European University Professors of Ophthalmology

EUPO2008
course

September 5-7, 2008 • Geneva, Switzerland

PROGRAMME

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Neuro-Ophthalmology and Strabismus

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Illustration: The Old Clown, Van Dongen (1906) - Musée du Petit Palais - Genève

PROGRAMME

Organizer: Avinoam B. Safran, MD
Professor and Head, Geneva University Eye Clinic

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Welcome address

Avinoam B. Safran, Organizer

We are delighted to welcome you at the 2008 Annual Course of European University Professors of Ophthalmology (EUPO).

This course follows a tradition established in 1988, involving an annual structured subspecialty course in ophthalmology. Most of the ophthalmology curriculum is covered over a 4 year period to allow residents to get an overview of theoretical knowledge during their residency period. Previous EUPO courses have been held once a year in different places in Europe.

In 2008 the course is taking place in Geneva, Switzerland, and is given by prominent neuro-ophthalmology and strabismus specialists.

The first day of the meeting will be devoted to an update on diagnosis and treatment in neuro-ophthalmology. On Saturday, September 6, sessions will focus on concepts of strabismology. Lectures will be given by renowned specialists in these fields, from Europe and abroad.

Finally, on sunday morning, a Satellite Symposium on higher visual functions will take place. It will deal with a number of fascinating newly recognized aspects of elaborate visual processing.

The venue in Geneva is unique. The city and its environment are superb. Geneva is located on a beautiful lake, the largest in Europe, set in magnificent mountain scenery. Numerous sites evoke Geneva's historical past and humanistic tradition: the streets of the old city, the magnificent medieval castle of Chillon located on the lake, the many international institutions based in Geneva, including the United Nations Organization, the World Health Organization, the International Committee of the Red Cross, and the European Centre for Nuclear Research, with its second largest particle accelerator in the world. Mt. Blanc is only a one-hour drive from the city.
We are therefore confident that the program and your stay in Geneva will be memorable.

Cordially yours,

Avinoam B. Safran, MD
Professor and Head, Geneva University Eye Clinic
Organizer of the 2008 EUPO Annual Course

The sequence of the EUPO courses

2008	Geneva	Neuro-ophthalmology and strabismus
2007	Vienna (SOE)	Glaucoma and uveitis
2006	Ghent	Retina
2005	Berlin (SOE)	Cornea
2004	Nijmegen	Neuro-ophthalmology and strabismus
2003	Madrid (SOE)	Glaucoma and uveitis
2002	Erlangen	Retina
2001	Istanbul (SOE)	Cornea
2000	Leuven	Neuro-ophthalmology and strabismus
1999	Stockholm (SOE)	Glaucoma and uveitis
1998	Amsterdam (ICO)	Chorioretina
1997	Budapest (SOE)	Cornea, conjunctiva, lids, orbit
1996	Athens	Neuro-ophthalmology and strabismus
1995	Milano (SOE)	Uveitis, lens, glaucoma
1994	Montpellier	Retina
1993	Santiago de Compostella	The external eye
1992	Brussels (SOE)	Neuro-ophthalmology and strabismus
1991	Torino	Uveitis, lens, glaucoma
1990	Bonn	Chorioretina
1989	Leuven	The external eye and orbit
1988	Nijmegen	

THURSDAY, September 4, 2008 17:00 - 19:00

Welcome reception

Geneva University Hospital

Registration and opening reception.

FRIDAY, September 5, 2008 19:00 - 23:00

EUPO Party

With the Swiss National Circus.
A cocktail will be served before the show at the Circus Bar.

PROGRAMME

THURSDAY, September 4, 2008

17:00 - 19:00 Registration & welcome reception

FRIDAY, September 5, 2008

09:00 **Welcome address**
G. VAN RIJ - President
A.B. SAFRAN - EUPO 2008 Course organizer

The Edmée Mariotte Session 1 — **first morning session**

Moderators: G. Van Rij - A. Schnider		Course	Page
09:05	**Arteritic ischemic optic neuropathies: giant cell arteritis and others** F.X. BORRUAT	*1*	17
09:25	**Neuro-ophthalmologic manifestations of AIDS** N. CASSOUX	*2*	23
09:45	**Isolated optic neuritis: management in the light of recent studies on early treatment of MS** J.D. TROBE	*3*	25
10:30	**Coffee Break**		

The Edmée Mariotte Session 2 — **second morning session**

Moderators: J.D. Trobe - W. Spileers		Course	Page
10:55	**Welcome address** by the General Director of Geneva University Hospitals		
11:00	**Optic disc edema: ultrastructural mechanisms and clinical manifestations** A.B. SAFRAN	*4*	33
11:20	**Drug-induced neuro-ophthalmic adverse effects** S. DOTAN	*5*	37
11:40	**Optic nerve protection and regeneration; current opportunities and perspectives, and critical considerations on electrical stimulation on the diseased optic nerve** L.A. LEVIN	*6*	39
12:00	**Historical vignette: Edmée Mariotte: From Gas physics to blind spot physiology** P. AYDIN	*7*	45
12:30	**Lunch**		

FRIDAY, September 5, 2008

The Charles Bell Session 3 — first afternoon session

Moderators: L.A. Levin - A. Vighetto		Course	Page
14:30	**Vision and the migrainous brain** D. MILEA	*8*	47
14:50	**Alterations of image interpretation** A. SCHNIDER	*9*	49
15:10	**An underestimated handicap: congenital prosopagnosia** T. GRÜTER	*10*	51
15:30	**Homonymous hemianopia: consequences and adaptive processes** S. TRAUZETTEL-KLOSINSKI	*11*	55
16:00	**Coffee Break**		

The Charles Bell Session 4 — second afternoon session

Moderators: P. Aydin - C. Vignal		Course	Page
16:30	**Alterations in motor control of the eyelids** C. VIGNAL	*12*	59
16:50	**Update on the Pupil Light Reflex: Clinical implications of a new class of photoreceptors** A. KAWASAKI	*13*	65
17:10	**New cerebral imaging in neuro-ophthalmology practice: indications and limitations** A. VIGHETTO	*14*	69
17:30	**The differential diagnostic problems of Van Dongen's Old Clown** R. MANOR	*15*	73
18:00	**End of session**		
19:00	**EUPO Party**		

PROGRAMME

SATURDAY, September 6, 2008

The Louis-Emile Javal Session 5 — **first morning session**

Moderators: J.R.M. Cruysberg - J.S. Elston		Course	Page
09:00	**Update on amblyopia** E.C. CAMPOS	***16***	75
09:20	**Spatial distortions, temporal instability and spurious colours: "Positive" symptoms in amblyopic vision?** R. SIRETEANU	***17***	81
09:40	**Development of ocular motor functions, critical periods and clinical implications** J. YGGE	***18***	85
10:00	**Diplopia** M. CORDONNIER	***19***	93
10:30	**Coffee Break**		

The Louis-Emile Javal Session 6 — **second morning session**

Moderators: H.J. Simonsz - M.C. Brodsky		Course	Page
11:00	**Convergence and divergence palsy - real or imagined ?** J.S. ELSTON	***20***	101
11:20	**Diagnosis and management of infantile nystagmus** I. GOTTLOB	***21***	103
11:40	**Historical vignette: Louis-Emile Javal, yesterday and today. Statics and dynamics of the ocular globe** A. ROTH	***22***	107
12:00	**Lunch**		

SATURDAY, September 6, 2008

The Alfred Bielschowsky Session 7 — first afternoon session

Moderators: A.Boschi - J. Ygge		Course	Page
14:30	**The management of congenital and acquired fourth nerve palsies** K. LANDAU	*23*	109
14:50	**Timely management of infantile strabismus** H.J. SIMONSZ	*24*	113
15:10	**Does infantile esotropia arise from a dissociated deviation ?** M.C. BRODSKY	*25*	117
15:30	**Coffee Break**		

The Alfred Bielschowsky Session 8 — second afternoon session

Moderators: I. Gottlob - K. Landau		Course	Page
16:30	**Congenital dysinnervation syndromes: new understanding of clinical manifestations** J.R.M. CRUYSBERG	*26*	125
16:50	**Diagnosis and management of restrictive myopathies** A. BOSCHI	*27*	131
17:10	**Historical vignette: the Bielschowsky legacy** H.J. SIMONSZ	*28*	135
17:30	**Concluding remarks**		
17:30	**Closing address** W. SPILEERS - Secretary General and Treasurer		

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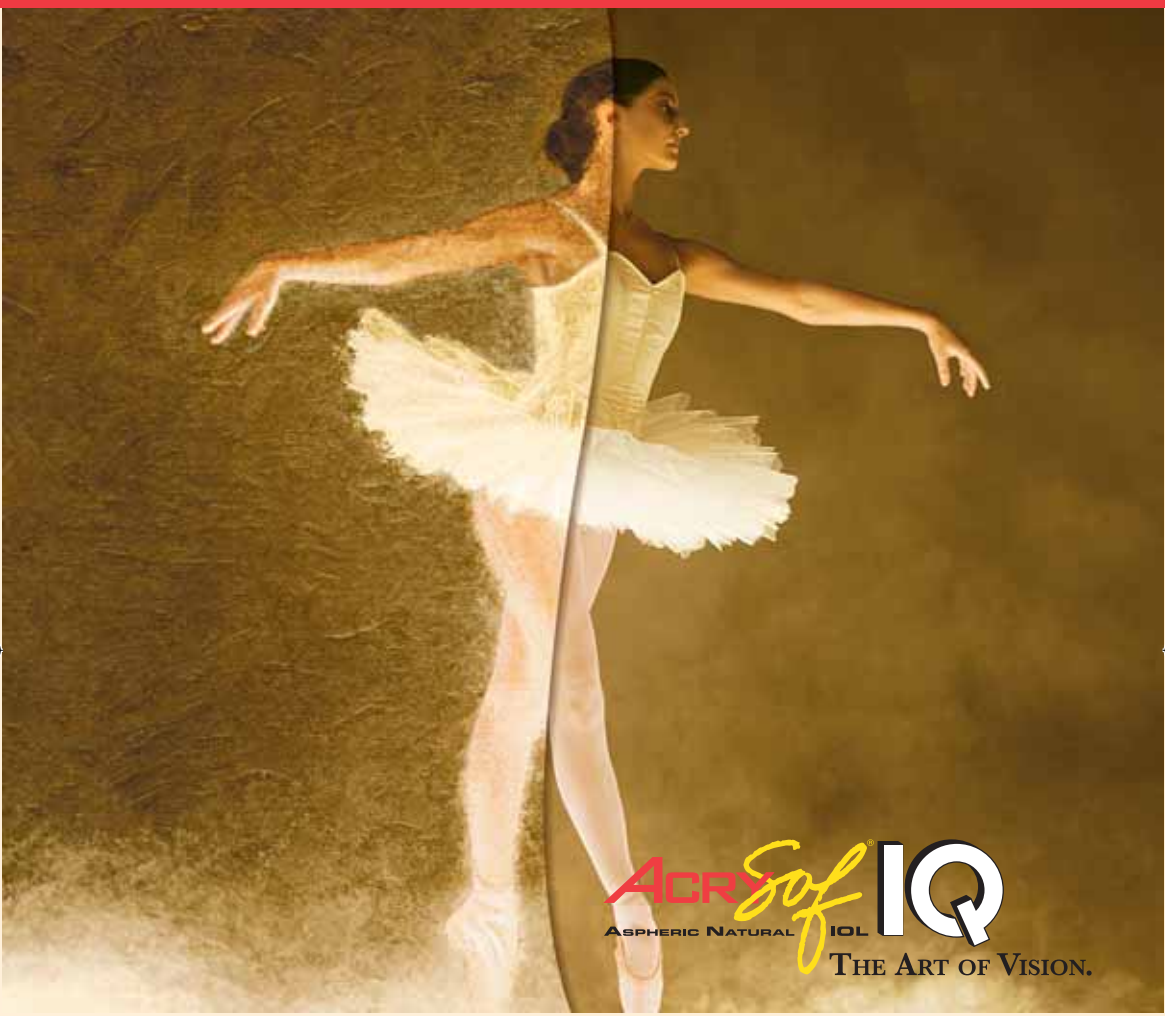

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SUNDAY, September 7, 2008

The Charles Bonnet Conference on Disorders of Higher Visual Functions

Organizers: A.B. Safran - T. Landis

08:30 **Morning coffee**

09:00 **Subliminal visual perception**
L. NACCACHE

09:30 **Normal false memory and pathological confabulation: How to manipulate an eyewitness**
A. SCHNIDER

10:00 **The emotional factor in visual processing**
SPEAKER TO BE CONFIRMED

10:30 **Autoscopy, heautoscopy and "out of body" experience**
T. LANDIS

11:00 **Synesthesia: visual sensations following stimulation of other sensory modalities. From normal to diseased conditions and impact on artists' experience**
P. BRUGGER


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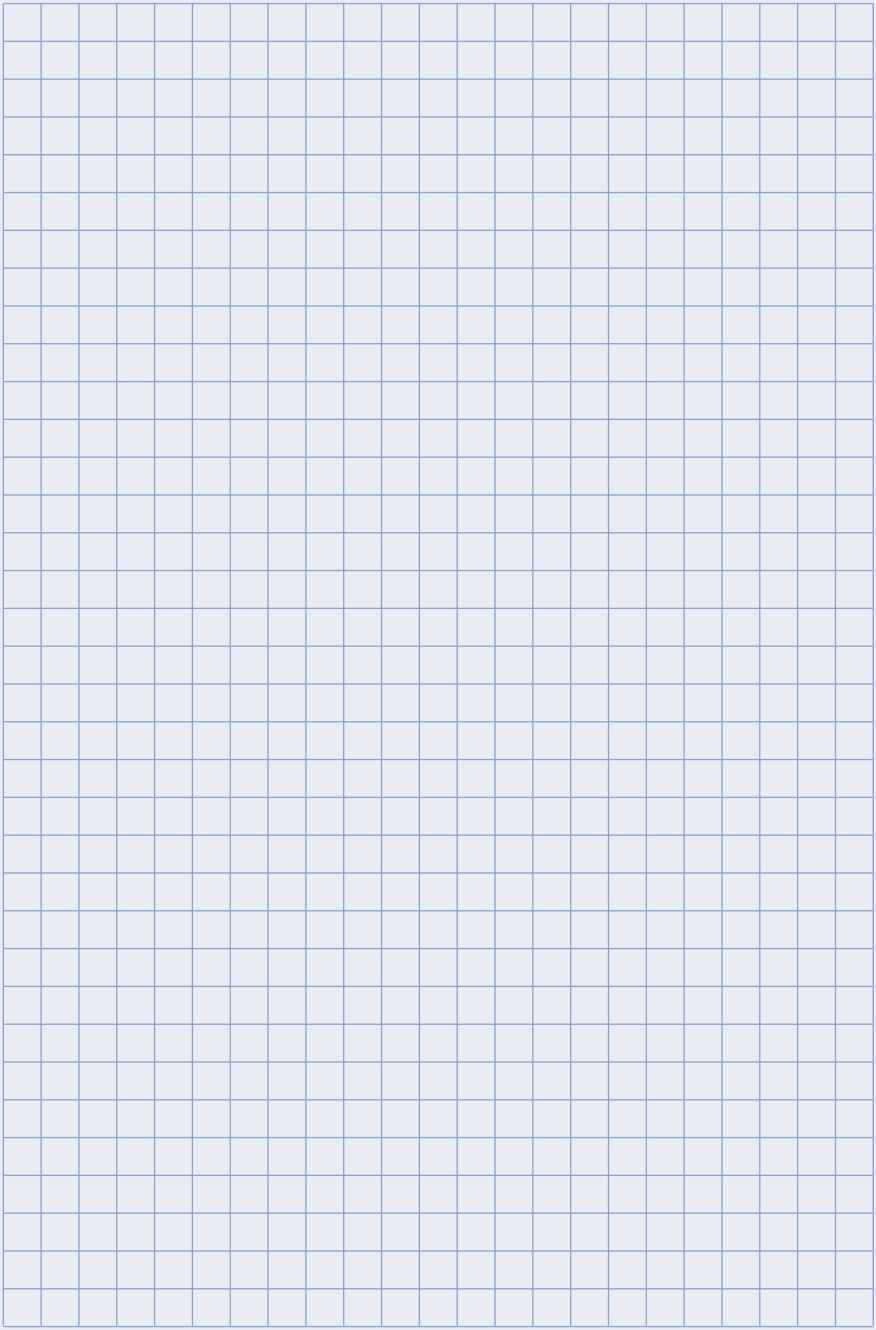


Arteritic ischemic optic neuropathies : Giant Cell Arteritis and others

| François-Xavier Borruat, Lausanne, Switzerland |

Ischemic optic neuropathy (ION) can be anterior (AION) or posterior (PION), AION being the most frequent presentation (90%) of ION. In the case of AION, a swollen optic disc will be seen on funduscopy whereas the fundus will initially appear normal in the case of PION. Depending on the site and the intensity of ischemia a variable combination of visual acuity loss, dyschromatopsia and visual field loss will be present.

ION can result from a non-arteritic or from an arteritic mechanism, the non-arteritic form being the commonest (90% of ION).

An arteritic mechanism has been implied in several various inflammatory disorders (herpes zoster, relapsing polychondritis, rheumatoid arthritis, Takayasu's arteritis, PAN, SLE, Churg-Strauss, Behçet's, Crohn's, Birdshot chorioretinopathy, delayed radiation necrosis), but giant cell arteritis (GCA) is by far the commonest cause of an arteritic ION.

Giant cell arteritis

1.Pathophysiology of GCA

GCA is the most common primary vasculitis of adults in the Western world. It affects mostly Caucasians., and is rare in African-American and Hispanic populations. The risk factors is increasing age, and women are more prone to develop it.

There is a genetic predisposition (HLA-DR4 and HLA-DRB1*04) but the trigger is still unknown, possibly a viral or bacterial infection.

GCA results from two inflammatory components: a local vasculitis and a systemic inflammation. The vasculitis of GCA affects large and medium-sized arteries, affecting the aorta, extracranial carotid , subclavian, axillary, vertebral; rarely, coronary femoral arteries.

2.Clinical Subtypes of GCA

a. Systemic inflammatory syndrome
Non-specific constitutional symptoms such as asthenia, arthralgias, myalgias, achiness, anorexia, weight loss, night sweats, fever of unknown origin are frequently present.

A high sedimentation rate, elevated acute phase reactants likeC-reactive protein, haptoglobin and fibrinogen, elevated liver function tests, low albumin levels, thrombocytosis and a normocytic normochromic anemia, elevated interleukin-6 are very frequently found.

b. Cranial arteritis

It results from a localized vasculitis with focal tissue ischemia, and the branches of the carotid arteries are most frequently affected. The symptoms consist of headaches, facial pain, carotidynia, scalp tenderness, jaw claudication, painful dysphagia, hoarseness and visual loss. Rarely, necrosis of the scalp or tongue are present and carry a grim prognosis (41% death).

c. Large vessel vasculitis

A localized vasculitis of the aorta, subclavian, axillary arteries will result in either aortic dilation and aneurysm (mostly thoracic aorta), or a stenosis in the superior branches of the aortic arch, subclavian or axillary arteries. A negative temporal artery biopsy is found in 50%. Its incidence is probably underestimated, being up to 27% of GCA patients. An annual abdominal ultrasound, chest radiograph and echocardiogram might be worthwhile.

3. Clinical Manifestations of GCA

a. Systemic signs and symptoms

The classic description (elderly, new headache, jaw claudication, fever, anorexia, polymyagia rheumatica, tender temporal artery) is found in only 50-65% of patients. Most GCA patients present one or more of the following: anorexia, asthenia, malaise, myalgia of the large proximal muscles, arthralgia, weight loss, fever.

b. Headache and craniofacial pain

Headaches are present in: up to 90%, and are frequently bilateral. Per se it is non specific but patients frequently report the unusual nature of their headaches. Scalp tenderness or an exquisite sensitivity (head on a pillow is painful) can be present.

Jaw claudication is the most specificsymptom but is present in only 40% of patients. It results from ischemia of the masseter muscle, secondary to a vasculitis and occlusive stenosis in the maxillary artery, and therefore correlates highly with a positive temporal artery biopsy.

c. Neurologic manifestations

Cerebral and brainstem stroke syndromes, dementia , psychosis and coma related to diffuse cerebral ischemia, spinal cord infarction, seizures, subarachnoid hemorrhage have been reported. However, peripheral neuropathies are more common (14% of neurologic complications).Audiovestibular dysfunction: hearing loss, tinnitus, vertigo, disequilibrium and dizziness can be found.

4. Occult GCA

A focal dysfunction (acute visual loss, respiratory symptoms, peripheral neuropathy, dementia, stroke, coronary ischemia, pulmonary artery thrombosis, hematuria, renal failure, mesenteric infarction, or even a tumorlike lesion of the breast, ovary or uterus) with minimal or absent systemic manifestations is found: in 5% to 38%

5. Visual Manifestations of GCA

It is common (14-70% of GCA patients), and GCA should be considered in any elderly patient with a new visual disturbance, be it transient or permanent.

a. Transient visual loss

Present in 30-54% of patients, it results from an insufficient perfusion of the optic nerve, retina or choroid. It is usually of short duration (1-2'), may recur, and can be precipitated by a change in posture. It precedes permanent visual loss in 50-64% of untreated cases and is therefore an ophthalmologic emergency requiring immediate high-dose steroids. Hospitalization and.strict bedrest is advised.

b. Permanent visual loss

Results from ischemia from the retina to the occipital lobe, but an anterior ischemic optic neuropathy (AION) most frequently found (80-90%). Arteritic-AION (severe pallid ("chalky white" disc edema, Figure 1) results from an inflammatory occlusion of the short posterior ciliary arteries, and is often accompanied by choroidal ischemia or ciliary artery occlusion.

Left untreated, there is a 25-50% incidence of contralateral visual loss within 1-14 days.

