatively small, and early surgical correction (when indicated) is more likely to achieve bifoveal fixation for these patients than for those with infantile esotropia.

Esotropia can also be secondary to other conditions. Poor vision may interfere with binocular fusion and cause squint. Various medical and anatomical conditions (permaturity, hydrocephalus, stroke, Duane, thyroid eye disease etc.) may also cause esotropia.

<u>The effect of esotropia</u>

Constant esotropia will cause loss of stereopsis, diplopia and confusion. Constant esotropia of one eye at a young age in which the visual system still develops will lead to amblyopia. Strabismic amblyopia results from suppression of the macula of one eye. Correction of amblyopia by glasses, occlusion and penalization is most effective in young children but may even be successful after the age of 12 years. Abnormal retinal correspondence and non-foveal fixation may also result from long standing esotropia.

Treatment

Amblyopia treatment is the most important aspect of treatment. The optimal outcome of treatment is alternate fixation. Stereopsis after treatment is rare, most often it will be coarse and restricted to patients with late onset strabismus.

Surgery for esotropia is often delayed until amblyopia is treated, the effect of hyperopic correction is fully understood and angles of strabismus can be measured. The timing of surgery, however, is controversial. In rare cases stereopsis and alignment were found normal after very early surgery. In a European study in which early and late surgery were compared only minor differences between groups occured.

A surgical dose-response relation has often been established. In case of concomitant horizontal esotropia the surgical dose is based on the horizontal squint angle, after full hyperopic correction, at distant fixation. Dose response relation in horizontal angles above 5^0, is between 1.4^0 and 2^0 per mm operation, if two muscles are being operated. In case of a non-accommodative convergence excess a retro-equatorial fixation of the muscle may help correct the different angle at near.

Patterns

A and V-patterns of horizontal squint angles often occur. Most often these patterns occur after the age of two years. In A pattern esotropia the horizontal angle is larger in upgaze and smaller in downgaze. In V pattern esotropia, the angle is larger in upgaze than in downgaze. Several studies show that orbital rotation during development of the skull may cause these patterns which only become visible after fusion is hindered. In Caucasians there often is a V –pattern, with upshoot in adduction and excyclotropia. This is very similar to fourth nerve palsy. The main difference is the upshoot in adduction which is concomitant in cases of non-paralytic strabismus and due to orbital rotation, whereas the upshoot is larger in adducted downgaze in case of fourth nerve palsy. A-patterns often occur with downshoots and incyclorotation.

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MCQ answers page 161

1. Answer: c

In IE eyemovements that are initiated in the cortex like smooth pursuit and saccades show nasal-temporal asymmetry. The VOR is a brainstem reflex

2. Answer: b

Congenital nystagmus dampens during near fixation and often changes in gaze direction and may change over time but a change of fixation between eyes will always differentiate the two. In latent nystagmus the direction of the nystagmus is determined by the fixating eye.

3. Answer: a

The vertical deviation in adduction is large in downgaze only in case of a fourth nerve palsy. In an upshoot in adduction the vertical deviation is more concomitant in adduction.

MCQ's

1. A True Divergence Excess Type Exotropia is:

a. Deviation is larger at distance than at near
b. Deviation is larger at near position that at distance
c. Deviation is approximately equal at distance that at near position
d. Examination with +3 spherical add augments the near deviation considerably
e. Examination with the patch test add augments the near deviation considerably

2. How do we call a case of a divergent misalignment that is not present unless fusion is disrupted?

a. Exotropia
b. Exophoria
c. Exclyclotropia
d. Excyclophoria
e. Hypertropia

3. A 65 patient year-old lady has a left manifest Exotropia and poor vision due to a retinal detachment. Examination reveals a large Exotropia. Which type of Exotropia it is?

a. Congenital Exotropia
b. Infantile Exotropia
c. Retinal Exotropia
d. Sensory Exotropia
e. Iatrogenic Exotropia

Objectives:

- To differentiate the most frequent types of Exodeviations
- To recognize Intermittent Exotropia as it is the most frequent type presented in children.
- To learn about Consecutive Exotropia, a frequent type of strabismus in adults.