Other causes of visual loss are: central retinal artery occlusion (10-13%) (Figure 3), posterior ischemic optic neuropathy, cilioretinal artery occlusion, choroidal infarction, ischemia to the chiasm or postchiasmal visual pathway. Cotton-wool spots can be found (Figure 2).

Fluorescein angiography frequently reveals delayed choroidal perfusion (Figure 3).

c. Diplopia

Transient or constant diplopia is found in 6-20% of patients with visual manifestations. Diplopia can result from ischemia to extraocular muscles, cranial nerves, brainstem ocular motor pathways. Clinically, there can be weakness of a single extraocular muscle, an isolated cranial nerve III, IV or VI palsy, combined cranial nerve palsies, skew deviation, internuclear ophthalmoplegia, one-and-a-half syndrome and upgaze palsy

d. Others

Pupils can be affected (tonic pupil, Horner pupil) or global ischemia to the eye/orbit can result in acute hypotony, ocular ischemic syndrome, or orbital ischemia (Figure 4).

6.Laboratory Investigations in GCA

a. Erythrocyte sedimentation rate
Classically, ESR is elevated in GCA (ESR ≥ 50mm/hour in 85%). However, 15% of biopsy-proven GCA have a normal ESR. A normal ESR does not formally rule out GCA.

b. C-reactive protein
CRP is a more sensitive indicator of active GCA compared to the ESR. CRP is nonspecific, but a specificity for GCA of 97% is reached when both ESR and CRP are elevated.

c. CBC
Elevated platelet count and a normocytic, normochromic anemia (< 12 g/dL) are frequent.

7.Diagnosis of GCA

a. Temporal artery biopsy
A biopsy ≥2 cm (>3-5 cm preferably) with multiple fine sections (0.25-0.5 mm) is necessary, due to the presence of skip lesions and post-fixation shrinkage. Frozen sectioning is unreliable, with a high rate of false negatives.

In case of a negative biopsy, the chances that a second biopsy will be positive are 5-9% if there is a high index of suspicion for GCA. If the index of suspicion is low, there is no need for a second biopsy. A negative biopsy is found in up to 10-15% of cases (large-vessel vasculitis, absence of systemic inflammation).

b.Pathology findings:
An active arteritis is detectable for up to 6 weeks after initiation of corticosteroids . Findings consist of panarteritis, granuloma formation, thickened intima, fragmented internal elastic lamina, infiltration (mononuclear cells, multinucleated giant cells in 50% of specimens).

c. Role of non-invasive imaging of the cranial arteries
Echography: can reveal a dark echo around the temporal artery lumen (“halo”) <-> edema of the vessel wall. The halo sign has a low sensitivity for detecting GCA (40-80%), is not a pathognomonic for GCA (i.e. Wegener’s granulomatosis) but is more specific for GCA if the halo sign is present with a thickness of 1 mm or more (Figure 5).

MRI: may reveal inflammatory vessel wall, but sensitivity and specificity not yet determined.

SPECT (promising tool), PET scanning (too low resolution)

8.Treatment and Prognosis of GCA

a. Corticosteroids
Universally used but no randomized, controlled studies !
Initial therapy: 60 mg or more of prednisone daily without delay (1mg/kg/d). There is no evidence that intravenous is superior to oral steroids. Also, there are potential ad-

verse effects of high dose intravenous steroids in the elderly population (sudden death, cardiac arrhythmia, aseptic osteonecrosis, acute psychosis, sepsis and anaphylaxis).

In case of any acute visual or neurologic symptom or sign: hospitalization, bedrest, intravenous methylprednisolone (1000 mg daily in single or divided doses given for 3 days) followed by prednisone 80 mg daily or 1-2 mg/kg/day.

Maintenance dose: high dose oral prednisone for at least 4-6 weeks until systemic symptoms have subsided and ESR and/or CRP have normalized.

Tapering regimen: slow process, individualized. Initial reduction: 5-10 mg per month, then more cautiously (1 mg per month when the daily dose reaches 10-15 mg).

- patient evaluation and laboratory markers before each reduction in steroid dosage

Duration of treatment: after 2 years, many patients are still on steroids.

Supplementary: calcium, vitamin D and peptic ulcer prophylaxis

Bone densitometry and physical counselling.

b. Visual outcome with corticosteroids

The reported rates of visual recovery in GCA, range from 15 to 34%, only 5% improving their central visual field. There are anecdotal reports of remarkable visual recovery. However, there is an overall trend for better visual outcome if steroids are begun earlier.

Core messages

1. **Suspect an arteritic form of ION if:**
   a. Bilateral simultaneous visual loss
   b. Very profound visual loss (hand motion or less)
   c. Pallid optic disc edema, no hemorrhages, normal cupping of the fellow optic disc
   d. Choroidal non-perfusion, cilioretinal artery occlusion
   e. Abnormal biological parameters (ESR, CRP, FBCC)
2. **Look for systemic signs and symptoms of inflammatory disorder**
3. **Consider GCA in any patient > 60 years-old with visual symptoms**
   a. Ask for unusual symptoms (headaches, jaw claudication, scalp tenderness)
   b. Assess both ESR and CRP
   c. Transient diplopia or visual loss can herald impending permanent visual loss
   d. High index of suspicion of GCA : immediate steroids
   e. Contralateral visual loss in 60% of untreated cases
   f. Temporal artery biopsy can be delayed by a few days/weeks
   g. Monitor steroids side-effects (calcium, glucose, blood pressure)

Figure Legends

Figure 1
Profound visual loss (bare light perception) resulted from this AION in a 75 year-old patient with GCA.
The optic disc is swollen, diffusely very pale, without papillary hemorrhages.

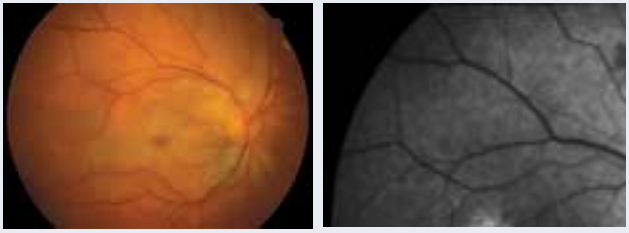


Figure 2
This 82 year-old man, otherwise asymptomatic, became suddenly blind in his right eye due to central retinal artery occlusion. ESR was 15mm, but fluorescein angiography revealed also a marked delay in filling the nasal choroid (42 seconds). Temporal artery biopsy was positive.

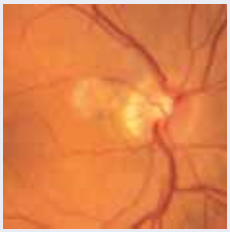


Figure 3
Cotton-wool spots were found in both eyes of this 77 year-old woman who complained of two episodes of transient visual loss.

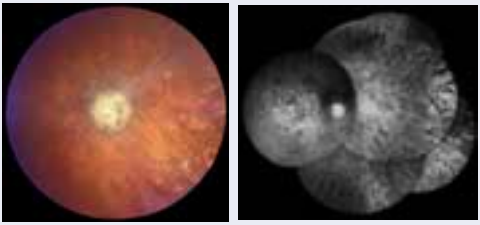


Figure 4
Complete blindness, ophthalmoplegia and ocular hypotension resulted from an orbital infarction. Three months after the acute event, the optic disc is white, there are ghost retinal vessels, and the retinal pigment epithelium shows scars from previous ischemia. Fluorescein angiography emphasizes the importance of choroidal ischemia.

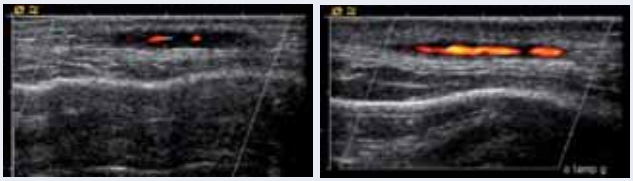


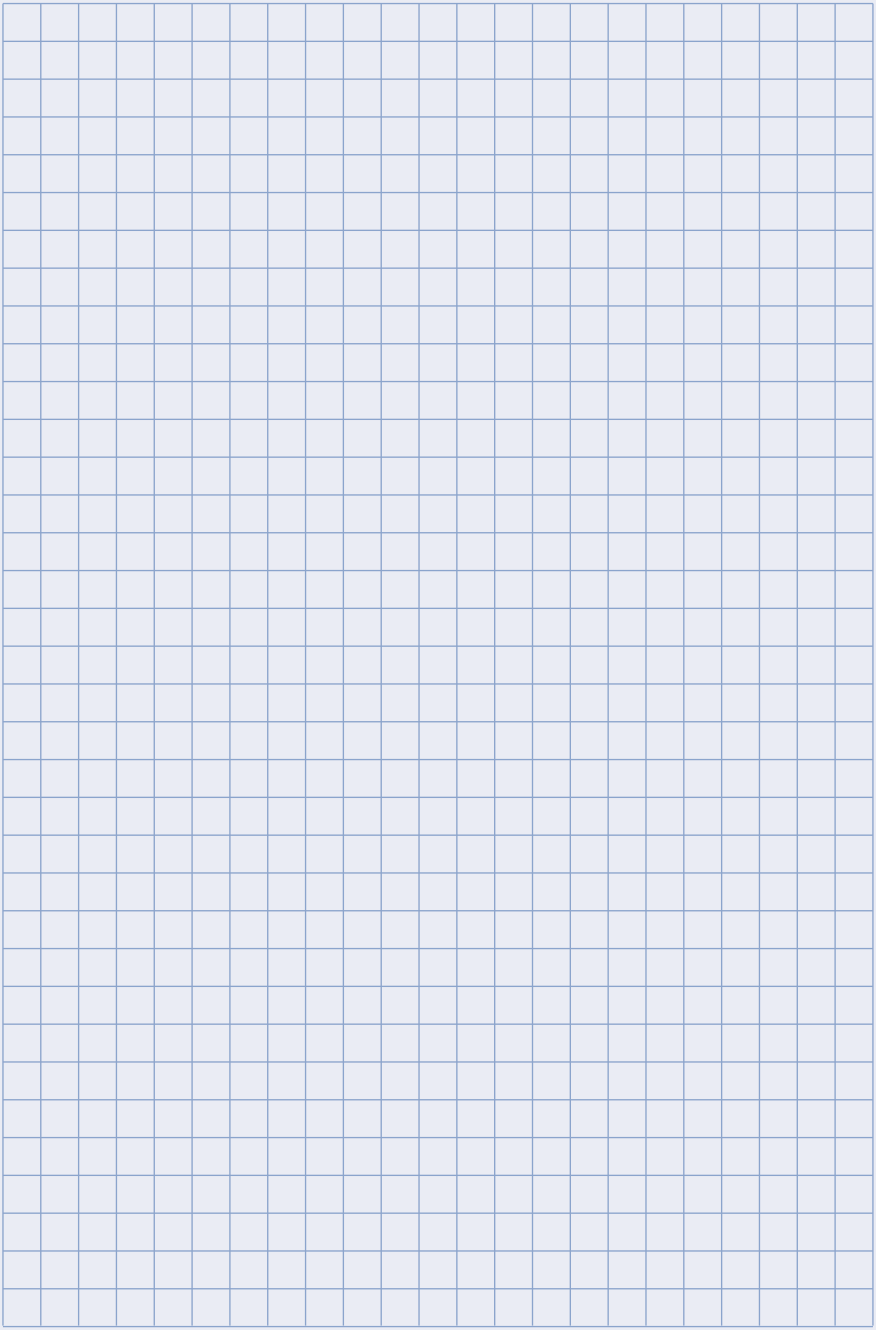
Figure 5
Echography of the temporal artery biopsy can reveal the edema within the vessel wall : the "halo sign". After corticosteroids, the lumen widens and the arterial flux regains a normal state.

Neuro-ophthalmologic manifestations of AIDS

| Nathalie Cassoux, Paris, France |

Département d'Ophtalmologie de l'Hôpital Pitié-Salpétrière, Paris, France

Neuro-ophthalomologic manifestations can affect 8% of AIDS patients. Since the introduction of highly active antiretroviral therapy (HAART), patients can be divided into 2 groups, those having an immune reconstitution and those having an immunodeficiency. Patients having an immunodeficiency because the treatment remains non efficient or because they can not take this expensive therapy for economical reasons, have neuro-ophthalmologic manifestations mostly due to opportunistic infections. Patients with immune reconstitution may present infections mostly related to syphilis but above all, neuro-ophthalmologic manifestations are related to tumors or HAART side effects. Tumors are to date the first cause of death in patients with immune reconstitution. HAART gives an immune recovery but also major side effects (diabetes, hyperlipidemia, hepatic toxicity….), main cause of ischemic optic neuropathy, cerebral stroke, venous thrombosis. Cooperation with infectiologists is of great importance to know immune status of patients and treatment side-effects.



Isolated optic neuritis: management in the light of recent studies on early treatment of MS

| Jonathan D. Trobe, Michigan, United States |

University of Michigan

I. What is "Optic Neuritis"?

Optic neuritis is the term used to describe inflammation of the optic nerve. In most cases, the inflammation is idiopathic, probably autoimmune, and directed against central nervous system (CNS) myelin or oligodendrogliocytes, or both. The myelin destruction is therefore considered "primary," and it may be an isolated manifestation or part of more widespread CNS demyelination in multiple sclerosis (MS). In this outline, this form of optic neuritis will be called "typical."

Optic neuritis may also be a manifestation of inflammation that is part of sarcoidosis, connective tissue diseases (including idiopathic pachymeningitis), or infectious meningitis. In these circumstances, the destruction of myelin is considered "secondary" to another process. This form of optic neuritis will be called "atypical."

Typical optic neuritis has the following clinical features: 1) usually first affects individuals aged between 15 and 45 years, women more than men; 2) usually affects one eye; 3) occurs in "bouts", in which visual acuity loss and nerve fiber bundle visual field loss develops rapidly over a period of no more than 14 days; 3) periocular pain exacerbated by eye movement is very common; 4) arelative afferent papillary defect (RAPD) is usually present in the affected eye; 5) ophthalmoscopy may be normal ("retrobulbar neuritis") or show mild optic disc swelling ("papillitis") in the affected eye; 6) visual recovery occurs fully or almost fully in 90% over a period of six months; 7) an RAPD and/or optic disc pallor may persist in the affected eye; 8) there may be a history or current clinical manifestations of multiple sclerosis; 9) brain (and cervical spine) MRI may show signal abnormalities of multifocal demyelination.

When typical optic neuritis occurs without any other manifestations of MS, but MRI shows typical signal abnormalities of MS, the term "clinically isolated syndrome" (CIS) of optic neuritis is applied.

II. Management of Optic Neuritis

The management of patients with optic neuritis is controversial. There are three aspects: 1) diagnostic evaluation; 2) corticosteroid treatment; and 3) immunomodulatory treatment.

A. Diagnostic evaluation

The Optic Neuritis Treatment Trial (1988-2006) (1) has shown that blood tests and lumbar puncture disclose no valuable clinical information in patients with typical optic neuritis. Brain MRI is extremely valuable in that a normal study (found in about 50%) reduces the likelihood of developing MS within 5 years to 20%, whereas one or more signal abnormalities characteristic of MS raise the likelihood of developing clinical MS to 50%. MRI is also valuable in excluding conditions that produce atypical optic neuritis or conditions that mimic optic neuritis (tumor, ischemia).

Therefore, in patients who have a first attack of typical optic neuritis, I do not order blood tests or a lumbar puncture. I offer to perform a brain MRI (some patients do not want this test because they do not want to know if their chances of developing MS are high). I order an MRI if the patient wishes to be treated with corticosteroids (see below).

B. Corticosteroid treatment

Corticosteroids, in one form or another, have been used to treat optic neuritis for over 50 years. The Optic Neuritis Treatment Trial (1), comparing a 14-day course of oral prednisone 1 mg/kg, a 3-day course of intravenous methylprednisolone 1 gm/day followed by 11 days of a tapering course of prednisone, and placebo, found that visual function improved slightly faster during the first week in the intravenous group but there was no difference in final visual outcome between the three groups. The intravenous group with abnormal MRI but no prior history of MS had a reduction in the development of MS at two years but that benefit disappeared by the third year. As compared to the other two groups, the oral prednisone group had a doubling in the frequency of recurrent optic neuritis, a negative effect that has become widely known.

In support of treatment with intravenous corticosteroids are three facts: 1) the risks of pulsed intravenous corticosteroids are low; 2) optic neuritis is an inflammatory disorder, and corticosteroids benefit most inflammatory disorders; 3) atypical optic neuritis, a diagnosis not always easy to exclude, is often responsive to corticosteroids.

Therefore, if I believe that the diagnosis is typical optic neuritis, I offer the intravenous corticosteroid treatment. But because this treatment may alter the course of disease, I prefer to have a brain MRI.

Although intravenous methylprednisolone (MP) is the standard medication, there is evidence that the bioavailability of oral prednisone 1250 mg is equivalent to that of 1000 mg of intravenous methylprednisolone after 24 hours. (2)

After a first attack of optic neuritis, should corticosteroids be used periodically (yearly, for example) even if there is no recurrence of optic neuritis? There is no hard evidence of long term benefit, but one study compared a regimen of intravenous methylprednisolone followed by prednisone given periodically to patients with and without MS

relapses (3) and found that the non-relapsing group showed fewer MRI "black holes," less global brain atrophy, and slightly less disability at 5 years. Until there is firmer evidence, I am willing to do periodic retreatment of these patients, but only if patients ask for it.

Should patients with recurrent optic neuritis be treated? The American Academy of Neurology practice guideline endorses this treatment for any "acute attack of MS" as a Class A recommendation (4) primarily on the basis of faster recovery. I support treating recurrent typical optic neuritis, especially when it affects the second eye.

C. Immunomodulatory agents

These agents reduce relapse rate and MRI signal accumulation modestly when given to patients with short-spaced relapses, but there is no convincing evidence that they retard MS disability.(5) The agents are expensive, inconvenient, and sometimes unpleasant. They create a constant reminder to the patient of being chronically ill. Moreover, natural history data on optic neuritis presenting as a clinically isolated syndrome (CIS) indicate that untreated patients do not have severe long term visual (6-8) or neurologic disability. (9-11).

1. Short-term effects

Trials clearly show that these drugs reduce the short-term relapse rate and the accumulation of MS-like MRI signal abnormalities in patients with established MS.(5) The United States Food and Drug Administration (FDA) approved them on that basis. But their beneficial effect is modest. At best, they have reduced relapse rate by only 35% over two years. Approximately 65% of treated patients experienced at least one relapse within the two-year trial period.

What is the effect of these agents on patients with optic neuritis? There have been no trials in patients with optic neuritis who have normal brain MRI because the likelihood that they will develop MS is low (5-year risk is 20%). The trials have involved patients with optic neuritis who have at least one MRI signal abnormality ("clinically isolated syndrome" of optic neuritis).

Trials of interferon beta 1a (Avonex) (12) and interferon beta 1a (13) have both shown a reduction in the development of MS and additional MRI signal abnormalities in patients with CIS of the optic nerve, brain stem, or spinal cord. However, when the 192 optic neuritis CIS patients with abnormal MRIs were analyzed separately from the entire CIS cohort in the Avonex (CHAMPS) study (14), there was only a $p = 0.05$ difference between the development of MS in the intravenous methylprednisolone/interferon beta-1a (Avonex) group and the intravenous methylprednisolone only group after two years. It was only if the outcomes of MS and development of one or more MRI signal abnormalities were combined that the interferon group showed a more powerful benefit ($p < 0.001$). Thus, the drug benefit in optic neuritis CIS may be more on the MRI than on the clinical changes. (The patients who had brain stem CIS or spinal cord CIS had a greater treatment benefit than did optic CIS in terms of reducing MS.(15)

2. Long-term effects

In the drug trials, the effect of immunomodulators on MS disability has been not been impressive. As judged by the Extended Disability Status Scale (EDSS), the most commonly used disability scale, Rebif only slightly reduces the 4-yr disability in r elapsing MS.(16) This study also showed a modest benefit of early vs delayed Rebif treatment on 4-year disability in a cross-over. But these data apply to MS patients, not to those with optic neuritis CIS.

In the optic neuritis CIS trials, there was no difference in disability after 2 (CHAMPS) and 3 years (ETOMS), respectively. In the report of the extended cross-over trial of CHAMPS, called CHAMPIONS, a 5-year EDSS of > 3 was present in 14% of the delayed Avonex-treated group as compared to 11% of the initial Avonex-treated group, a non significant difference (unpublished data presented at 2004 AAN Annual Meeting). An argument has been made that one would have to extend the trials out even longer to detect differences in disability among treated and untreated CIS or MS patients. However, Pittock et al (17) found that untreated MS patients with an EDSS of 2 or less at five years after disease onset have a >90% chance of remaining neurologically stable for the next 10 years or more. Some have argued that we are using a disability scale that fails to measure subtle but real differences.

3. Predictors of disability

If the immunomodulatory trials are not showing a treatment benefit on disability, can the use of these agents be defended on the basis of their effect on surrogates that ought to predict disability? (18) This argument is based on the following evidence:

a. Histopathology shows that inflammatory plaques often lead to axonal loss, a development widely acknowledged as being correlated with clinical disability. (19) The imaging equivalents of inflammatory plaques are enhancing focal white matter signal abnormalities which have been predictive of CIS conversion to CDMS. (12)
b. Immunologic evidence suggests that early epitope spreading leads to a predisposition for further demyelinating attacks. (21, 22)
c. Clinical studies show that frequent relapses and accumulation of MRI abnormalities in the early stages of MS predict a greater future disability. But evidence here is mixed. Weinshenker et al (23) showed that frequent relapses in the first two years after an initial attack predicted future disability, acknowledging that others had not found this association. For example, in a later large community study in Olmstead County, Pittock et al (24) did not find this association. The discrepancies may lie in the definition of a relapse. A true relapse should include new neurologic symptoms rather than an exacerbation of old symptoms and should not occur in a setting of a constitutional illness (which may simply be bringing out symptoms in vulnerable, previously demyelinated, regions). Brex et al (25) found only a modest correlation (r = 0.61) between MRI signal abnormality accumulation in the first five years and future disability. The ONTT found no correlation between the degree of MRI abnormalities at the time of first-attack optic neuritis

and future disability from MS. (9) It has been suggested that the conventional MRI parameters may not be sensitive enough to axonal loss, thought to be the determining pathologic substrate of neurologic deficits in MS. Indicators like diffusion tensor or spectroscopic MRI may be better predictors but the studies are premature.

4. Natural history of optic neuritis

A strong argument against treating CIS optic neuritis with immunomodulatory agents is based on the fact that untreated patients have very favorable long-term visual and neurologic outcomes.

The best natural history information about the visual and non-visual neurologic outcomes after first-attack optic neuritis comes from the ONTT.(6, 9) Disability is relatively mild ("benign MS"), much better than in patients whose MS is ushered in by brain stem or spinal cord symptoms. (23, 25) Ten years after first-attack optic neuritis, over 90% have at least 20/25 acuity in one eye; only 38% of patients develop MS, and if they do, they are rarely neurologically disabled. These findings are not at variance with those of other less ambitious studies, once proper corrections are made.(10, 11)

a. Visual outcome
   Ten years after optic neuritis in the ONTT, 70% had 20/20 acuity in both eyes, 86% had 20/20 acuity in one eye. (6) Even in patients with MS, visual acuity was >20/20 in the better eye in 88%, and >20/20 in the worse eye in 61%. Oddly—and importantly—relapses of optic neuritis did not appear to cause a major decrement in vision.
b. Neurologic outcome
   Ten years after optic neuritis, only 38% of patients developed MS in the ONTT. (9) Among 111 patients with MS examined ten years after optic neuritis, 66% had an EDSS < 3, which means that they had very mild disability. Only 14% had an EDSS > 6, or severe disability (only half of whom needed ambulatory assistance or could not walk). The long term EDSS in MS ushered in by brain stem or spinal cord CIS is much higher. (23, 25)

III. Conclusions about management

A. Diagnostic evaluation

If clinical features favor a diagnosis of typical optic neuritis, lumbar puncture is unnecessary. Brain MRI is also unnecessary unless patients wish information about prognosis for MS or if they will be treated with corticosteroids. Blood tests are unnecessary unless patients are to be treated with corticosteroids.

B. Corticosteroid treatment

For an attack of optic neuritis, intravenous methylprednisolone provides slightly faster visual recovery and is therefore optional. There is rationale but no evidence to

support prophylactic periodic retreatment of patients who have had optic neuritis in the past without clinical recurrence.

C. Immunomodulatory treatment

Although there is no strong evidence that these agents reduce long-term disability from MS, they reduce relapses and accumulation of MRI signal abnormalities which, in some studies, correlate with future disability. However, these measures are crude predictors of future disability. More refined MRI measures have been proposed (diffusion tensor, spectroscopy) but not widely tested. The lack of evidence for impact on disability may be because follow-up has not been long enough or because disability measures are not sensitive enough. However, natural history studies of optic neuritis CIS show that most patients who develop MS are not substantially impaired visually or neurologically after 10 years or more ("benign MS").

Based on my review of the evidence, I manage optic neuritis as follows:

1) Decide if diagnosis of typical optic neuritis is justified from clinical features. If so, I order blood tests only if patient wishes corticosteroid treatment. Order brain MRI if patient wishes prognostic information or if patient is to be treated with corticosteroids. I order a brain MRI periodically after optic neuritis to make sure "lesion burden" is not increasing, which might warrant immunodulatory treatment.
2) Treat with intravenous methylprednisolone 1 mg/kg for 3 days only if the patient wishes.
3) Treat with long-term immunomodulatory agents only if: a) accompanying brain stem or spinal cord manifestations of MS; b) frequent attacks of optic neuritis; c) a very high "lesion burden" on MRI; 4) a rapidly worsening MRI; or 5) emotional factors, such as a strong family history of MS or patient fear of MS.
4) If clinical features suggest an atypical optic neuritis or a mimicker of optic neuritis, I perform blood tests, MRI, other imaging studies, and lumbar puncture as indicated. If studies are negative, I treat empirically with corticosteroids. If necessary, I would consider other anti-inflammatory treatments.

IV. Future Directions

The role of the new drug natalizumab (Tysabri) in treatment of MS is promising but uncertain. This medication appears to be much more effective for MS than the previous immunomodulatory agents. However, because it caused progressive multifocal leukoencephalopathy in three patients in past trials, it was removed from clinical use. Reapproved under strict guidelines, it is infused monthly under physician supervision and should not be used except in patients who have failed conventional treatment.

The discovery that tumor necrosis factor inhibitors and plasmapheresis/intravenous immunoglobulin may be effective in neuromyelitis optica (NMO, Devic disease),

a disease that closely resembles MS—and may even be a variant of MS—has opened the question of whether these methods may also be more effective than conventional treatment in MS. Many trials are underway.

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Optic disc edema: ultrastructural mechanisms and clinical manifestations

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All neurons rely on axonal transport to maintain cellular viability. Transport is performed by motor proteins, kinesin and dynein, which move a variety of cargoes on microtubule tracks, including membrane organelles, protein complexes, signaling molecules, repair molecules, and cytoskeletal components.

Axonal transport is an energy-dependent process. It has been categorized into the following two main classes, fast and slow axonal transports.

- ***Fast axonal transport*** (20 to 400 mm/day) conveys many axonal and synaptic components, including mitochondria, vesicular precursors, and membrane components.
- ***Slow axonal transport*** (0.2 to 8 mm/day) is thought to move elements of the cytoskeleton, such as subunits of neurofilaments, and subunits of microtubules and proteins such as clathrin, actin, actin-binding proteins, and cytosolic enzymes.

Within axons, microtubules possess side arms composed of microtubule-associated proteins, linking the microtubules to neighboring microfilaments and neurofilaments. Neurofilaments also have side arms that interact with neighboring neurofilaments and microtubules. These side arms may be involved in the translocation of polymers down the axon for both microtubules and neurofilaments to produce slow axonal transport.

Microtubules are polarized, their minus ends being aligned towards the soma and their plus ends towards the synapse.

- The plus end directed motor protein transports cargoes at the nerve terminal anterogradely (***orthograde transport***),
- while the minus end directed motor protein retrogradely transports cargoes returning to the cell body (***retrograde transport***).

Kinesin, might be involved in orthograde axonal transport, whereas dynein, or microtubule- associated protein lC (MAP lC), apparently catalyzes vesicle movement in a direction opposite to that of kinesin. Dynactin may contribute to regulate both kinesin- and dynein-mediated transport pathways, by enabling dynein to participate in bidirectional transport by increasing its ability to stay “on” during minus-end transport and to stay “off” during plus-end transport. Motor proteins consist of two func-

tional parts: a motor segment that interacts with cytoskeletal filaments, and converts chemical energy into movement; and a tail that interacts with cargo.

Because of the narrow caliber and extreme length of numerous neuronal processes, as well as the large volume of cargoes vehiculated, alterations in axonal transport may have a disastrous outcome. Numerous conditions can result in perturbations of this transport system, including mechanical compression, ischemia, and toxins. Disorders of axonal transport may thus represent a final common pathway for a variety of optic nerve diseases.

Clinical importance of axoplasmic transport in the optic nerve has been studied in numerous disorders, including glaucoma, disc edema following ocular hypotony, disc edema due to orbital neoplasm, and optic neuritis. Moreover, many disease-related proteins have been identified as motor interacting proteins or as proteins present within cargo carrying vesicles. Actually, the axonal transport pathway may be a major cellular target for the development and progression of neurodegenerative diseases. Viruses also use axonal transport to invade the central nervous system. Some viruses enter the human body via mucous membranes where they presumably penetrate into sensory neurons. Then, by retrograde axonal transport they are vehiculated to cell bodies, where they become latent. Reactivation is followed by anterograde transport into skin or mucous membrane. Viral components presumably interact directly with motor proteins.

Following increase in intracranial pressure, axoplasmic flow disturbances appear to be a primary cause of papilledema. In monkeys, classical experimental studies conducted by Hayreh and Tso, who raised cerebrospinal fluid pressure in the sheath of the optic nerve, showed axoplasmic flow stasis in the optic nerve head. This caused axonal swelling, manifesting as early optic disc edema. Eventually, retinal vascular changes occurred. Stasis of both rapid and slow components of the axoplasmic flow was seen, rapid component accumulating in the lamina cribrosa and prelaminar regions, whereas the slow component accumulated in the nerve fibers of the entire optic nerve head anterior to the lamina cribrosa. The authors suggested that pathogenesis of optic disc edema seen in various conditions without raised cerebrospinal fluid pressure, cannot be explained by any single mechanism in spite of the occurrence of axoplasmic flow stasis in most cases.

In atrophic sectors of the optic disc, no swelling develops following increase in cerebrospinal fluid pressure, because in these areas, there are no nerve fibers to swell, in spite of the persistence of nearly normal optic disc vasculature.

Disc elevation due to optic nerve head drusen is presumably also related to axonal flow obstruction. As a result of small scleral canals commonly present in eyes with optic nerve head drusen, optic nerve axons may be compressed at at the lamina cribrosa level, impairing axonal transport of mitochondria. Mitochondria are eventually extruded from affected cells, with calcium heavily deposited in these now extracellular cell organells. This serves as starting point for further calcification leading ultimately to drusen formation.

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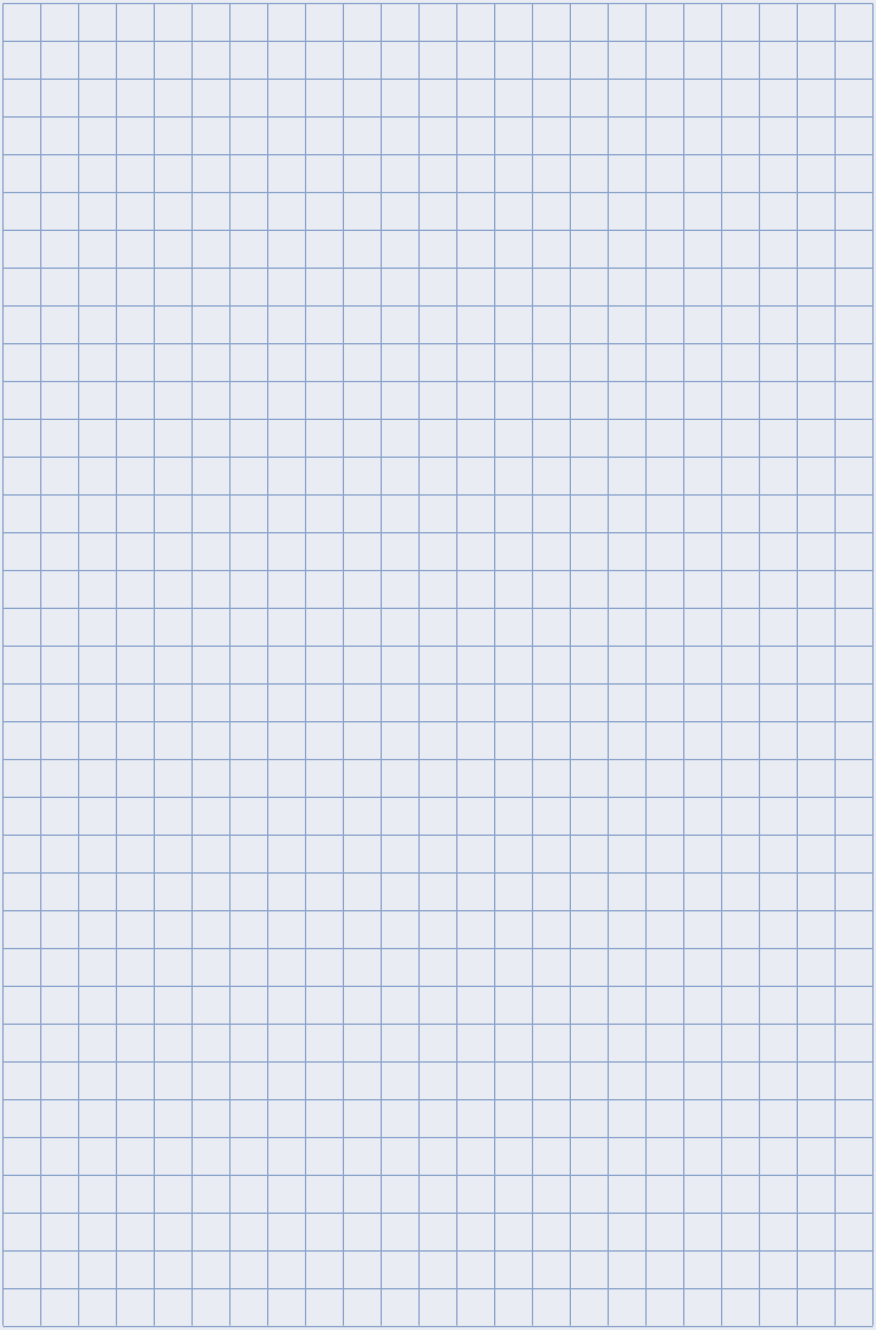

Drug-induced neuro-ophthalmic adverse effects

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The list of substances that are suggested to be toxic to the human optic nerve is long. The WHO Causality Assessment Guide of Suspected Adverse Reactions classifies the reported adverse drug-related events into the following categories: certain, probable, possible, unlikely, conditional and unclassifiable. The 'certain' category includes plausible time relationship to drug administration and inability to explain the adverse effect by concurrent disease or other drugs. The typical signs of toxic optic neuropathy consist of subacute or chronic, bilateral and symmetrical painless loss of vision. The visual field defects are central or cecocentral. The optic discs are initially normal in appearance, but later they can become pale. The most important aspect of treatment is recognition and drug withdrawal.

Ethambutol, a widely used agent in the treatment of tuberculosis, is one of the most commonly encountered drugs associated with an optic neuropathy. Patients are often on combined therapy with isoniazid, which may have an additive adverse effect. Amiodarone-associated optic neuropathy varies from an acute onset unilateral ischemic optic neuropathy-like event, to an insidious and progressive bilateral optic disc edema with reversible visual loss.

This possibly results from a chronic neurotoxic effect via drug-induced lipidosis. It is still controversial whether sildenafil, a phoshodiesterase 5 inhibitor prescribed for erectile dysfunction, may cause permanent visual loss by triggering anterior ischemic optic neuropathy, either through local changes in the optic nerve perfusion or systemic hypotension. Both cyclosporine, a widely used immunosuppressant, and other chemotherapeutic agents [cisplatin, carboplatin, nitrousureas and vincristine] have been associated with optic nerve toxicity. Vigabatrin, an anti-epileptic, is well-known to cause bilateral concentric and irreversible visual field defects, loss of visual acuity and color vision deficits. A clinical syndrome of both retrobulbar and anterior optic neuritis has been associated with the use of infliximab. The toxicity of this tissue necrosis factor alpha inhibitor is thought to be mediated by stimulating peripheral autoreactive T-cells, some of which may be myelin specific. Many drugs are associated with intracranial hypertension. These associations have been reported in a variety of ways, but not confirmed by controlled studies. Historically, the earliest recognized cause of medication-induced elevated intracranial pressure was Vitamin A. Nowadays, the All-trans retinoic acid used in the treatment of pediatric acute promyelocytic leukemia has frequent intracranial hypertension side effects. Other medications include corticosteroids (withdrawal and not excessive use), anabolic steroids and

gonadal hormones, tetracyclines and fluoroquinolones, amiodarone, indomethacin, lithium, cimetidine and tamoxifen.

Patients with drug-induced abnormalities of eye movements most often complain of diplopia and oscillopsia, caused by spontaneous nystagmus or an inappropriate vestibulo-ocular reflex. Therapeutic doses of various drugs may affect smooth pursuit, eccentric gaze holding and convergence.

Diazepam, methadone, phenytoin, barbiturates and chloral hydrate impair smooth pursuit tracking. At toxic levels, neuroactive drugs can impair all eye movements, especially when consciousness is impaired. Phenytoin may cause opsoclonus or complete ophthalmoplegia in awake patients. Tricyclic antidepressants may cause complete ophthalmoplegia or an internuclear ophthalmoplegia in stuporous patients, and lithium a variety of abnormalities, including fixation instability and downbeat nystagmus.

Drug-induced disturbances of neuromuscular transmission occur at the pre-or-post-synaptic levels, causing prominent ptosis and ophthalmoparesis as well as variable degrees of extremity muscle weakness resembling true myasthenia gravis. It may occur in patients with previously unknown myasthenia gravis or worsen known myasthenia by concurrent drug therapy, for example: procainamide, antibiotics (aminoglycosides, polymyxins, tetracyclines, quinolones), phenytoin, beta blockers, chloroquine, lithium and statins. This myasthenic syndrome can also result from D-penicillamine induced autoimmune damage to the neuromuscular junction.

Optic nerve protection and regeneration; current opportunities and perspectives, and critical considerations on electrical stimulation on the diseased optic nerve

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Most optic neuropathies do not have effective treatments. Examples include ischemic optic neuropathy, Leber's hereditary optic neuropathy (LHON), optic neuritis, and traumatic optic neuropathy. In some cases, we do not fully understand the pathophysiology of how the optic nerve gets injured. Ischemic optic neuropathy is probably a compartment syndrome for which the triggering edema is unknown. Leber's hereditary optic neuropathy is a mitochondrial disorder, but it is not known why the optic nerve (and retinal ganglion cells) are specifically involved. While the demyelinating aspects of optic neuritis have been studied, the mechanism by which the axonal loss occurs is less apparent. In other cases, we believe we understand the pathophysiology of an optic neuropathy, but we still have difficulty treating the disease, e.g traumatic optic neuropathy and some compressive optic neuropathies

In response to this therapeutic dearth, the concepts of neuroprotection and regeneration has arisen. *Neuroprotection* is a therapeutic paradigm for prophylaxis or prevention of death of neurons from injury, so as to maintain physiological function. In the case of optic neuropathies, the corresponding neuron is the retinal ganglion cell. *Regeneration* is in the setting of optic neuropathies is relevant to the injured retinal ganglion cell axon. If the cut end cannot regenerate, then even if neuroprotection is successful, the absence of connectivity to the brain implies an absence of function.

Neuroprotection is Controversial

The concept of neuroprotection has been controversial because there have been multiple clinical trials in neurological disease which failed to show efficacy of a neuroprotective strategy[1]. This raises the question of why a treatment should work in optic nerve disease, when it has failed to work in well performed clinical trials are of other neurological diseases. Specifically, large numbers of trials of stroke, using a variety of drugs including NMDA antagonists, ROS scavengers, and other therapies have not shown efficacy. In fact, virtually no trials of neurological disease have shown that a neuroprotective strategy works, with the possible exception of spinal cord trauma, Alzheimer's disease, and amyotrophic lateral sclerosis. In spinal cord trauma, the NASCIS 2 and 3 studies demonstrated that very high doses of methylprednisolone or tirilazad mesylate are associated with better function[2], but the results have been controversial[3]. Several

studies of the NMDA antagonist memantine demonstrated efficacy in slowing the rate of progression of Alzheimer's disease[4]. Finally, riluzole decreases the rate of progression in amyotrophic lateral sclerosis[5], although the effect is small.

Which Neuro-ophthalmic Disorders Are Good Targets for a Neuroprotective Strategy?

Any disorder in which neurons die as the result of injury are putative targets for a neuroprotective therapy. However, it is likely that some disorders are better targets than others. For example, giant cell arteritis causes a vasculitis involving the posterior ciliary arteries and central retinal artery, resulting in blindness from ischemic optic neuropathy and/or retinal ischemia. The implication of each of these two types of ischemia is quite different. In ischemic optic neuropathy, the injury occurs at the level of the retinal ganglion cell axon, while in retinal ischemia, the retinal ganglion body itself is infarcted. As mentioned above, damage to the axon, usually through crush or transection, results in retinal ganglion cell death only after several days to weeks. The implication of this disparity between axonal disease and neuronal disease is that there is a difference in the length of time that can ensue between symptoms and disease[6]. Although data is lacking, it is likely that axogenic diseases (diseases resulting from a primary axonal injury) may be far more amenable to neuroprotective strategies than somagenic diseases (disease in which the cell body is primarily injured)[7].

The vast majority of optic neuropathies involve axonal injury and are a major cause of visual loss. The most common optic neuropathy is that associated with glaucoma, i.e. glaucomatous optic neuropathy. A wide variety of other optic neuropathies also cause visual loss, e.g. inflammatory, ischemic, infiltrative, and traumatic optic neuropathies. Some of these are discussed below.

Laboratory Evidence Supports a Neuroprotective Strategy in Optic Neuropathies

Neurobiologists have used optic nerve injury as a model of central nervous system injury for decades. The optic nerve, a central nervous system white matter tract, duplicates the physiology and anatomy of other white matter tracts, but has the advantage of being simple to experimentally manipulate, and having a complete separation of cell bodies from their axons. Because of the value of the optic nerve as a model for axonal injury, a large number of research studies in animals (primarily rodents) have demonstrated that multiple pharmacological interventions are helpful in preventing retinal ganglion cell death after optic neuropathy. For example, it is known that embryonic and early postnatal retinal ganglion cells depend on certain neurotrophic factors for their viability. Although the same is not known for adult neurons, studies of rodents that have previously undergone optic nerve crush have shown that intravitreal administration of some of these neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), extends the viability of retinal ganglion cells[8].