Exodeviations are latent or manifest divergent misalignment of the visual axis. 60% of the newborn infants have a transient deviation that resolves by 4-6 months of age.

1. Exophoria: Exodeviation controlled by fusion. The deviation appears when binocular vision is interrupted (cover test, fatigue, alcohol intake, sedation, unilateral diminution of VA, ex. patient developing an asymmetric cataract…). Patients may have good stereopsis although he may have aesthenopia while reading. Convergence should be checked. Treatment include refraction, some patients need prism or orthoptic exercises and eventually surgery for the most decompensate situations.

CLASSIFICATIONS - EXODEVIATIONS
EXOPHORIA
INTERMITTENT XT
EXO - DHD
MANIFEST - CONCOMITANT XT
Consecutive XT
Infantile XT
Sensorial XT
Monofixation XT
MANIFEST - INCOMITANT
III Nerve palsy, Internuclear
Duane Syndrome (Most frequently type II)
Congenital Fibrosis of the Extraocular muscles

2. Intermittent Exotropia: The most frequent type of XT in children. **Etiology**: combination of mechanical and innervational factors (imbalance between fusional convergence and divergence. It may begin before 12 months of age but as often is

quite compensate and many times the family detects it much later. The periods of decompensation may be variable upon the cases and over the years. Examination: Important a) Distance measurements should be made at least at 6 mt. (better 20 mt. through a window) and with a prolonged CT b) test the distance - near disparity with the cover test, if > 10 check it with near add of +3.00 and occluding for 30 minutes the deviated eye; c) check lateral incommitance to avoid overcorrection, d) test retinal correspondence and stereo at near but also at distance and e) evaluate the degree of control of the deviation

Intermittent XT subtypes	DEV. Distance/Near (10 PD)	+3.00 / Occlusion 30 min No change (-) Increase Near Dev (+)
Divergence Excess	> Distance	(-)
Convergence Insufficiency	> Near	
Basic	=	
Simulated Divergence Excess (majorityof apparent DE)	> Distance	+3 (+) Occl (-) : High AC/A +3 (-) Occl (+): Tenacious proximal fusion +3 (+) Occl (-) : Tenacious proximal fusion

Degree of Control of the deviation	Parents XT	XT at examination	Realignment
Good	< 5 times a day	XT - CT	Spontaneously
Fair	> 5 times a day > (50%)	XT – spontaneously infrequent	Needs more time / or blinking
Poor	Frequent	XT spontaneously Near and distance	Blinking / no recovery

The **natural evolution** of this type of strabismus is controversial: some patient's progresses from compensated situations to more decompensate ones and even from divergence excess to a basic type. Intermittent exotropia may be associated to oblique muscle dysfunctions and V and A patterns. Most patients have good stereopsis with different degrees of suppression at distance fixation. Amblyopia if present usually is mild. Patients frequently close one eye when they are exposed to bright light but exceptionally have asthenopia. **Treatment**: Nonsurgical management is indicated in patients with good control. Accommodation and fusional mechanism may improve the degree of control of the exodeviation. Myopia, astigmatism and any anisometropic correction should be prescribed. Even "over-minus lenses" -1,5 to -4 dp lenses may help to control the deviation (better in younger children and smaller deviations). Treatment of amblyopia reduces suppression and helps to control the deviation. Some doctors use unilateral patching some hours per day over the dominant eye to control the deviation. Orthoptic exercises and prisms are also used to control smaller deviations although. Most of the times the patients have a temporary benefit. **Surgery is indicated** when a: there is a) Poor control of the deviation, b) Progressive decrease of stereoacuity specially at distance c) More frequent exotropic than latent phase d) Progressive inhability to regain fusion sponteneously when the deviation becomes manifest. Most surgeons prefer to delay surgery if possible until the child is 4-6 years old.