Over the last several years there are several animal models of specific optic nerve diseases for which a neuroprotective therapy has been tested[9]. The most commonly studied model is optic nerve crush or transection, in which the axons of the retinal ganglion cells are physically damaged with a forceps or other instrument. Transection or crush is a sudden injury, and probably mimics the effect of optic nerve transection associated with direct traumatic optic neuropathy, e.g. from a stab wound. A more chronic injury is produced with partial crush of the optic nerve, in which special forceps or an aneurysm clip is used to produce pressure across the optic nerve. The pressure is designed to be enough to cause axonal damage, but not great enough to completely transect all the axons. The acute injury corresponds to what might be expected from trauma, whether direct or indirect, but the chronic injury partly replicates what might be seen in compressive optic neuropathy.

Testing Neuroprotection in Neuro-Ophthalmic Disorders

Although cell culture and animal studies support the concept that neuroprotective therapies may prevent retinal ganglion cell death after diverse kinds of injuries, these data by themselves are insufficient to prove clinical efficacy. As alluded to previously, the lesson from studies of neuroprotection in neurological diseases is that preclinical studies which demonstrate efficacy do not predict the results of clinical studies. Phase III studies, in which two or more groups of patients are randomly assigned to masked treatment with either the drug or placebo, have failed to replicate strong evidence of neuroprotection in stroke. Therefore, until a randomized controlled clinical trial is completed in a neuro-ophthalmic disease, it is impossible to recommend any particular neuroprotective strategy.

There is one published study of neuroprotection in NAION, using the 2 adrenergic agonist brimonidine[10]. Thirty-six patients with NAION who are older than 40 were randomized to either brimonidine (0.2%) or placebo. The primary outcome measure was visual acuity. Other outcome measures were 30-2 Humphrey visual fields, Goldmann visual fields, and an automated swinging flashlight test. The trial was stopped before the planned number of patients were enrolled, and no significant difference was found between the treated and untreated groups in either visual acuity all visual field.. However, there was a nonsignificant trend towards improvement in the visual field in the patients treated with brimonidine. The lesson from this study applies to tests of neuroprotection in virtually all neuro-ophthalmic diseases. Most of these diseases are uncommon, and enrolling sufficient patients within a short enough time span may be difficult.

To date there been no studies of neuroprotection in optic neuritis, but this disease has attracted great interest because it is associated in the majority patients with the eventual development of multiple sclerosis[11]. Researchers have focused on the use of optical coherence tomography (OCT) and other methods to measure the thickness of the nerve fiber layer[12]. A neuroprotective treatment that prevents axonal loss would also be beneficial to vision in the long term, based on the partial correlation between nerve

fiber layer thickness and various functional measures of vision in optic neuritis[13].

Brimonidine was studied in Leber's hereditary optic neuropathy[14]. Nine molecularly confirmed patients with Leber's hereditary optic neuropathy who had visual loss in one eye for less than six months and normal vision in the fellow eye were treated with brimonidine (0.15%). The outcome measure was vision in the fellow eye, which would be expected to undergo vision loss from the disease process. In the study all patients had deterioration of vision in their fellow eye, ruling out a strong neuroprotective effect of the treatment. However, in one of two patients who were treated with in 16 days after their first I was involved, good visual acuity was maintained in the fellow eye at 15 months of follow-up, despite a mildly abnormal baseline visual field.

Optic Nerve Regeneration

Optic nerve regeneration is a scientific problem that has been studied for many years. The mammalian optic nerve does not regenerate after it is transected, unlike lower animals such as the goldfish, which readily regenerate and form appropriate connections to targets in the brain. Two decades ago, Aguayo and colleagues demonstrated that transection of the optic nerve, followed by replacement of part of the optic nerve with a sciatic (peripheral) nerve graft allowed limited regeneration[15]. Regenerating axons are derived from retinal ganglion cells that express growth-associated protein-43 (GAP-43)[16]. Subsequently, studies of the factors which prevent regeneration in the central nervous system focused on the role of myelin-associated substances[17] (e.g. myelin-associated glycoprotein[18]) and glial (astrocyte-derived) scarring (e.g. proteoglycans[19])[20] as inhibitory factors. Downregulation of the receptor for Nogo, a myelin- associated protein[21], enables regeneration of retinal ganglion cell axons when appropriately sensitized[22]. Instead of focusing on the receptors by which the inhibition of axonal extension is signaled, some groups have focused on the subcellular transduction pathways for inhibition. For example, up-regulation of cAMP allows regeneration of spinal cord[23] and retinal ganglion cell[24] axons, and mice lacking receptor protein tyrosine phosphatase sigma have increased retinal ganglion cell axon regeneration past a glial scar[25]. Finally, there is a dramatic reduction in the axonal extension rate of retinal ganglion cells around the time of birth. This switch appears to be signaled by contact with amacrine cells[26], and the nature of the signal and how it is transduced is being studied.

Regeneration of optic nerve axons is just one small part of the larger problem of allowing the optic nerve to be recreated. Primarily, this is the guidance of extending axons from the RGC within the retina, to the optic nerve head, through the optic nerve, taking the appropriate crossing of nasal fibers at the chiasm (or not crossing for temporal fibers), and then continuing along the optic track to the retinotopic map within the lateral geniculate nucleus within the appropriate layer. In development, this complex pathway is determined by cell surface molecules and secreted chemotactic gradients. It is unclear whether the same set of molecules is present in the adult organism. If not, those molecules would have to be recreated in order to allow an extending axon to find its appropriate target.

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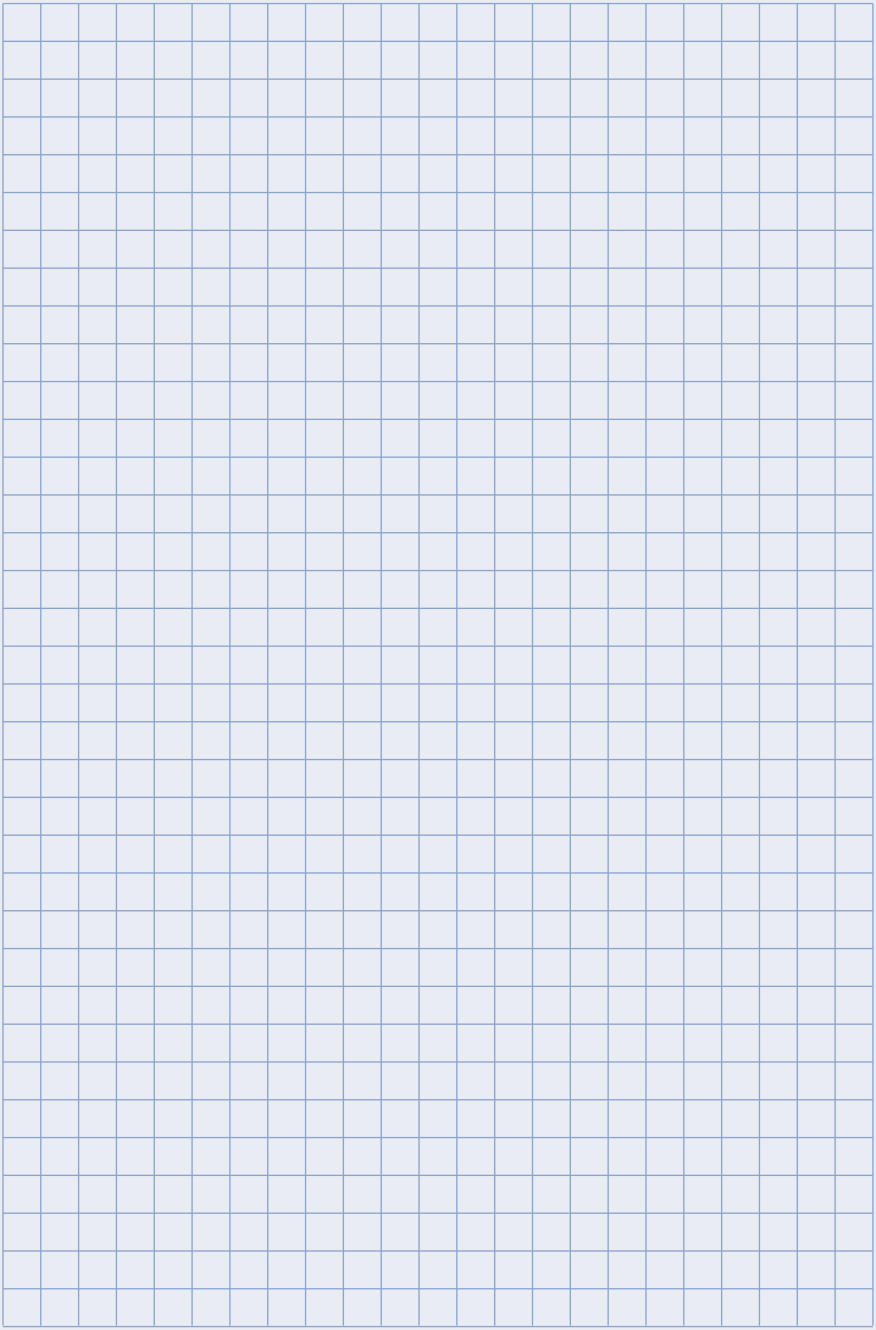
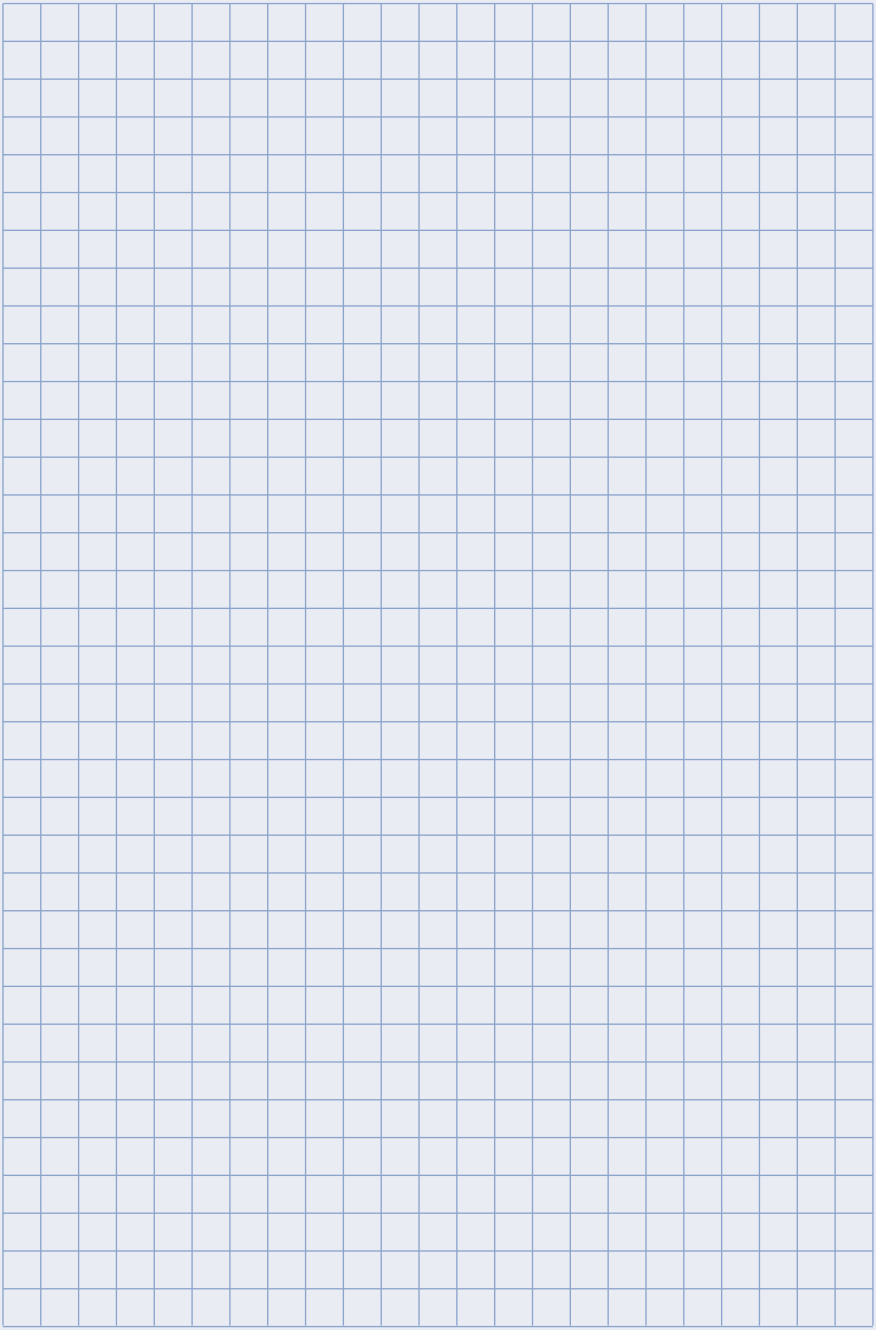


Edme Mariotte: From Gas physics to Blind Spot physiology

| Pinar Aydin, Ankara, Turkey |

Edme Mariotte, a Roman Catholic priest and a founding member of l'Academie des sciences de Paris in 1666, is mainly remembered as the first scientist to discover the blind spot, known as Mariotte's Spot, in visual fields. His extensive work on optics and color perception is less well remembered. In addition, he made other important discoveries in different areas of science such as physics, mechanics, hydraulics, optics, plant physiology, meteorology, surveying, and research methodology. Mariotte was an active experimenter whose experimental principles separated science from metaphysics. His work was known to many of his fellow great scientists of his day, including Newton and Descartes, and his lengthy correspondence was a pioneering form of scientific international cooperation. Mariotte's observations, experiments, and demonstration of the blind spot led to a lively debate in the scientific community as to its explanation. Although he falsely assumed that it was the choroid, not the retina, that was the site of perception in the eye, he may be considered as a forerunner of neuro-ophthalmology due to his experiments and interest in the fundus.



Vision and the migrainous brain

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Migraine is a specific diagnosis based on history and on normal objective findings during a detailed neuro-ophthalmic and neurological examination. By a language abuse, many patients with a history of headaches report themselves as being « migrainous », although it may not be a « true » migraine. In migraine, the central nervous system dysfunction plays a pivotal role, but structural changes are not found in this very common condition. Dynamic functional changes, such as cortical spreading depression may play a role and modulate the disorder, being possibly the underlying pathophysiological process in migraine aura. Aura can be a myriad of neurological symptoms, typically starting before the typical headache phase. Headaches are typically hemicranial, shifting sides between attacks. Headache is often, but not always associated with photophobia, sonophobia, nausea. Visual, sensory, motor, or language disturbances may rarely occur, indicating that other areas of the cortex, distinct from the occipital lobes must be affected.

The most common form of migraine aura is visual, typically as fortification spectra, flashes of light, bright zigzag, horseshoe shaped expanding visual perceptions. During these attacks lasting typically 10-30 min, the expanding scintillating scotoma is present in both eyes, typically in a hemianopic pattern, although patients may have the subjective feeling that the symptoms are unilateral. A thourough history and asking the patients to hide one eye during a subsequent attack can be helpful to rule out differential diagnosis, such as transient monocular visual loss. In visual aura, vision returns to normal in both eyes, being followed by the typical migrainous headache. The neuro-ophthalmic examination is normal during the attacks.

Patients with transient visual loss related to migraine seek care of an ophthalmologist in most of the cases, either because the visual loss occurs without the typical headache (acephalgic migraine), or because the visual prodromes are new in an otherwise typical migraine.

Other relatively rare complex visual abnormalities may occur in migraine. Lilliputian hallucinations, characterized by the vision of either people or objects as miniatures or small fantastic little animals or creatures, have been described, as well as splitting or misinterpretations of the body image, macro- and microsomatoagnosia. In the socalled 'Alice in Wonderland syndrome', which may be associated with migraine or epilepsy, patients experience bizarre perceptual sensations. The occipital cortex is considered the area where the visual phenomenon of migraine-related spreading depression starts, based on electrophysiological and functional neuroimaging data.

Investigations are not needed if there is a clear previous history of typical migraine and if the neuro-ophthalmic examination , including the visual field testing is normal. In atypical cases, a neurological examination is mandatory, since differential diagnosis include intracranial tumors, epilepsy, vascular malformations, and therefore neuroimaging may be indicated..

Normal false memory and pathological confabulation: how to manipulate an eyewitness

| Armin Schnider, Geneva, Switzerland |

It has been established that false memories also occur in healthy people and are sometimes held with strong conviction. Even without explicit manipulation, memories for events may undergo significant transformation. Flashbulb memories – the memories for the circumstances in which one first learned of a personally engaging event – appear to be relatively protected from distortions, although modification of significant elements over time has been reported.

Falsifications of memory are of particular importance to eyewitness testimony. Suggestive questioning may modify the way in which memories are reported and may induce new distortions of memories. Weakly established memories are particularly vulnerable. Much research has shown that it is possible, and actually quite easy, to implant fictive elements into the record of an event and to manipulate the conviction subjects hold in their memories.

An analysis of eliciting circumstances suggests that normal false memories mainly result from normal physiological processes at encoding, processes associating the pieces of information constituting the memory of an event. There is no ostensible need to invoke defective processes during the retrieval of memories. Hence, normal false memories might have a different mechanism than pathological confabulations, which mostly reflect erroneous compositions of memories stored before the onset of brain disease (Text from Schnider, 2008).

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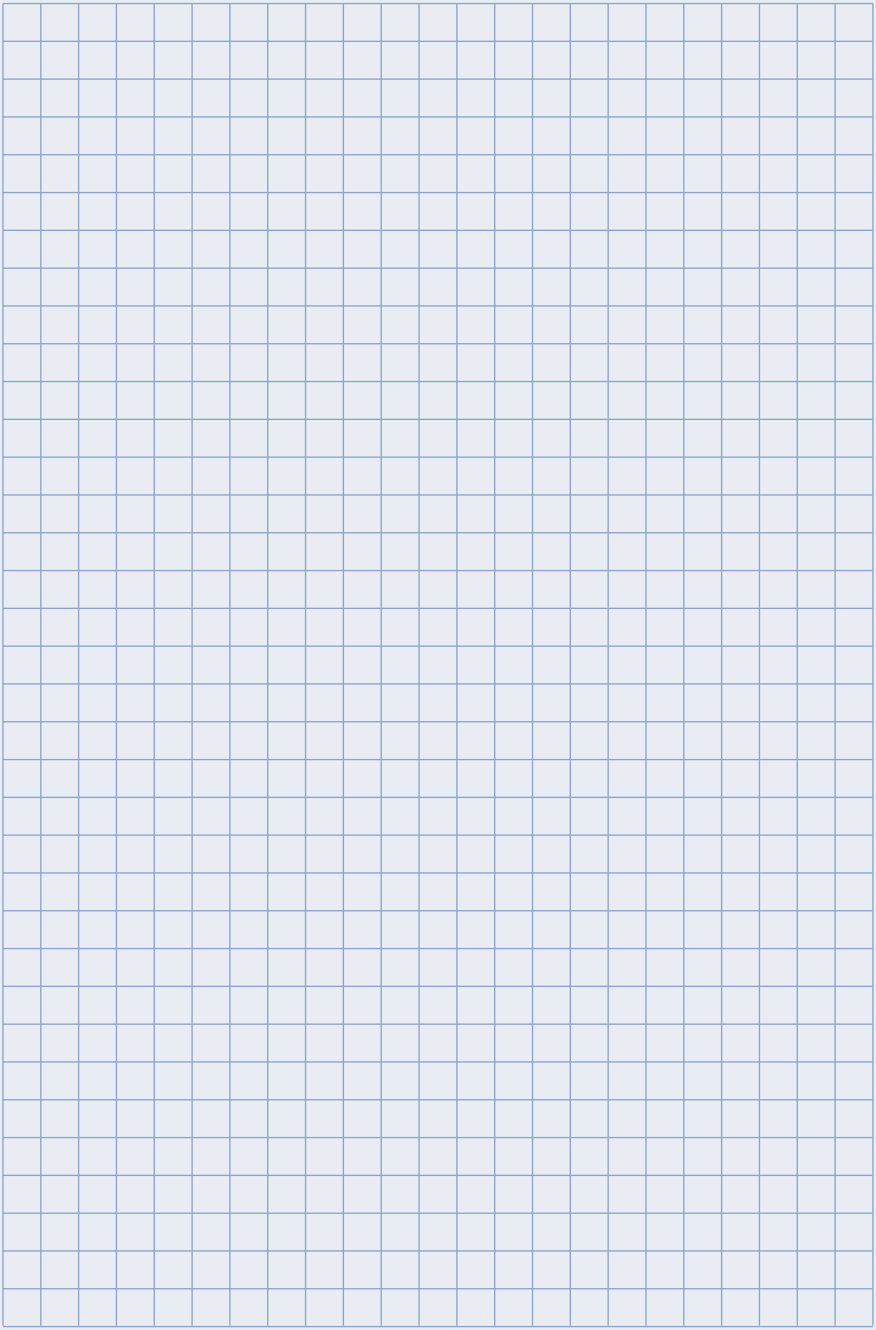

An underestimated handicap: congenital prosopagnosia

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Prosopagnosia can be defined as a selective deficit in the visual recognition and learning of faces. The word is a scholarly Greek compound from prosopon (the face) and agnosia (non-recognition or non-knowledge). The German Neurologist Joachim Bodamer (1947) introduced the term, when he published a thorough description of two soldiers with a markedly decreased face recognition after severe brain injuries in the second world war. In the following years, several case were reported and prosopagnosia was regarded to be a rare consequence of a damage to the temporal or occipital lobe.

In the first few weeks after a temporal stroke, a degradation of face recognition seems to be more common than previously expected. Rosler and his colleagues tested the face recognition ability in 31 patients in the second week after a right (16) and left (15) temporal lobe infarction. They found that most of them were impaired, some of them severely, but none complained of face recognition problems. Bodamer already stated, that his two patients never complained about their face recognition problem. Instead, he identified the deficit from their behaviour. Most patients don't really notice their problem, only in very severely cases they will complain about the deficit.