The most frequent type of surgery is the bilateral lateral rectus recession although an alternative is a unilateral medial rectus resection and a lateral rectus recession.

3. EXO-DHD (Dissociated Horizontal Deviation): It is the horizontal component of the dissociated complex syndrome. Primary cases presenting XT It may be confused with intermittent XT. Also associated to Consecutive XT. Horizontal deviation is different while fixating with either eye; usually it is associated to DVD and nystagmus latent rare to find on an Intermittent XT.

4. Infantile Exotropia: Exodeviation that develops within the first 6 months of age. It may be associated to ocular or neurological pathology (hydrocephalus, periventricular leukomalacia, craniofacial syndromes, cerebral palsy…) Usually the deviation is large, they alternate fixation (amblyopia occurs < 25% of the cases). They may have, DVD, Oblique muscle dysfunction, mild nystagmus latent and X, V or A patterns. It is important to rule out any ocular and systemic pathology. Surgery is indicated if

deviation is large and after any refractive errors and amblyopia have been treated. Early surgery may be beneficial but it is controversial. Reoperations are required up to 50% of the cases.

5. Consecutive XT: ET that converts to an XT, most of the cases appear after ET surgery (immediate or long term cases) but there are also spontaneous cases. Etiology: surgical dosage, slippage of the MR, stretched scars; change in muscle tonus and fusion over the years. Taking the glasses off in cases of anisometropia and severe amblyopia are associated to consecutive XT. It is important to evaluate the patient as a new case taking care if there are any muscle limitations.

6. Sensory XT: Exotropia associated to severe reduction of VA of one eye or to chronic poor vision.

7. Other forms of XT: A) Exotropia associated to III nerve palsy and internuclear palsies. B) XT associated to Duane Syndrome (type II) or other congenital fibrosis of the extraocular muscles. C) XT with hemianopic visual defects

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MCQ answers page 167

1. **Answer: a**

2. **Answer: b**

3. **Answer: d**

Nonsurgical management of strabismus

Jan Tjeerd DE FABER, The Netherlands

25

MCQ's

1. Strabismus can have a negative impact on

a. Employability
b. Eye hand coordination
c. Social eye contact
d. Dating
e. All of the above

2. Which drug has no effect on strabismus

a. Mestinon
b. Botox
c. Ibuprofen
d. Bupivacaine
e. Steroids

3. In order to treat diplopia which of the following statement is not true:

a. Occlusion is a safe method
b. Strabismus surgery can cure diplopia
c. Monocular diplopia is caused by strabismus
d. Prisms can help in diplopia due to commitant strabismus
e. Glasses can sometimes cure diplopia

Why should we manage strabismus?

- Diplopia
- Binocular single vision
- Stereopsis
- Psychosocial aspects

Double vision is a very disturbing handicap of acquired strabismus in patients older than 6 years of age. In younger children diplopia complains disappear due to cerebral suppression of the second image sometimes leading to amblyopia. In visually mature patients the diplopia can be a very disturbing symptom and may prevent normal functions like driving a car and job requirements. Several treatment options will be described in this lecture. The benefits of binocular single vision are lack of diplopia, the possibility of stereopsis, which in return will facilitate good eye hand coordination and optimal integration of vision in the Gestalt of perception with the help of all 5 human senses.
As human primates (Homo Sapiens) one of our evolutionary benefits is the use of stereovision and working with tools (Homo Faber). This has given us an evolutionary advantage over other species resulting in space technology and microsurgery just to name a few.
Another disturbing aspect of strabismus can be disfiguring eye motility. As human beings we rely among other things on non-verbal communication in which proper social eye contact is crucial. In most cultures strabismus has been associated with negative interpretations, like witchery, the evil eye etc. However in some cultures it was seen as a gift of the gods creating a career as a priest. In the modern western society straight eyes will give a person a better chance of getting jobs, friends and partners. Even children from the age of less than 6 years will show their negative feelings towards peers with strabismus.