It has been debated for some time, if face recognition is really a discernible brain function. Tarr and Gauthier (2000) developed the theory, that face recognition is part of the brains ability to discriminate very similar objects. The report (Carlesimo et al. 2001) about a patient with an acquired global visual object amnesia who could learn and recognize faces at a normal level contradicts this view, because it supports the existence of independent neural structures for face and object recognition, at least to a certain extent.

Prosopagnosia can also be a congenital condition, in fact, most cases are. The first scientific publication about the condition, a single case report, dates back to 1976 (McConachie, 1976). Only a few years ago the condition was recognized to be about as common as dyslexia or dyscalculia (Kennerknecht et al. 2006).

As in the acquired type, most affected people don't recognize their condition. They know that they are having trouble to remember faces and wonder how others can do this without obvious effort, but over time they have learned to cope and don't really suffer except in a few embarrassing situations per year.

Congenital prosopagnosia is inheritable and compatible with a simple autosomal

dominant mode of inheritance. This means that a point mutation in a single gene may be responsible for the condition (Grüter et al. 2007).

For diagnosis, it is necessary to first exclude other ophtalmological and neurological conditions which may affect face recognition like myopia, brain tumours, a history of brain tissue damage or psychiatric conditions.

The cardinal symptom of congenital prosopagnosia is a lack of confidence about the familiarity of faces. Prosopagnosic people cannot determine the familiarity on a valid basis. Therefore, they not only overlook familiar people, but also confuse strangers with familiar persons (for an overview see Grüter et al., 2008).

Most have developed an auxiliary system of person recognition. They recognize other people by voice, gait, bearing, hairstyle or special marks like scars or tattoos. Most people won't understand the question how they recognize people, because they "just do it". Prosopagnosics will normally be able to give a detailed account of the clues which they use to recognize an individual person. People with congenital prosopagnosia have no mental images of faces, not even of their nearest relatives. On the other hand, they recognize emotions from faces as easy as other people. They also have a normal judgement of gender, age and attractiveness. While the cardinal symptom in autism spectrum disorders (ASD) is a lack of empathy, or a defective "theory of mind", this function is perfectly normal in congenital prosopagnosia. While prosopagnosia may accompany ASD, congenital prosopagnosia on the other hand is not a disorder of the autistic spectrum (for a comparison of symptoms see Fig. 1).

The underlying brain defect has not been localized as of yet. Anatomic MRI scans show normal cerebral structures, except for a slight grey matter deficit in parts of the anterior temporal lobe (Behrmann et al. 2007). It should be noted that a cataract at birth causes a lifelong degradation of face recognition, even if the cataract is surgically corrected within a few month (Le Grand et al. 2001). Recognition of other objects is not affected as strongly. While face recognition is present from birth, the cognitive functions for other objects mature later in life. Any disorder or developmental retardation of the visual processing system at birth will therefore affect face processing more than other functions.

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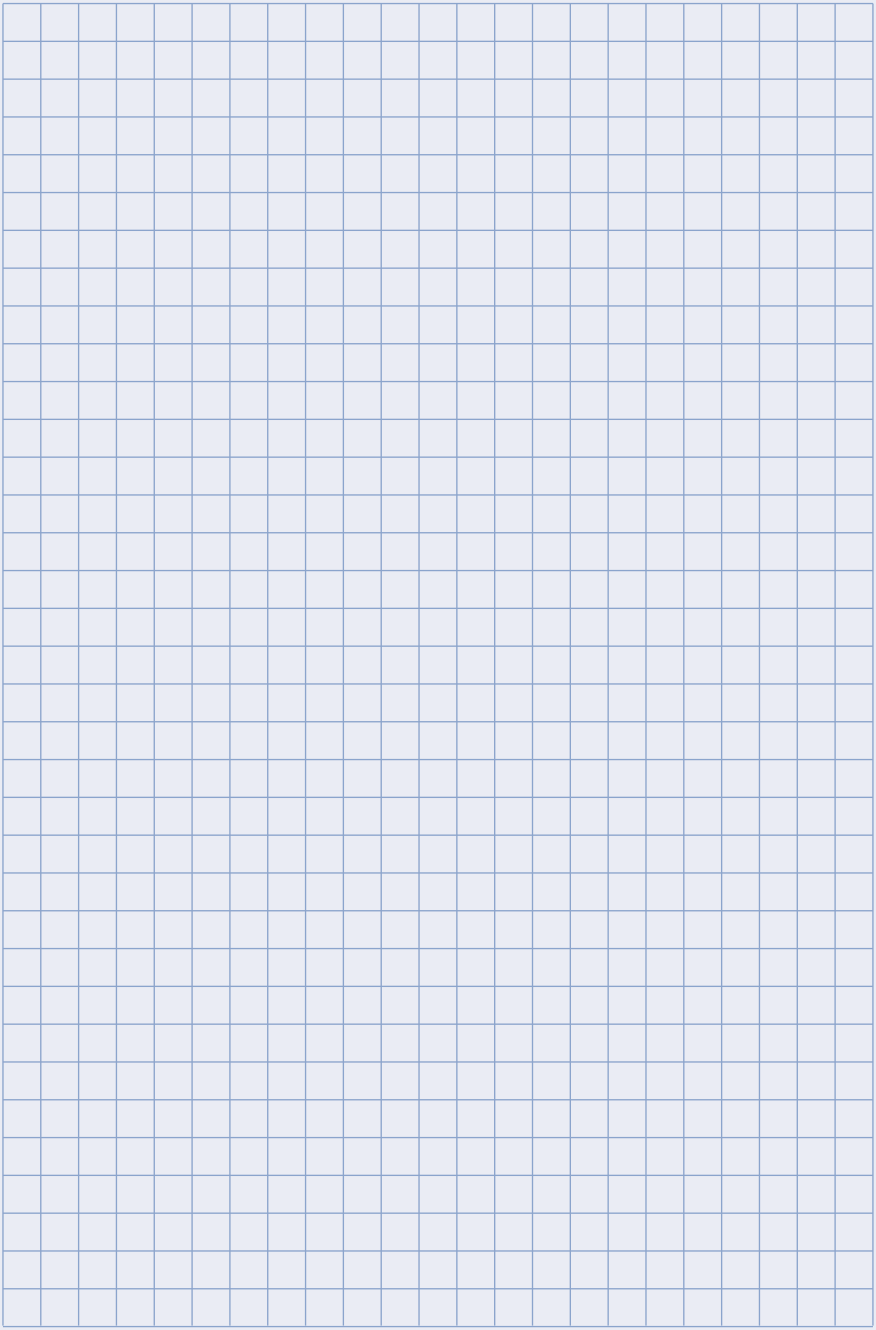
Symptoms	Hereditary PA	Acquired PA	Autism spectrum disorder
Feeling of familiarity	Not triggered (lasting uncertainty)	Lost, no feeling of familiarity	No data
Colour blindness	Not associated	Frequently associated	Not associated
Quadrantanopsia	Not associated	Frequently associated	Not associated
False negative and false positive recognition events	Always present	Inconsistent, rare	Not associated
Emotional expression recognition	Normal	Inconsistent	Impaired
Gaze contact necessary	No	No data	Gaze contact avoided
Impaired visual recognition of objects and scenes	Always present	Inconsistent	Not associated
Empathy ("Theory of mind")	normal	normal	Impaired

Fig 1.: Table for the comparison of the symptoms of congenital and acquired prosopagnosia with those of autism spectrum disorders



Homonymous hemianopia: consequences and adaptive processes

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Homonymous hemianopia causes severe disability for daily living, mainly for orientation and reading.

The hemianopic reading disorder

In complete hemianopia half of the reading visual field is covered and functionless (fig. 1, A1). If there is a macular sparing, the reading visual field can be preserved and reading can be normal, despite there is a large field defect in the remaining hemianopic side (fig.1, A2). On the other hand, a small paracentral homonymous scotoma, occuring in an isolated lesion of the occipital pole, causes a severe reading disorder. (fig.1, A3). These small paracentral scotomas are easily overseen in automated perimetry if the grid of the program is not dense enough. A specially dense grid program has to be chosen, or by manual perimetry the small scotoma can be specifically searched for.

The reading disorder does not only depend on the distance of the visual field defect from the centre, i.e. the size of the reading visual field, but is also influenced by the side of the defect: In left to right readers a hemianopic field defect to the right side is extremely impairing, because the visual field defect is in reading direction. Figure 2 shows on the left the eye movements for a normal subject, in the middle for a patient with right hemianopia: This patient needs many more saccades per line and makes a lot of regressions to come through the line. A patient with left hemianopia (right) has difficulties to find the beginning of the next line which is shown by the additional steps during the return sweep.

Patients with macular splitting can learn a valuable compensating strategy: Eccentric fixation (fig. 1B): The patient uses a slightly eccentric retinal fixation locus, sacrificing part of visual acuity and creating a small perceptual area along the vertical midline, which is crucial for reading. Eccentric fixation causes a shift of the field defect towards the hemianopic side in conventional perimetry, which can be misinterpreted as improvement of the visual field. This process indicates a high cortical plasticity, because the new eccentric fixation locus is not only used as the new centre of the visual field but also as the new centre of the coordinates of the reading eye movements, which means a shift of the sensory and motor reference. It has to be emphasized that these patients have intact foveal vision and are still able to use an eccentric fixation locus if it is required by the task. When visual acuity is tested they use their foveola for highest resolution (Trauzettel-Klosinski 1997).

Another compensating strategy can be explorative saccades (staircase, overshoot, predictive), specially in left hemianopia (see also training) (Meienberg et al 1981).

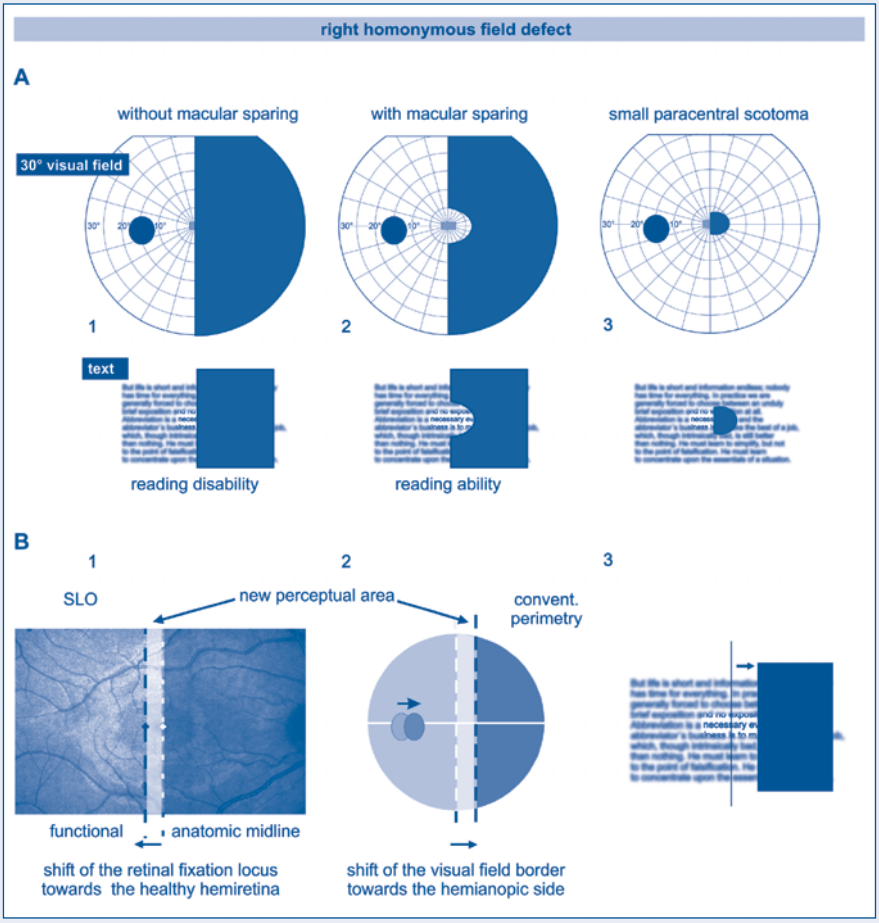

Figure 1:
The impact of a homonymous field defect to the reading performance:
A1: In macular splitting half of the reading visual field is covered by the field defect, there is no reading ability. A2: If there is macular sparing, reading ability is preserved, even though there is a large defect which causes orientation problems. A3: A small paracentral homonymous defect causes severe reading disorder. B1: Eccentric fixation of 1°-2° by a shift of the retinal fixation locus towards the healthy retina (SLO-image). This creates a new functional midline and a shift of the visual field border towards the hemianopic side in conventional perimetry (B2). B3: Eccentric fixation creates a small perceptual area along the midline, regaining reading visual field.

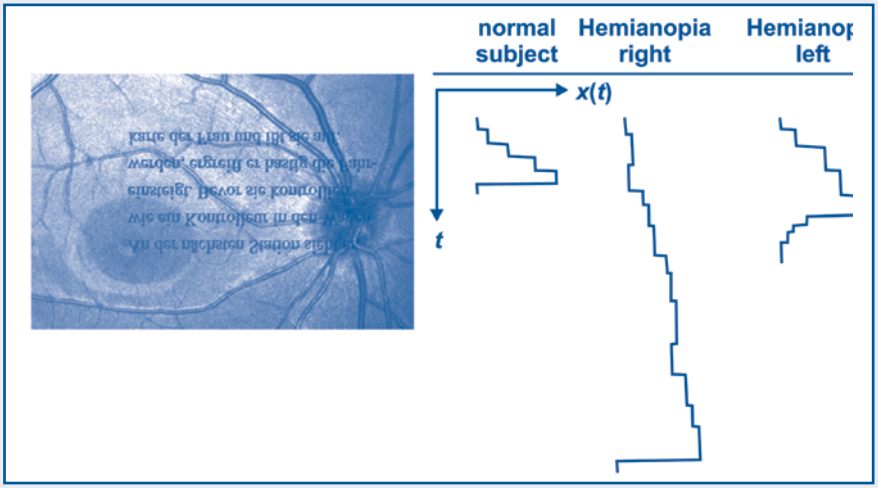

Figure 2:
Left: Text on a SLO-fundus image (for the subject it is upright, for the examiner it is upside-down). Right: Eye movements during reading one line of text (schematic). Left: The normal subject needs four saccades to come through the line and performs an accurate return sweep. Middle: A patient with right hemianopia makes much more saccades and several regressions per line, has a highly prolonged reading time, but has no problems with the return sweep. Right: A patient with left hemianopia has no major problems to come through the line, but he/she has difficulties to find the beginning of the next line, indicated by several additional steps during the return sweep.

The heminaopic orientation disorder

Patients with hemianopia are severely impaired in orientation, often they bump into obstacles and therefore they have to learn to perform explorative saccades towards the hemianopic side. Many patients spontaneously start to perform frequent saccades towards the blind hemifield. In conventional perimetry, this behaviour shifts the field defect to the blind side and this is often misinterpreted as an improvement of the visual field.

Rehabilitation

The aim of rehabilitation programs is to regain or optimize these impaired functions for improving the patients' quality of life.

There are 2 principal approaches of training methods: restitution and compensation. Restitutional visual field training aims to restore and enlarge the visual field by visual stimulation in the blind hemifield (Kasten et al 1998). One problem, however, is the insufficient fixation control during conventional perimetry. Eccentric or unstable fixation can cause a shift of the visual field border towards the hemianopic side, which can be misinterpreted as a visual field improvement. Until now, there is no evidence for a relevant improvement of the visual field by visual stimulation (Reinhard et al 2005,

Schreiber et al 2006). Compensating methods have been successfully used: training to shift attention and to perform saccades towards the hemianopic side supports exploration and better use of the blind field by enlarging the field of gaze (Zihl 1995, Pambakian et al 2004). The value of optical aids (mirrors, prisms) is controversial.

The value of a training method has to be related to its relevance to everyday life. Compensating strategies, which have to be adapted to the task, are effective to improve the utilization of the blind hemifield.

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Alterations in motor control of the eyelids

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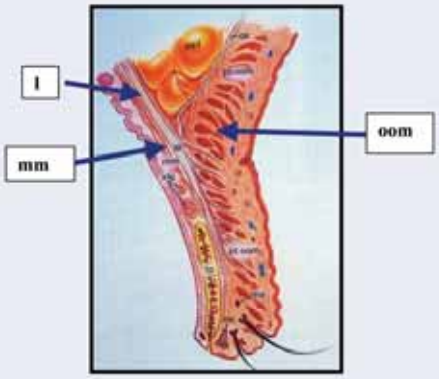
Eyelids dysfunction can have various mechanisms : the main are neurogenic, myopathic, aponeurotic and mechanical. These disorders are the consequence of local ore more extensive process. Detailed examination of eyelid position and movements is important to determine which element(s) of the lid system is affected ; careful history of the eyelid problem, completed by familial and past medical history, and by careful examination of the eye, of the pupil and of ocular and facial motility, will allow to determine the cause of the disorder. We will discuss first the anatomy and examination of eyelids and after neurogenic processes which lead ptosis, eyelid retraction, synkinesias and finally, abnormalities of eyelid opening and eyelid closure.

Anatomy

The eyelids contain **three main muscles** innervated by **three different neural networks**

Figure 1 :



- The **levator palpebrae superioris** (l) is the principal muscle involved in opening the upper eyelid and maintening normal eyelid posture ; it is innervated by branche of the superior division of **oculomotor nerve** (III).
- The **Müller's muscle** (mm) assists levator ; it is a smooth muscle innervated by **the oculosympathic nervous system**.
- **Orbicularis oculi muscle** (oom) is innervated by the **facial nerve** (VII). Its force permits eyelid closing and also facial expression around the eye. It can be divided in three parts : pretarsal (pt oom), preseptal (ps oom) and orbital

Furthermore, fontalis and associated muscles control the eyebrow and contribute in a small part to the eyelid elevation and so, contraction of the frontalis raises the eyebrow and the upper eyelid

Examination of eyelid function

It must be practised after a complete interrogation about past medical history with particular attention to thyroid, diabetes, facial paresis....The complaint has to be clarified :

- eyelid abnormality : ptosis, retraction, or abnormal movement of the eyelids,
- Other complaints : diplopia, blurred vision or other associated visual or non visual problem. Often, old photographs are useful in establishing the chronology of the disease.

Eyelid examination has to proceed as follows :

- General observation of contour, shape and symmetry of eyelids, and appreciation of a possible prominence of the eye,
- Static inspection with mesure of palpebral fissure in primary position and evaluation of the distance between the upper lid margin and the cornea light reflex. Exam has to notice position of the upper eyelid crease.
- Dynamic examination with mesure of the levator function and observation of eyelid movements during pursuit of a target from donwngaze to upgaze. We shall look for a fatigability of the levator by the Cogan lid twitch and maintaining maximal upgaze on a target for one minute
- Research for abnormal spontaneous movements : fasciculations, synkinesis with other muscles, blepharospasm.
- The strenght and function of the orbicularis oculi is evaluated by observing blinking and testing the strenght of closure by attempting to pry open the closed eyes.

This examination must be completed by careful examination of the eye, and especially of ocular motility and pupil, which have a common innervation with eyelids.

Neurogenic ptosis

Ptosis may be produced by damage to the motor system controlling eyelid elevation (levator palpebrae superioris or Müller's muscle) at any point along the pathway from the cerebral cortex to the muscle. In many cases associated symptoms and signs may help to found the location of the lesion.. The diagnosis of the nature of the lesion bases on clinical history, imaging and results of the biological examinations.

1. ***Ptosis from lesion of the oculomotor nucleus, fascicle or nerve is the most common location.***

- Both levator palpebrae superioris muscles are innervated by a single midline caudal subnucleus, so midbrain ptosis resulting from nuclear midbrain lesion is usually bilateral and severe. Its is commonly associated with other signs of mesencephalic

dysfunction but may be the only manifestation of the nuclear lesion. The lesion may be congenital, consequence of dysplasia or aplasia of the nucleus ; most of cases are acquired and include ischemia, inflammation, infiltration, compression, metabolic and toxic process.

- When the lesion affects the fascicle of the III, it produces unilateral dysfunction, usually with papillary involvement, isolated or associated with other neurologic manifestations depending on whether adjacent structures are affected in the midbrain. As with nuclear palsies of the III, facicular lesions may be ischemic, hemorrhagic, infiltrative, compressive, or rarely inflammatory.
- Ptosis that accompanies lesion of the peripheral III is unilateral and accompanied by ophtalmoparesis with or without pupillary involvement. Isolated ptosis is described in compressive lesions but there are usually mild pupillar dilatation and mild superior rectus dysfunction, only evident on extreme gaze and with a red filter. Mechanisms are the same that in the fascicular nuclear lesions.

2. ***Ptosis from lesions of the oculosympathetic pathway*** is usually associated wit ispilateral reactive miosis and realises Horner syndrom. Ptosis from Horner syndrom is often mild, with good function of the levator and involvement of lower eyelid retractors and elevation of the lower eyelid which produces appearance of enophthalmos. The problem is to localize the lesion and determine its nature. Ispilateral facial anydrosis may exists with first-order or second-order neurons lesions; heterochromia of the affected eye signs a congenital or very long standing case. **Recent and painful Horner syndrome is an emergency and has to rule out a dissection of the internal carotid artery by imaging.**

3. Less frequent is ***ptosis resulting from supranuclear lesion.*** It has been described ipsi or controlateral to ischemic stroke and sometimes bilateral, then associated most frequently with extensive non dominant hemisphere lesions.

Neurogenic retraction

1. ***Supranuclear eyelid retraction*** or Collier sign is bilateral and most commonly occurs with lesion of the dorsal mesencephalon, associated with other signs of the dorsal midbrain syndrome : supranuclear deficiency of upward gaze, convergence retraction nystagmus and pupillary light-near dissociation. The retraction increases as the patient looks up and follow eyes in downgaze. Common causes include hydrocephalus, stroke, MS, shunt malfunction, tumors and neurodegenerative conditions as PSP.

2. ***Pourfour Dupetit syndrome*** is unfrequent and characterized by ipsilateral eyelid retraction and mydriasis ; it is caused by sympathetic irritation or hyperactivity.

Synkinesias

They cause ptosis or retraction arising in certain conditions and may be congenital or acquired

1. ***Ptosis associated with eye movements :*** it may develop in eccentric positions of gaze from congenital supranuclear inhibition of the levator. These supranuclear oculopapebral synkinesias may be isolated or associated with other congenital syndrome as the Duane retraction

2. ***In Marcus Gunn phenomenon,*** there is usually a mild **congenital** ptosis in primary gaze position with mouth closed and paradoxical elevation of the ipsilateral eyelid with certain movements of the jaw, sometimes when the patient opens the mouth. The cause of the synkinesis between the pterygoid and the levator muscle in unknown. On the contrary, in *Inverse Marcus Gunn*, the initial ptosis increases when patient opens his mouth.

3. ***In aberrant regeneration of the III,*** occurring after a non ischemic Oculomotor nerve palsy, there is usually a ptosis when the patient is looking straight ahead and a lid retraction during infraduction, adduction or both.

Abnormalities of eyelid opening

Apraxia of eyelid opening is a supranuclear involontary inhibition of levator. The patient can't initiate the lid opening despite frontalis contraction, absence of any evidence of orbicularis contraction and absence of signs of myopathic dysfunction . It occurs most commonly in patients with PSP and Parkinson disease

Abnormalities of eyelid closure

1. ***Insufficiency of eyelid closure*** may be supranuclear, nuclear or infranuclear. The associated symptomes can help to localize the disease.

- Supranuclear inability to voluntary close the eyelids usually develops with bilateral frontal lesions and can occurs in patients with frontal infarcts, tumors, PSP, and Creutzfeldt Jacob disease.
- Nuclear and fascicular insufficiency of eyelid closure and facial movement results from damage to the facial nucleus or fascicle and is sometimes associated with other signs of brainstem dysfunction (VI ispilateral, contralateral hemiparesis).
- When the disease affects the peripheral part of facial nerve, the weakness of eyelid closure is associated with weakness of other facial muscles supplied by the nerve. Causes include lesions of the cerebellopontine angle, of the facial canal, and lesions of the distal facial nerve : traumatisms of the temporal bone, inflammations (otitis, herpes Zoster), neoplasms and mostly idiopathic facial palsy called Bell's palsy. Clinical examination of reflex tearing, hearing, taste and electrodiagnostic tests help determine the extent of dysfunction and prognosis of facial nerve disease.

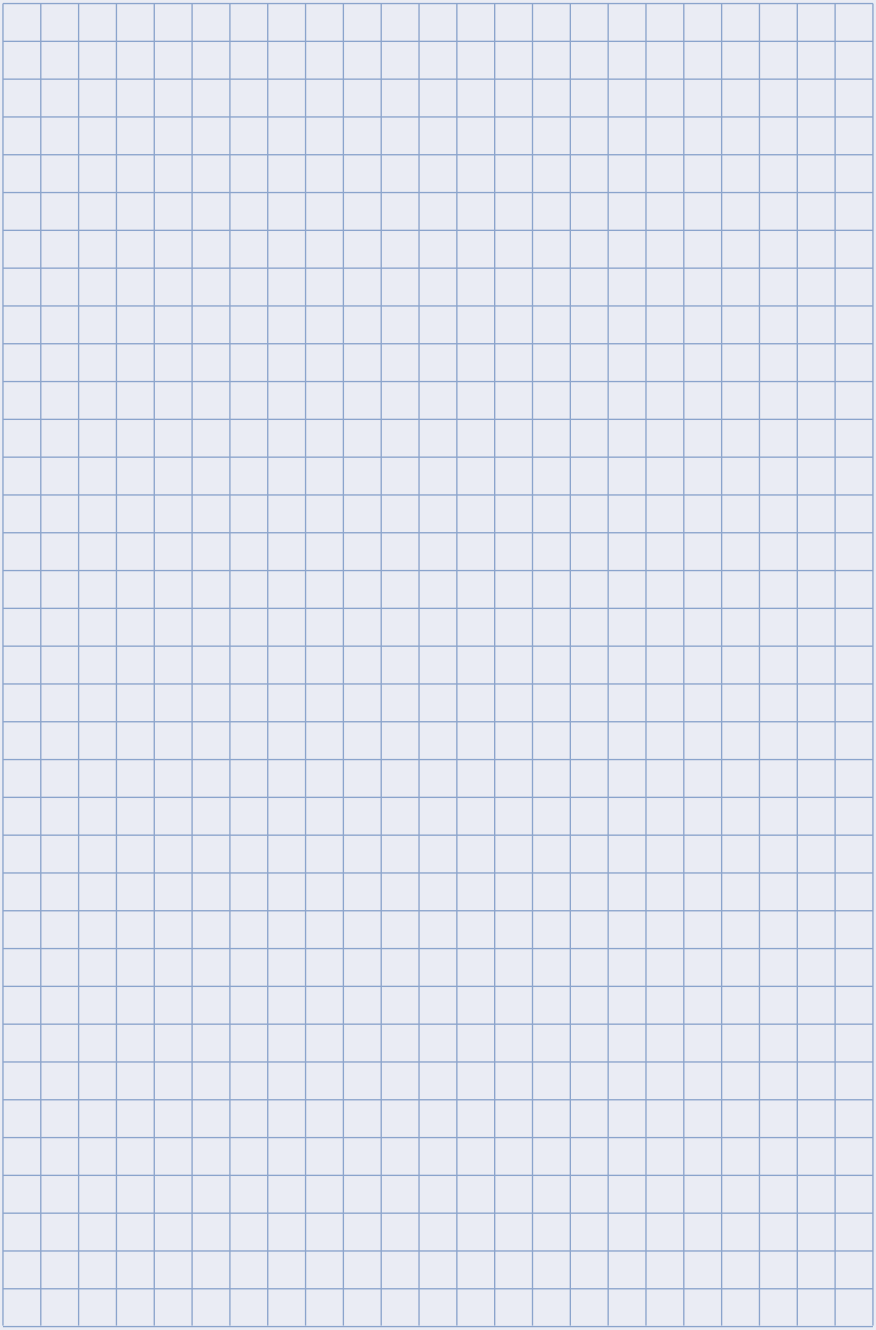
2. ***Excessive eyelid closure***

- *Blepharospasm* is a **facial dystonia** with an involuntary closure of the eyelid and contraction of the orbicularis. It may be isolated or associated with dystonic movements of other cranial muscles (Meige syndrome). It occurs most frequently

in women over 50 years of age. It may be essential, or associated with numerous lesions and disorders of the basal ganglia and mesencephalic region (stroke, PSP, Parkinson, MS..), or drug induced (dopamine stimulating agents, antipsychotic or neuroleptic drugs..) The treatment rests on Botulinium toxin.

- *Hemifacial spasm* occurs commonly in middle age adult and is almost always sporadic. Neuroimaging must be performed to eliminate compression of the proximal Facial nerve, most often caused by a blood vessel and more rarely by tumor.. Treatment depends on the cause of the disease.

In conclusion, the driving motor control of the eyelids movements rests on three different neural networks (III, VII and oculosympathetic pathway). Clinical presentations are various ; careful clinical examination is essential to arrest the diagnosis, plan the additional examinations and finally decide on the treatment.



Update on the Pupil Light Reflex: Clinical Implications of a New Class of Photoreceptors

| Aki Kawasaki, Lausanne, Switzerland |

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Introduction

The pupillary light reflex is composed of an afferent limb and an efferent limb (Figure). Damage to afferent limb of the light reflex results in a subnormal pupil response to direct but not consensual light stimulation. The standard clinical technique for identifying asymmetry of afferent pupil input between the two eyes is the alternating light test, and the asymmetry is referred to as the relative afferent pupillary defect , or RAPD.

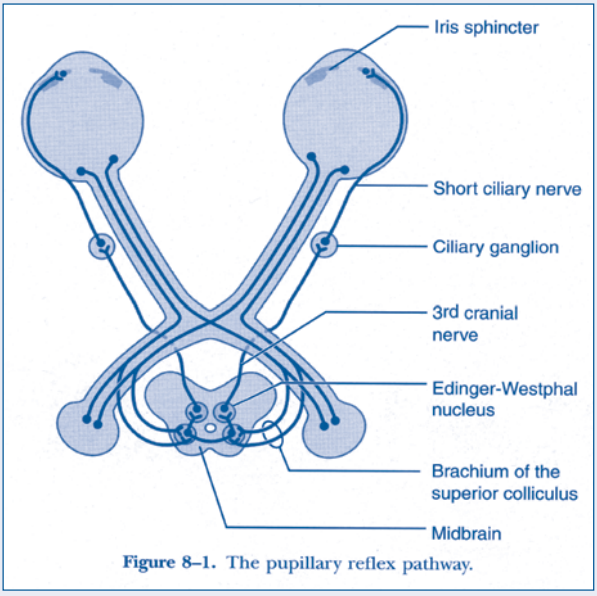

Figure 1. The pathway of the pupil light reflex.

Utility of the RAPD

The RAPD is an objective indicator of unilateral or asymmetric injury to the afferent limb of the pupillary light reflex. It is associated with visual loss due to optic nerve or retinal damage and in general, is proportionate to the amount of neuroretinal damage. One great advantage of the RAPD is that it can be quantified and thus used to monitor improvement or worsening of the patient's clinical condition.

Limitations of the RAPD

The correlation between the RAPD with the visual field mean defect or the nerve fiber layer thickness is been moderate, at around r2= 0.66. In specific conditions, the pupil-visual dissociation is marked. For example, it has been reported that symptomatic patients with Leber Hereditary Optic Neuropathy can have significant visual loss with only a small pupil deficit. Conversely, individual patients with a compressive lesion of the optic nerve, e.g. nerve sheath meningioma, may not have much visual loss but the size of the RAPD is impressive. Then there are the clinical mysteries. How can a patient who is NLP from retinitis pigmentosa have a pupil light reflex? Why do some patients with visual loss have pupilloconstriction when the light is turned off? In fact, from where in the retina does the afferent pupillomotor input originate and how is it signaled to the brain?

The Pupil Light Reflex Revised

The neural afferent signal of the pupil light reflex is transmitted to the dorsal midbrain by a tiny subset of retinal ganglion cells, the melanopsin-expressing ganglion cells. These non-visual neurons are capable of intrinsic phototransduction using a novel photopigment called melanopsin and thus function as a new class of photoreceptors (Table 1). These neurons will depolarize either from transynaptic activation initiated by phototransduction in the rods and cones or by intrinsic activation via melanopsin-mediated phototransduction (or both). In other words, the afferent pupillomotor input originates from the outer retina (rod and cone activation) and also within the inner retina (melanopsin activation). This new information has direct implications in our understanding of the pupil light reflex.

From electrophysiologic experiments in primates, the familiar early and transient pupil contraction under photopic conditions to a bright light flash represents a predominantly cone-driven pupil response. In contrast, the sustained pupil contraction to continuous light stimulation, particularly blue light, represents a summation of both the adapted cone response and the steady-state intrinsic retinal ganglion cell activation. This is evident in a patient with unilateral retinitis pigmentosa tested with chromatic light (Figure 2).

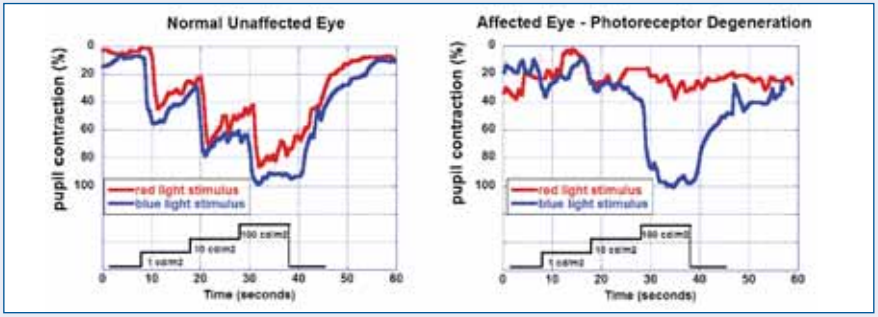

Figure 2. Example of pupillographic recordings to equiluminant chromatic light stimuli in a patient with severe unilateral photoreceptor degeneration.
The pupil responses shown in red were elicited using a 10 second, long wavelength (600-620 nm bandwidth) red light at 3 different light steps (1, 10 and 100 cd/m2). The pupil responses shown in blue were elicited using a 10 second, short wavelength (465-485 nm bandwidth) blue light at similar intensity steps. In the normal eye (left), blue light stimulation produces a larger pupil contraction compared to red light stimulation, and the difference is greatest at the brightest light intensity (100 cd/m2). These pupil responses to red light and blue light in the normal eye of this patient are similar to normal subjects tested with the same protocol. In the eye with no light perception due to severe photoreceptor degeneration (right), there is no recordable pupil response to red light even at the brightest intensity. However, a bright blue light stimulus (100 cd/m2) still evokes a large amplitude, sustained pupil contraction.

Conclusion:

The RAPD obtained from the alternating light test is a generally a measure of the cone input received and processed by the melanopsin ganglion cells. The amount of asymmetry of pupillomotor input however, depends in part on the wavelength, intensity and duration of the light stimulus used to evoke a pupil contraction (Figure 3)

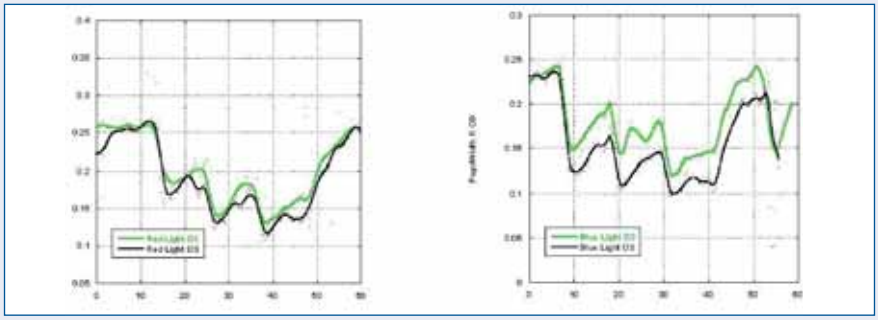

Figure 3. Example of pupil recordings to equiluminant red light and blue light in a patient with a right optic neuropathy due to an optic nerve sheath meningioma. Her clinical RAPD is moderately large, about 2.1 logunits. Both graphs relate pupil size (Y-axis) as a function of time in seconds (X-axis). The red and blue light stimulus paradigm is detailed in the legend for Figure 2. Left: The pupil responses to right eye stimulation (green line) and left eye stimulation (black line) using red light are shown. Note there is not much difference in the pupil contraction between right eye and left eye stimulation , i.e. little RAPD. Right: The pupil responses to blue light stimulation are shown. When the right eye is stimulated, the pupil responses are markedly diminished, indicating a significant asymmetry in pupillomotor input between the 2 eyes, i.e. moderately large RAPD.

The future may find that pupil analysis to non-white light stimuli of varying duration may be a new way to measure the RAPD and may lead to novel analyses for differentiating normal eyes from diseased eyes and facilitating the localization of pathology.

Table 1. Features of the rod and cone versus ganglion cell photoreceptors

Photoreceptor cell	rods and cones	melanopsin-expressing ganglion cells
Location	outer nuclear layer	ganglion cell and inner nuclear layers
Photopigment	rhodopsin cone opsin	melanopsin
Total number	92,000,000 rods 5,000,000 cones	several 1000s
Receptive field	very small	very large (photoreceptive net)
λ sensitivity	all visible wavelengths	broad band, most sensitive to blue wavelength light
Function	image formation pupillary light reflex	circadian clock pupillary light reflex

New cerebral imaging in neuro-ophthalmology practice : indications and limitations

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The objective of the presentation is not to provide a technical description of neuroimaging, but to provide a schematic overview of current indications and pitfalls of the available methods to image the brain and the orbit in the diseases seen in neuro-ophthalmology practice, as well as to illustrate some future directions.

I Indications

Non invasive imaging of the brain and the orbit is based upon Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT). Several new developments of MRI are currently available, including volumetric contrast enhanced MR angiography (CE-MRA) displaying 3D rotational angiography, motion-suppression imaging, proton spectroscopy (MRS), and tensor diffusion imaging. Higher magnetic fields (≥3T) will allow to track smaller lesions along with a shorter duration of imaging. Similarly, development of CT includes 3D rotational angiography (CTA). Neuroimaging provides several types of information. The more straightforward information expected by the clinician is to detect a focal lesion, to precise its location and morphology, and to indicate its nature. Beside this structural information, metabolic / functional information may also be relevant. Imaging brain perfusion has become routinely available with MR and CT to evaluate patients with acute ischemic stroke, especially when a thrombolytic treatment is considered. Other tools will become more readily available to clinicians in future, including analysis of brain tissue compounds with MRS, which may be useful in differential diagnosis of brain tumors or in positive diagnosis of mitochondrial diseases, study of brain plasticity with functional MRI, in particular to evaluate the effects of a remote lesion or of a therapeutic intervention, and direct analysis of extra ocular muscles dynamics during eye movements.

Skull and orbit fractures, as well as bone tumors and dysplasia, remain the only conditions for which CT is more informative than MRI. In some other conditions, CT and MRI may offer equivalent information, but in most cases of neuro-ophthalmology diseases, especially for tumor detection, MRI is more informative and should be prefered. In acute ischemic stroke, new generation of MR and CT allows direct thrombus imaging, and CT depicts composition of the plaque at the carotid artery bifurcation. Diagnosis of arterial dissection has become easily made with either MRA or CTA, while MRI offers the advantage of a greater specificity due to the direct visualization

of the mural haematoma. Intracranial aneurysms can usually be detected with high and similar sensitivity using MRA and CTA. However, small aneurysms of less than 6 mm can still be missed by non invasive neuroimaging. Digital subtracted angiography (DSA) with 3D reconstruction remains therefore necessary whenever suspicion is high, the prototypical case being painful IIIrd nerve palsy that is frequently symptomatic of a posterior communicating-internal carotid artery junction aneurysm. CT or MRI is highly suggestive of a diagnosis of carotid cavernous sinus fistula when it shows enlarged ophthalmic veins. In work up of intracranial hypertension, both CT and MRI can visualize a dural sinus thrombosis, but MRI is advantageous in providing additional information related to CSF sequestration in the optic nerve sheaths. Evaluation of brain tumors with MRI requires gadolinium enhancement, and evaluation of intra orbital tumors or myositis needs in addition fat suppression. MRI has become the reference imaging in inflammatory optic neuropathy, depicting almost constantly T2 hypersignal of the optic nerve or gadolinium enhancement at the acute phase, in addition to the visualization of brain T2 or FLAIR hypersignals in 50% of cases of isolated acute optic neuritis. More rarely, MRI is helpful for diagnosis of some neurodegenerative disorders seen in neuro-ophthalmology practice, such as progressive supranuclear palsy, cortico-basal degeneration, and visual variant of Creutzfeldt-Jakob's disease.

Suspected condition	Delay	technique
Aneurysm fissuration	< 1 hr	MRA = CTA
Acute ischemic stroke	< 1 hr	MRI > CT
Arterial dissection	< 1 hr if stroke	MRI > CT
Sinus dural thrombosis	< 6 hrs	MRA = CTA
Acute sinusitis	< 6 hrs	MRI or CT (CT >)
Intracranial hypertension	< 6 hrs	MRI > CT
Carotid Cavernous sinus fistula	< 24 hrs	MRI > CT
Multiple sclerosis	days	MRI > CT
Brain / orbital tumor	days	MRI > CT

Table 1. Indicative delay for performing neuroimaging according to the suspected conditions (these are both ideal and schematic data, as other factors have to be taken into account, such as severity and evolution of the condition, as well as the facilities available for the patient's care)

II Limitations

Despite tremendous improvement of diagnostic conditions based on neuroimaging in neuro-ophthalmology, several limitation factors persist and deserve to be known.

- Absolute and relative contraindications to MRI are listed below. A CT scan that is then performed as a substitute can alter the capacity of the clinician to identify relevant pathology.

Absolute	Relative	Usually allowable
Pacemaker	Heart valve	Pins
Otic implant	Aneurysm clip	Screws
Metal in eye	Claustrophobia	Rods
Implanted defibrillator	Pregnancy	
	obesity	
	Stents, coils, staples	

Table 2. Contraindications for MRI

- Claustrophobia and obesity may prevent the patient from receiving MRI.
- A poor quality or poorly ordered study could yield negative results although the pathology may still exist and is potentially visible. Most common situations include the lack of fat suppression for orbital MRI, or the lack of gadolinium administration. In some cases, standard orbital CT scan includes only axial views, meanwhile the diagnosis might require coronal images, for example to visualize enlarged extra ocular muscles. Without diffusion weighted imaging (DWI), epidermoid cysts cannot be reliable differentiated from arachnoid cysts. In some cases, CT represents the diagnostic modality of choice over MRI and vice versa. This is the case, in particular, for fibrous dysplasia in which CT shows pathognomonic findings and for allergic fungal sinusitis. Numerous examples exist of the superiority of MRI over CT.
- Another cause of negative result may result from the absence of underlying lesion. Examples include myasthenia gravis, many instances of headache, and retinal diseases.
- Finally, a major limitation of neuro-imaging lies in its inability to detect reliably all neuro-ophthalmic disorders secondary to intracranial or orbital etiology. Several examples can be provided, including anterior and posterior ischemic optic neuropathy, microvascular cranial nerve palsies, vergence disorders, essential blepharospasm.
- Artifacts may affect the quality of brain and orbital MRI. Aliasing occurs when the body part to be imaged is larger than the field of view of the scanner. Motion artefact can result from arterial pulsation, CSF pulsation, respiration and patient's movements including the eyes. Ferromagnetic substances produce localized field changes resulting in image distortion and concealing areas of localized interest. Common causes include aneurysm clips, dental crowns or dentures, braces, and

even some types of mascara or eyebrows tattoos. Poor fat suppression occurs at bone – air and bone – tissue interfaces, such as the paranasal sinuses. This may be important in the case of eye pain, as the incomplete fat suppression may be mistaken for orbital fat or extra ocular muscles inflammation. Changing the technique of fat suppression may suppress the artefact. CT of the brain and orbit may also demonstrate artefacts. Metallic objects in the field of view cause streaking artefacts, because the density of the metal is much higher than the range of densities for which the computer accounts sets bone at one extreme and one at the other. This problem may be overcome by changing angles to avoid the metal in the field of view or by using thinner slices to reduce partial volume artifact. Motion of the patient may also reduce quality of images. Despite their impressive visual impact, three-dimensional reconstructions of both MRI and CT images are also prone to artifact. Such reconstruction is usually performed by stacking the axial images one on top of the other (multiplanar reconstruction) using edge detection software to delimitate various structures, or determining the intensity of each volumetric voxel. These reconstructions may delete or magnify subtle changes or areas of interest. CTA and MRA have a tendency to overestimate the degree of stenosis of intracranial vessels and may miss smaller aneurysms up to 6 mm. Diagnostic accuracy can improve with viewing the source images, but they are usually not accessible except for the neuroradiologist.