The main stay of strabismus treatment is surgical correction to solve the problems with diplopia,, to correct binocular single vision and restore stereovision if at all possible. For laymen the correction of disfiguring strabismus is by far the most recognizable benefit of strabismus correction ensuring normal social eye contact.

However not all strabismus can be corrected with surgery. So the mainstay of this presentation will show examples of non- surgical treatment of symptoms of strabismus.

Non-surgical management of strabismus:
- Optical
- Pharmaceutical
- Orthoptic exercises

Optical treatment of strabismus:
- Plus or minus glasses
- Prism glasses
- Bifocal glasses
- Bangerter foils
- Occlusion
- Occlusion IOL
- Eccentric iris-print scleral contactlens

Plus glasses can correct full accommodative esotropia (Swimming pool ET). In some cases bifocal add can correct convergence excess esotropia at near.

Minus glasses can correct intermittent exotropia by stimulating accommodation and thus keeping the exotropia under motor control.

Prism glasses can correct small angle commitant strabismus with diplopia to give the patient the comfort of single vision in primary gaze and alleviate also acquired diplopia in: Thyroid related strabismus, 4th and 6th nerve palsy, post traumatic strabismus. Fresnel stick on prisms can correct up to 40 prism diopters. Ground in prims are limited to 5 prism diopters (heavy and thick).

Bifocal glasses can correct high AC/A refractive accommodative esotropia.

Bangerter foils with increasing density (from 10-90%) can suppress the double image without visual haze of the glass to the bystanders. A cheaper solution is Scotch tape or leucoplast.

In severe cases an occluding IOL can be used. Either Artisan in phakic eyes or PCIOL in aphakic or pseudophakic eyes. This is a permanent solution but deprives vision and visual field of the treated eye.

Occluding contact lenses can be used ad liberty of the patient without surgical intervention. Some iris-print scleral contact lenses can be printed eccentral to correct underlying disfiguring strabismus.

MEDICAL TREATMENT OF STRABISMUS:

Botox can paralyse an overacting eye muscle (antagonist) in acute 6h nerve palsy or in traumatic eye muscle injury.
Bupivacaine can cause a constriction of an eye muscle.
Steroids in Thyroid eye disease, acquired Browns syndrome and myositis
Anticholinesterase agents in residual esotropia
Mestinon in (ocular) myasthenia

ORTHOPTICS: The only proven eye exercises are convergence training programs, like pencil push-ups in convergence insufficiency.

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MCQ answers page 173

1. **Answer: e**

2. **Answer: c**

3. **Answer: c**

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Friday October 7, 2016

• Common Optic Neuropathies in Adults: Diagnosis, Treatment and Prognosis	08:30 - 10:00
• Break	10:00-10:30
• Case Presentations I: Odd and Unusual Things in Neuro-ophthalmology	10:30 - 11:00
• Systematic Approach to the Ocular Motor System	11:00 - 12:30
• Lunch	12:30-13:30
• Uncommon but Important Causes of Visual Loss	13:30 - 15:00
• Break	15:00-16:00
• Recognizing the Emergencies: From Symptom to Diagnosis	16:00-17:30
• Case Presentations II: Odd and Unusual Things in Neuro-ophthalmology	17:30-18:00

Saturday October 8, 2016

• Paralytic Strabismus: Diagnosis, Evaluation and When to Treat	08:30 - 10:00
• Break	10:00-10:30
• Case Presentations I: Odd and Unusual Things in Strabismus	11:30 - 11:00
• Amblyopia, Nystagmus and Secondary Strabismus	11:00 - 12:30
• Lunch	12:30-13:30
• Nonparalytic Esodeviations and Exodeviations	13:30 - 15:00
• Case Presentations II: Odd and Unusual Things in Strabismus	15:00 - 15:30