- In some cases, neuroimaging is not capable of distinguishing pathologic processes. This is the case of certain orbital lesions despite imaging with both CT and MRI, of some brain abscesses, necrotic tumors and cystic lesions. White matter lesions shown by MRI are rather non specific findings that can be related to small vessels disease, inflammation, migraine or changes with aging. Other lesions that are often asymptomatic and unrelated to the reason the patient underwent neuroimaging, may be revealed by neuroimaging. These incidental findings, or "incidentalomas" are mostly pituitary adenomas, meningiomas, arachnoid cysts and aneurysms. They are discovered with increasing incidence due to generalized availability of high quality neuroimaging. In addition to being not helpful and even misleading for diagnosis, these findings lead to anxiety and costy repetition of neuroimaging.
- Finally, in addition to above mentioned pitfalls and difficulties, the greatest limitation of neuroimaging lies with the interpretation. Experience of the radiologist is critical for evaluating lesions, particularly of the orbit or cavernous sinus. A good clinical history work up providing localization or historical information reduces the risk for the neuroradiologist to overlook even obvious intracranial or intra orbital pathology and helps at limiting differential diagnosis. There is obvious necessity for the clinician in charge of a determined patient to access to the images and not only to the conclusion, even if this is considered to be normal. The neuro-ophthalmologist is the best placed to focus attention on the relevant part of the brain or orbit depending on the clinical manifestations, and this helps to pick up not exceptionally some diagnosis from allegedly normal CT or MRI.

The differential diagnostic problems of Van Dongen's Old Clown

| Riri Sylvia Manor, Petah Tikva, Israel |

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"***Art is a lie that enables us to realize the truth***" wrote Pablo Picasso in 1923.

In the context of painting – art may enables us to unveil sometimes the ocular problems of the artist as well as some ocular problems of the model inspiring the picture: Moreover the exposed to our view model may become a virtual patient harboring a broad spectrum of diagnostic alternatives as in the case of the famous Van Dongen's picture "The old clown", picture selected to serve as the poster of the European University Professors of Ophthalmology 2008EUPO residents course on Neuro-ophthalmology and Strabismus.

As a matter of fact I saw the first time the Old Clown picture in 1974 while visiting the Geneva Petit Palais Exposition "From Impressionism to Picasso" and I was then struck by the psychological study of an aging man pathetically trying to give the impression that he is still funny: The wrinkled ravaged face and tired; dropping hands contrasted sharply with his clown costume and bright red hair, strengthening even further the impression of old age. Van Dongen, who was quite young when he did this painting; could intuitively express all the deep human loneliness and tragedy accumulated in aging old men.

Cornelis Theodorus Maria Van Dongen known as Van Dongen was born in the suburbs of Rotterdam and lived the majority of his life in Paris; Nice and Monte Carlo: At the beginning the belonged to the German expressionist group "Die Brucke" and later on to the famous "Fauves" bright colored picture school.

The strong artistic impression that the Van Dongen"s portrait of the Old Clown made on me in 1974 did not prevent my looking at it through professional eyes and I published a letter in the Journal of Ophthalmology in November 1975 as concerning the ophthalmologic interest aroused by the portrait:

If we assume that the old clown is looking to the left; then the left eye remains in the middle; the left palpebral phanta is a little wider and it may be that it was Duane syndrome that Van Dongen observed:

If our virtual patient - clown by profession – was looking straight ahead with his left ewe; which in my opinion seems more plausible, then the differential diagnosis alternate between two possibilities :

1) Right strabismus convergent concomitant
2) Right strabismus paralytic due to a right abducens palsy: To add to this the evident emaciation of the patient it could be even the presence of a carcinomatosis with brain metastasis.

I finished the letter to AJO by pointing out that the last diagnostic possibility the old clown is seeing us, the visitors of the exposition, double from this frame!

Then another ophthalmologist send to AJO a comment concerning, my letter! That a forth diagnostic possibility does exist i.e. a right, micro cornea producing the childhood long lasting squint: He wrote that he measured the both corneas diameter on the picture and found the right one smaller !

At this I published a reply: the right eye being in strong esotropia – the right cornea was not shown frontally as the left cornea was: Thus the right cornea even normally dimensioned could look shortened by the perspective.

The legendary editor then of the AJO Frank W Newell ended the discussion writing that it will be a basis to reopen it only with one condition: if the old clown is showing up himself in a self-assessment!

But as usual there exists surprises in life and you may never know when you do something – when and where it will be result of this in the far future.

Thus I did not imagine the consequences when in 1993 – being invited to Geneva to give a speech at the International Ocular Trauma Congress – I revisited the Petit Palais Exposition and "my Old Clown". Then a museum guide approached me and tried to explain about Van Dongen painting. I told him that I do not need explanation; that I saw it in 1974 and published about this medical problems. The guide asked me then to send a reprint for the Museum collection.

After sending it I received a thanks letter from Dr Oscar Ghez, the President of the "Fondation du Petit Palais" and an extremely precious gift in my eyes : an artistic reproduction of the picture giving exactly the same impression like the original one and finding itself now at his best in my Tel Aviv living room!

Dr Ghez wrote me that Van Dongen arriving the first time at his home in Geneva and seeing there his picture said to him that The Old Clown is the "chef d'oeuvre de ma vie" and that the Old Clown from Medrano Circus was in fact very sick when he painted him and died few weeks after it.

Thus it seems to be that the last differential diagnosis I pointed out in my QJO letter was the real diagnosis – a generalized malignancy with abducens palsy.

The last scene of my 33 years involvement with the Old Clown squint was to visit the Medrano circus representation in Tel Aviv – who knows why? Perhaps to see what was the ambiance where my peculiar patient lived, perhaps to found some echo of the children laugh at his joked?

Anyhow, the Old Clown in spite of his despair and disease was kept alive through the genial art of Van Dongen and still teaches us a remarkable amount of neuro-ophthalmology lessons.

"***Art is a lie that enables us to realize the truth***" wrote Pablo Picasso in 1923.

Update on Amblyopia

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Introduction

The most up-to-date definition of amblyopia is: *an alteration in the development of the visual function in either one or both eyes, which occurs during the period of plastic development of the visual system.* Amblyopia is caused by abnormal binocular interaction and/or the lack of clear images forming on the retina during that period. During this period, various visual functions can be affected by noxae which interfere with normal developmental processes; within certain limits, however, the effects of amblyopia can be reduced or overcome by appropriate treatments.

The prevalence of amblyopia varies, according to available statistics, from 1.6 to 3.6%1. This means that several million people are affected in the European and North American population. It is suspected that the prevalence of amblyopia may be higher in countries with less developed health systems. Due to both the notable prevalence of amblyopia and the rapid technological developments in our society that entail a growing need for activities requiring increasingly sophisticated visual performance, amblyopia represents a real socioeconomic problem.

Classification and etiology

Amblyopia has always been subdivided from the clinical point of view *into strabismic amblyopia, anisometropic amblyopia,* and *amblyopia by visual deprivation*. Physiological and pathological mechanisms are similar in the different types of amblyopia, and can be summarized as follows: abnormal binocular interaction, lack of formation of clear images at the foveal level, or a combination of both of these factors. Strabismic amblyopia, which is always monolateral, is caused by an abnormal binocular interaction, while anisometropic amblyopia is caused by both an abnormal binocular interaction and the lack of formation of clear images on the fovea. Amblyopia by deprivation is caused: in the monolateral form, by both the lack of formation of clear images on the fovea and an abnormal binocular interaction; in the bilateral form, essentially by the non-formation of clear images on the retina. Strabismic amblyopia, which is typical in non-alternating strabismus, is commonly considered to be a consequence of suppression. Yet, suppression does not appear to be the only cause of amblyopia: in strabismus there can be amblyopia without suppression and an inverse correlation exists between severity of amblyopia and the depth of suppression. Various studies have revealed that causes other than suppression can contribute to the occurrence of amblyopia in strabismus1. In anisometropic amblyopia – which is typical of hypermetropic anisometropia – there is an active inhibition of the fovea of the more

ametropic eye, thus causing worse visual acuity in the amblyopic eye under binocular conditions than in monocular vision. There is also an active inhibition of the fovea of the more ametropic eye, thus causing worse visual acuity in the amblyopic eye in binocular conditions than in monocular vision. As for the relationships between amblyopia and refractory development of the eye, it has to be noted that amblyopia can be a consequence of hypermetropic anisometropia but, as proven by animal experiments, it can also be the cause of an altered refractory development of the amblyopic eye – which shows a decreased development of the axial length – thus remaining more hypermetropic than the other eye[1].

Amblyopia by visual deprivation is caused by the opacity of the media, complete monolateral lid ptosis, indiscriminate occlusion or prolonged atropinization during anti-amblyopic treatments. Usually, unilateral forms are more severe, as they are complicated by the occurrence of a secondary strabismus of the amblyopic eye.

Pathogenesis and Pathophysiology

At birth there is a semi-independence of the eyes, and then binocular collaboration is rapidly established. However, during the development of the primary visual cortex, there is still a neuro-physiological competition between the two eyes, which is the underlying factor in amblyopia. In fact, one eye may prevail over the other in gaining synaptic connections at the primary visual cortex level. The susceptibility of the visual system to possible amblyogenic factors is at its highest during the first 3 years of life, gradually decreasing and disappearing by the age of 8. It was demonstrated that in amblyopia there is a dissociation between the parvocellular system – which is essentially in charge of the perception of shapes and colors, and the magnocellular system, which is in charge of the perception of movements, with a selective deficit of the parvocellular system1. As for the sensitivity to contrast and light sensitivity, the amblyopic eye shows better functional performance in mesopic and scotopic conditions than in photopic conditions. Amblyopia, especially that caused by strabismus, is characterized by a marked lack of spatial precision with localization errors. The presence of interocular inhibitory phenomena, which is a typical event in amblyopia, causes the poorer visual acuity of the amblyopic eye when the other eye is open and a better acuity when the other eye is closed. Many studies based on electro-physiological tests have attempted to detect the locus of amblyopia. The electro-retinogram (ERG) has not demonstrated any alteration at the retinic level in amblyopia; it is, however, a mass response of the entire retina which is unable to evidence alterations which involve any retinal sub-systems. The electro-oculogram (EOG) has revealed abnormalities in adult amblyopes, but provided results which depend on the ocular motility, which is frequently altered in amblyopes, especially in strabismic amblyopes or amblyopes who have no normal binocular collaboration. Also, the visual evoked potentials (VEPs) in amblyopes have given controversial results: as a matter of fact, the reduced VEP width is not directly correlated with the degree of amblyopia. Furthermore, patterns of both binocular summation with increased width of the evoked

response in binocular conditions and binocular inhibition with reduced VEP width in binocular conditions have been described in amblyopes.

Experiments in animals with induced amblyopia have evidenced the decimation of both the binocular neurons and neurons connected to the amblyopic eye, at the level of the primary visual cortex. In experimental amblyopia, the loss of binocular neurons is permanent, whereas the recovery of the monocular neurons connected to the amblyopic eye is possible after treatment. Histological studies, both in animals in which amblyopia was experimentally induced and humans with either strabismic or anisometropic amblyopia, have demonstrated the presence of morphological alterations at the level of the lateral geniculate body. These changes correspond to the reduced cell size at the level of the geniculate laminae which are connected to the amblyopic eye1. Lastly, studies which included PET (positron emission tomography) scans revealed a reduction in both the relevant cerebral blood flow and the glucose metabolism at the visual cortex level during the stimulation of the amblyopic eye1.

Different and numerous molecular mechanisms seem to be elaborately involved in the development of visual function and in the progressive reduction of ocular-dominance plasticity. In a recent study Maffei *et al.* [2]suggest a role for many factors: NMDA ((N-methyl-D-aspartic acid) receptors, neurotrophins, GABA-mediated intracortical inhibition, intracellular kinases, regulation of gene expression by means of activated kinases traslocated to the nucleus and extracellular matrix. Even if a limit of these findings can be that most of the molecules and molecular mechanisms have been studied only using animal models, they also highlight the possible molecular basis of plasticity in the visual cortex which might imply new therapeutical approaches.

Treatment

To be most effective, amblyopia must be treated during the first years of life, while later treatments can offer only partial or temporary improvements. There is also a risk of causing diplopia due to the occlusion-induced weakening of the anti-diplopic mechanisms. The classic treatment of amblyopia consists of three main components: the correction of the refractory fault by eyeglasses, occlusion, and penalization (optical or pharmacological) of the other eye. Nowadays it is necessary to add medical treatment.

- ***Optical Correction***

Both optical correction and occlusion improve sight: since they are often prescribed together, their individual contributions to this result cannot be differentiated in either daily medical practice or research. Recent studies have shown that improvement from wearing eyeglasses (which are necessary in most amblyopic children) takes a long time, varying from 15 to 18 weeks, with a so-called refractory adaptation process. It is imperative to provide the amblyopic patient with a total optical correction of the refractory defect – both spherical and astigmatic – of the amblyopic eye.

- *Occlusion (patching)*

Occlusion of the healthy eye by patching – for the purpose of stimulating the visual function of the amblyopic eye – is still the most advisable proven and effective method for the treatment of amblyopia, also in the presence of nystagmus. The occlusion regimen varies depending on the patient's degree of amblyopia and age. It has been demonstrated that the earlier the occlusive treatment, the faster the visus increase will be; furthermore, hours of occlusion being equal, the fastest results will be obtained with the youngest children. As for the number of hours of occlusion which are useful in the treatment of amblyopia, the series of publications of the "Pediatric Eye Disease Investigator Group" during the period 2003-20053 has caused a certain perplexity at the international level, because of their statement that an occlusion of just a few hours gives the same results as total occlusion. This immediately spurred complaints by many parents to their doctors whenever they insisted on prescribing the bothersome "old-fashioned" total occlusion. Therefore, in our opinion, especially as far as severe amblyopia in early childhood is concerned, before discontinuing a treatment which has a long history of proven effectiveness, it is necessary to collect more clinically valid data. The knowledge of the exact number of hours of occlusion used in the child – a prerequisite for the determination of a dose-response relationship – is still the basic factor for defining a therapeutic prescription regimen based on evidence.

- *Penalization*

Penalization is based on the principle of image defocusing in one eye in order to encourage the use of the other eye. Defocusing can be obtained using drugs, sometimes in combination with optical means. In an article of 2003[3], the "Pediatric Eye Disease Investigator Group" reports the positive results of the treatment of amblyopia using pharmacological penalization with atropine, as already suggested by Kushner in 2002[4]. In this article, the Authors suggest a new dosage for atropine administration. As a matter of fact, they state that identical improved results in the visual acuity of the amblyopic eye can be obtained with the topical administration of 1% atropine sulphate either daily or limited to weekends only. They maintain that the reason for this is the prolonged cycloplegic effect of the drug.

As for us, the old pharmacological penalization method is used very little today for a series of reasons: unconvincing results, the lengthiness of the treatment time, the risk of pharmacological poisoning, induced photophobia, risk of amblyopia by deprivation that may be induced in the atropinized eye if it is hypermetropic. From the technical standpoint, it must be added that cycloplegia does not guarantee a change in fixation: the patient may continue fixating through the non-amblyopic eye and thus end up having cloudy, blurry vision, both nearsighted and farsighted. Indication for the use of penalization is restricted to cases where there is a patent lack of tolerance to the eyepatch in the child or his/her parents.

- *Medical treatment*

Often, the treatment of amblyopia based on blocking the visual input in the fixating eye – for the purpose of stimulating the vision of the amblyopic eye – seems insufficient due to compliance problems concerning the occlusion regimen as well as to the tendency to lose the benefits obtained with time. Therefore, the combination of occlusive treatment with pharmacological stimulation can render the effects of occlusion more effective and long-lasting. In this regard, several experimental studies have been carried to find drugs capable of stimulating the visual system. The most-studied drugs are: levodopa[5], carbidopa[6] and cytidine-5′-diphosphocholine (cyticholine). All of these are precursors of dopamine, an important intra-retinal neurotransmitter and mediator in communications between certain ganglionar cells and the visual cortex. The proven effectiveness of levodopa or carbidopa in improving visual acuity is frequently accompanied by significant side effects such as: nausea, headache, excitement, insomnia, changes in humor.

Studies carried out during the period 1995-1998 report that cyticholine administered by intramuscular injection, combined with occlusion, improves its effects in amblyopes of various ages[7,8,9]. A recent study showed that CDP-choline administered by os achieved results overlapping those described for intramuscular injection, thus suggesting the actual possibility of an early pharmacological treatment of amblyopia with no side effects, unlike other effective substances such as levodopa and carbidopa, and with a more convenient administration procedure[10,11].

The oral administration of cyticholine, in addition to the traditional anti-amblyopic effect, enhances its medium-/long-term effect (90 days), while stabilizing the improvement of the visual function. Improvements also registered in the effectiveness variables tested for the healthy eye proved that this is not an amblyope-specific treatment, and thus does not carry a risk of diplopia.

Maya Vetencourt *et al.* investigated in a most recent study the role of the antidepressant fluoxetine in restoring plasticity in the adult visual cortex showing encouraging results in adult rats. These data suggest a potential clinical application for fluoxetine in amblyopia[12] .

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Spatial distortions, temporal instability and spurious colours: "Positive" symptoms in amblyopic vision?

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Amblyopia ("blunt vision") is a developmental disorder of the visual system, commonly defined as a reduction of visual acuity in one or both eyes in the absence of ocular deficits (von Noorden,1980). Prevention of vision in one or both eyes in early life (visual deprivation), an early ocular misalignment (strabismus), or a refractive imbalance between the two eyes (anisometropia), may be potential sources of amblyopia. In addition to reduced visual acuity and compromised binocular vision and stereopsis, perceptual deficits like reduced contrast sensitivity (Hess & Howell, 1977), deficits in spatial localization (Bedell & Flom, 1981; Levi & Klein, 1983), crowding (Levi & Klein, 1985), and loss of positional information, in form of increased spatial uncertainty (Wang et al., 1998) have been described in adult amblyopes. The patients describe vision through their amblyopic eyes as fragmented, distorted, or scotomatous. In addition to these stable errors, amblyopic subjects often report their percept as being temporally unstable (Hess et al., 1978). Images are seen as permanently changing, as "seen through hot air" (Sireteanu, 2000). Although amblyopia is usually regarded as an ophthalmological disorder, it might be more appropriate to interpret it as a neurological condition, since neither the eye structures, nor the neural components of the retina are affected.

In previous studies, the spatial misperceptions experienced by amblyopic subjects were graphically illustrated. In most cases, these illustrations were completed by the subjects, who used their unaffected eyes for drawing the memorized percepts of the amblyopic eyes. Mary Pugh (1955) asked her amblyopic subjects to draw their perceptions of drawings of single letters. The drawings showed fragmentation, asymmetric degradation and blurring of part of the letters. Hess et al. (1978) asked their subjects to sketch their perception of circular patches of vertically oriented sinusoidal gratings of different spatial frequencies. The drawings showed spatial "aberrations", consisting in fragmentation, bending or bifurcation of the single lines of the gratings, affecting mainly gratings with higher spatial frequencies. Barrett et al. (2003) asked a group

of 30 amblyopic subjects to draw their impressions of circular patches of sinusoidally modulated gratings of different orientations and spatial frequencies. They categorized the individual distortion patterns into five distinct classes of anomalous perception (1) wavy appearance of straight gratings; (2) a "jagged" type with abrupt positional shifts orthogonal to the grating orientation; (3) errors in perceived orientation; (4) fragmented perception, in which the gratings appear broken; and (5) scotomatous distortions showing large gaps in the gratings. For most subjects, the type of perceptual distortion was not constant across different spatial frequencies or orientations. Barrett et al. (2003) proposed a model, in which these "non-veridical perceptions" were interpreted as originating from errors in the neural coding of orientation in the primary visual cortex.

We investigated the non-veridical visual perception in subjects with amblyopia of different aetiologies, with a main focus on temporal instabilities and their relationship to the spatial misperceptions and the clinical history of the subjects. About 40 subjects with strabismic, anisometropic and mixed amblyopia and strabismics with alternating fixation and good vision in both eyes were asked to describe and sketch their subjective perception of different geometrical patterns (single vertical lines, square-wave gratings of lower and higher spatial frequencies, checkerboards or grids), as seen with the affected eye. Based on these records, the experimenters completed two-dimensional illustrations of the perceptual experience of each amblyope, which were then validated by the subjects. In addition to the spatial distortions, we investigated the temporal instabilities in amblyopic vision, as well as their relationship to the spatial distortions experienced by the same subjects. The results were related to the clinical data of each subject.

Most amblyopic subjects, but none of the strabismics with alternating fixation, showed spatial distortions, more frequently for higher than for lower spatial frequencies. The resulting drawings contained bending of the single lines, bifurcations, confluences of the individual lines in the gratings, and large scotomatous gaps, affecting mainly the central parts of the patterns (Fronius & Sireteanu, 1989; Sireteanu et al., 1993; Bäumer & Sireteanu, 2006; Sireteanu et al., 2007). These illustrations were compared with the computer-generated reconstructions of the same patterns, based on a two-dimensional, point-by-point mapping of the central 12° of the visual field of each subject (Lagrèze & Sireteanu, 1991; Sireteanu et al., 1993; Sireteanu et al., 2007; Iftime et al., 2007). Both the subjective illustrations and the objectively determined point-by-point mappings of the investigated amblyopes showed severe distortions, but the subjectively experienced distortions could not be completely predicted by the computer-reconstructed images. Based on these findings, we concluded that perceptual description and point-by-point mapping might tap onto different levels of the visual pathway, which might be affected differently by the amblyopic deficit.

Temporal instability was perceived mainly by strabismic and strabismic-anisometropic amblyopes and occurred only at higher spatial frequencies. We found two categories of temporal instability: a) the whole pattern was perceived as jittering, b) single lines

or parts in a pattern were perceived as moving. Subjects with temporal instabilities often experienced spurious colours with their amblyopic eyes (for an example, see Fig. 1)

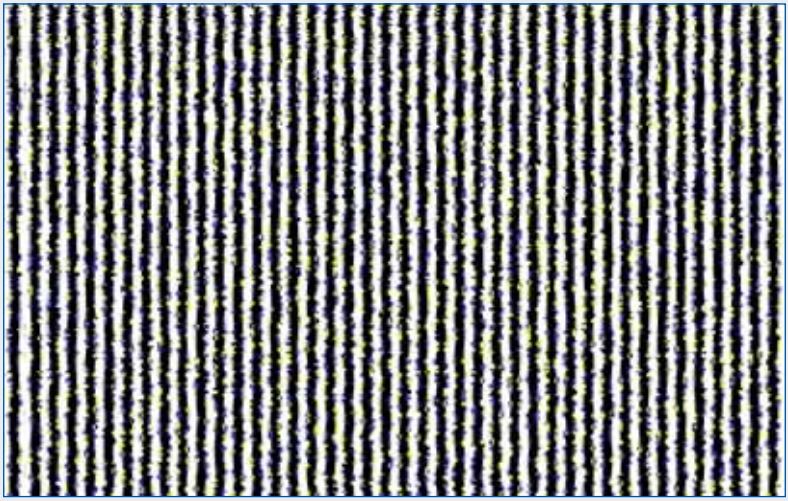

Figure 1. Example of spatial misperceptions and colour illusions in a subjects with strabismic-anisometropic amblyopia (subject CL; subtype "whole-pattern-flicker"). The colour illusions appeared in addition to spatial and temporal misperceptions.

Graphical illustration of non-veridical visual percepts has proven valuable as a diagnostic tool in several brain disorders (treated idiopathic Parkinson's disease, idiopathic occipital epilepsy, Charles Bonnet syndrome, or migraine aura). Our results suggest that spatial and temporal misperceptions in amblyopia could be regarded as positive symptoms of a neurodevelopmental disorder. Their similarity to the visual hallucinations experienced in healthy subjects after prolonged visual deprivation (Schultz & Melzack, 1991; Burke, 2002; ffytche, 2005; Merabet et al., 2004; Sireteanu et al., in press) suggest a common neural mechanism.

Together, these findings suggest that, while part of the spatial distortions in amblyopia might reflect stable local deformations in cortical topography, the temporal instability and the spurious colours experienced by some amblyopic subjects could be regarded as a positive symptom of a hyperexcitable, disordered visual cortex.

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Development of ocular motor functions - critical periods and clinical implications

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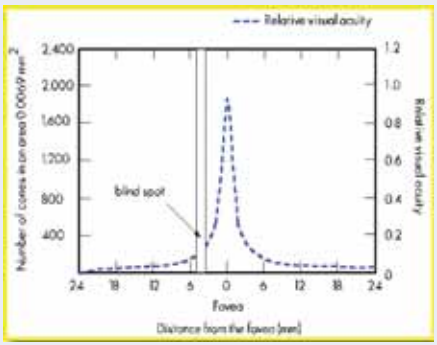
A good visual function is dependent on several factors such as:

- a high visual acuity
- the ability to keep the fixation steady on a target although moving body/head
- the ability to track moving targets
- the ability to change fixation between different targets

Eye movements necessary for a good visual function:

- Fixation
- Saccades – to change gaze
- Smooth pursuit – to track moving targets
- VOR – vestibulo-ocular reflex – to keep a steady fixation
- OKN – optokinetic nystagmus – to keep a steady fixation
- Vergence eye movements – to track moving targets in depth

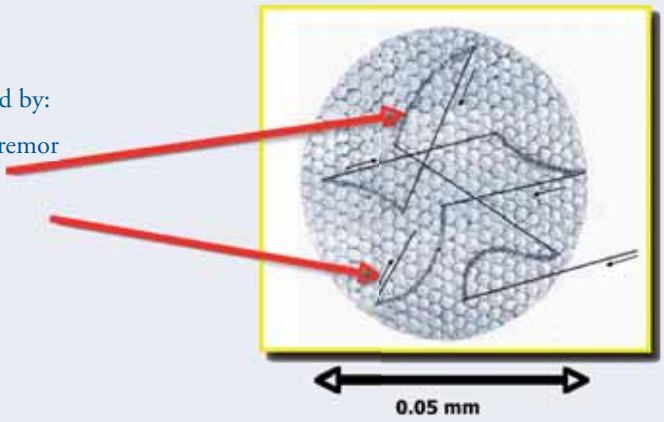
Clear vision of an object requires that the image is held fairly steady on the retina (fovea)



- amplitude < 0.5 deg.
- velocity < 5 deg./sec

Fixation is interupted by:

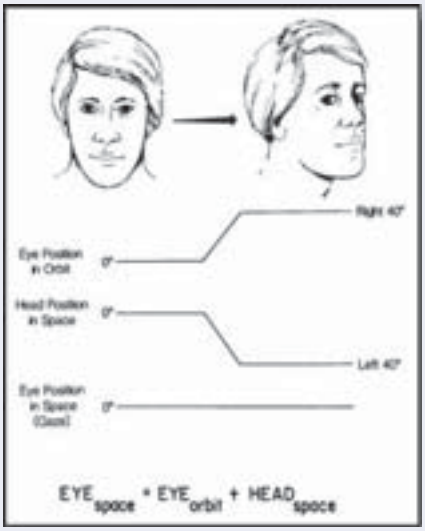
- high frequency tremor
- drifts
- microsaccades



How to keep the image steady on the retina (fovea) ?

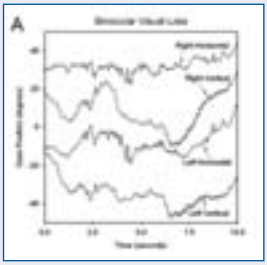
VOR – vestibulo-ocular reflex

- Eye movements compensate head perturbations
- Very effective reflex – short latency -- 15 ms



Fixation and visual impairment / low vision

Nystagmus in congenital binocular blindness



- pendular/jerk nystagmus
- wandering null point
- change in nystagmus quick phase direction

- a gaze-holding mechanism never been calibrated by visual inputs
- similar to experimental cerbellectomy

Blindness since birth (Leber´s congenital amaurosis)

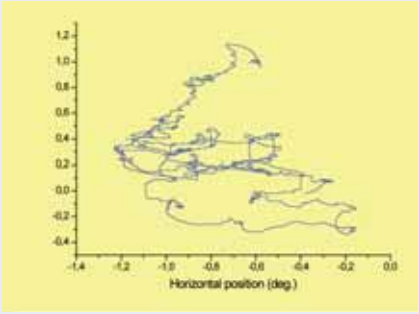
Figure and video from Dr D. Zee

Method:

- IR-recordings of eye movements
- XY-1000 (IOTA Inc. Sweden)
  - resolution 0.01 deg.
  - linearity 10% (manufacturers data)
  - recording frequency 100 Hz
- Chin- and front rest
- Monocular calibration

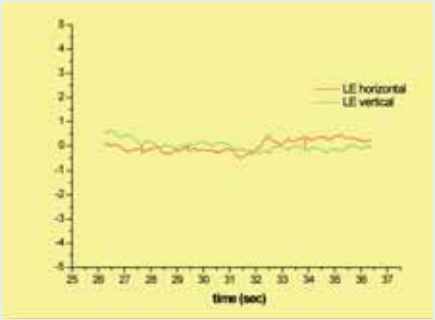
Eye movements during fixation:

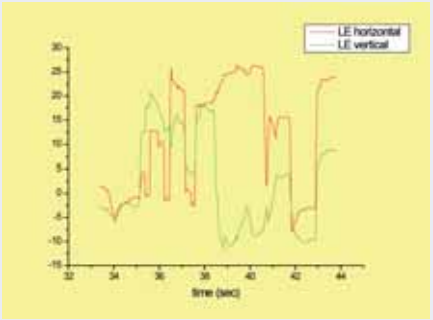
- tremor
- drifts
- microsaccades
- blinks



10 secs recording (RE) of a 10 years old normal child fixating a tationary target

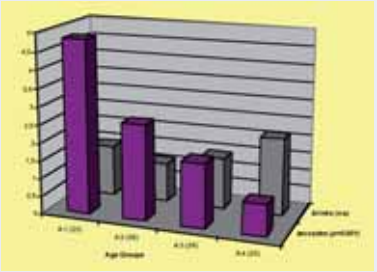
Large variation in fixation stability among subjects



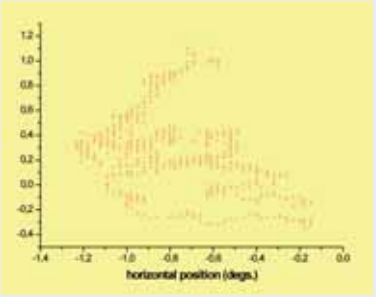


Results:

- no of blinks during 30 secs.
  No difference between age groups -- n.s.
- no of intruding saccades (>3 degs.)
  during 30 secs. decreased with
  increasing age group – p=0.001



- center of gravity (CG) for fixation
  points calculated = mean of horizontal and
  mean of vertical position
- distribution of fixation points
  around the CG
  - distance from CG
  - angle from 0 deg



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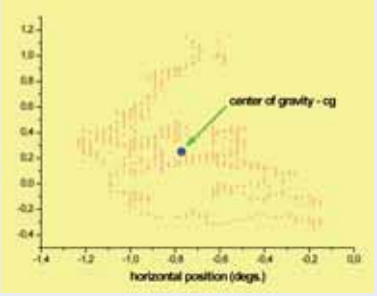
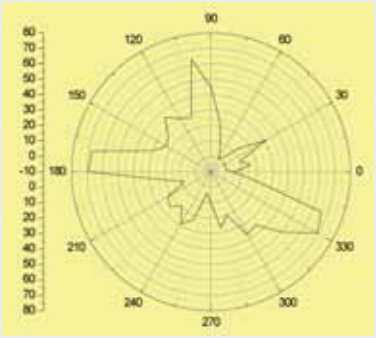
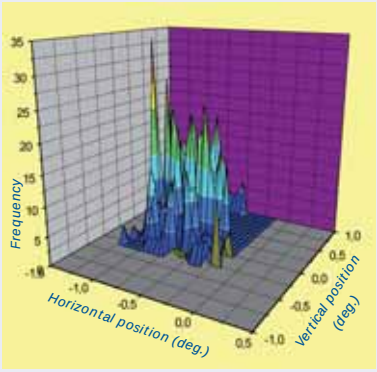
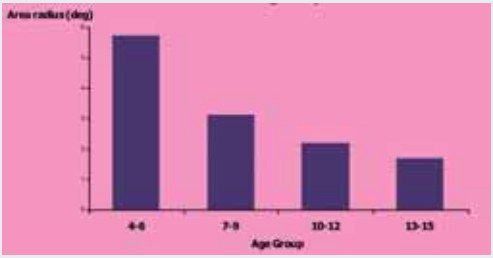


- no of fixation points in each direction

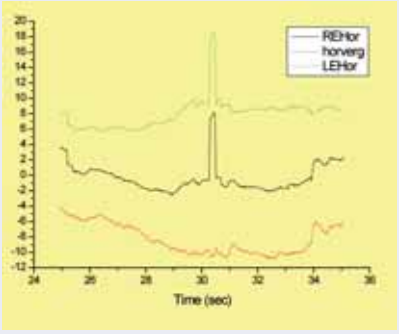


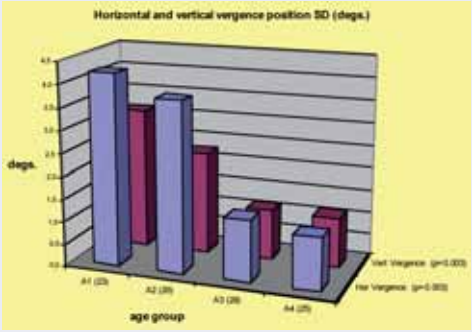


- area radius of the central most 63% of fixation points around the CG (p=0.001)



Horizontal and vertical vergence position



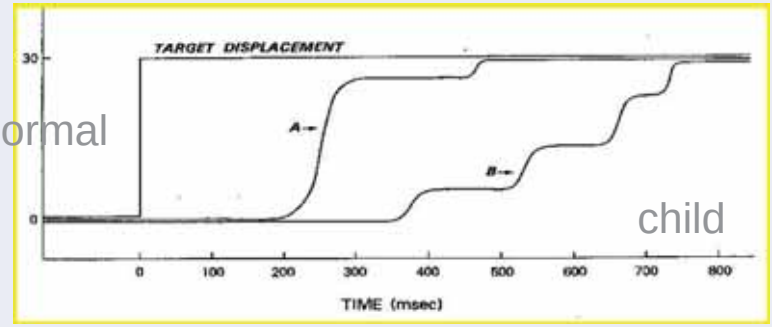


Conclusions fixation development:

- No difference in number of blinks during fixation between the different age groups
- Decreasing number of intruding saccades with increasing age group
- Less area radius (corresponding to more stable fixation) containing 63% of fixation points with increasing age group
- No directional preponderance in fixational position
- Increased vergence stability, both horizontal and vertical with increasing age group.

Saccades - development

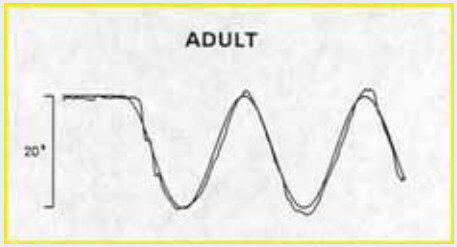
- main sequence
- precision and latency dependent on attention
- hypometria common among children

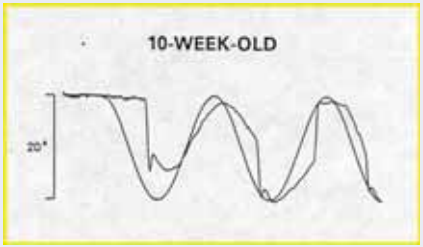


Smooth pursuit - development

SP – dependent on foveal function

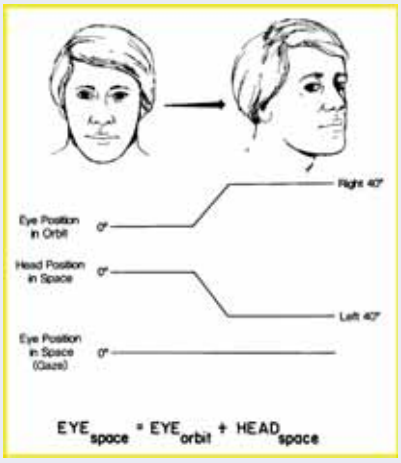
• low gain common in children





VOR / OKN - development

- early development – already seen at birth
- cannot be volontary suppressed
- reflex
- Doll´s head movement

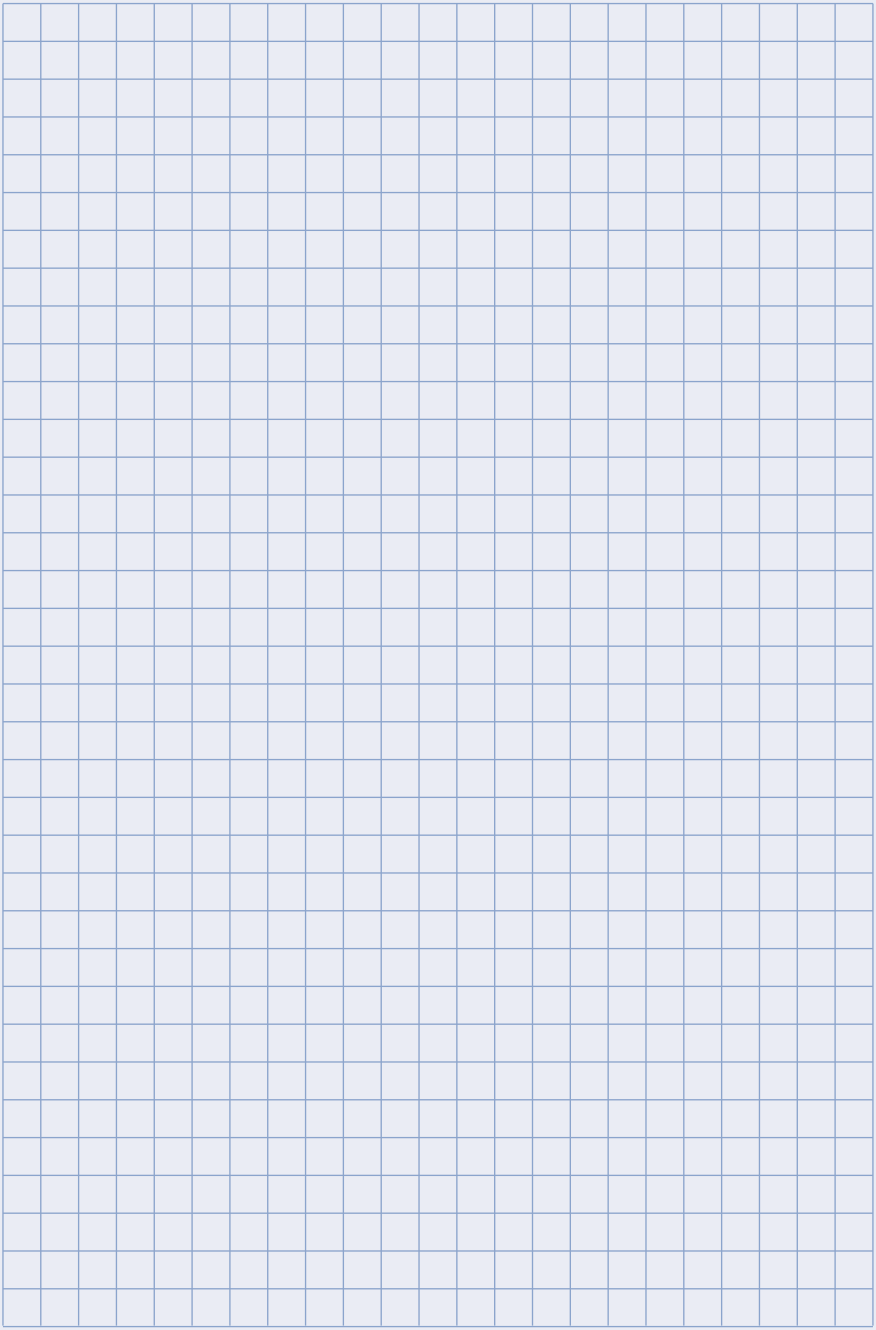


Vergence - development

- vergence development in line with accommodation development
- accommodation development in line with foveal development
- develops at around 2 months age

Take home message:

- Consider ocular motor development when examining a child
- With age the following ocular motor functions change:
- Fixation stability increases
- Saccadic latency decreases
- Saccadic precision and conjugacy increases
- Smooth pursuit gain increases
- VOR / OKN is fairly developed at birth
- Vergence function parallels visual acuity



Diplopia

| Monique Cordonnier, Brussels, Belgium |

Université Libre de Bruxelles, Hôpital Erasme

Introduction

Diplopia is a common and distressing symptom which may be the presenting feature of a wide variety of ocular and neurological conditions. Many patients with double vision present directly to an ophthalmic casualty department and the ophthalmologist is the first clinician with the opportunity to establish the diagnosis and prevent unnecessary, time consuming and expensive investigations.

Diplopia represents approximately 1.4 % of all ophthalmic casualties. Among diplopia patients, 25 % presents with monocular diplopia and 75 % with binocular diplopia. Cranial nerve palsies are the commonest cause of binocular diplopia and are most frequently due to diabetes and microvascular disease. Other causes of binocular diplopia consist of convergence or accommodation problems, decompensating phorias, traumatic, muscular, orbital lesions, supranuclear lesions, and other miscellaneous conditions. In some cases, no specific cause can be identified (1).

In a very restricted number of cases, diplopia will be the presenting feature of a potentially life or vision threatening illness and the work-up has to be done without delay. These cases represent true or relative emergencies and the ophthalmologist must be able to recognize them.

In the presence of diplopia, the investigating physician must consider two basic questions :

1. Monocular/binocular diplopia ?

A monocular diplopia is not an emergency. Monocular diplopia is a problem of different etiologic significance and, for the most part, less serious consequence than that of binocular diplopia. With few exceptions, monocular diplopia reflects optical aberrations within the refracting media of the eye itself : uncorrected astigmatism, corneal irregularity, cataract, IOL dislocation, macular irregularity. The diplopia generally disappears with the pinhole (2).

2. Incomitant/comitant misalignment ?

If it is a true binocular diplopia with similar images seen by each eye, there is a misalignment of the eyes in one or several positions of gaze and the motility examination will reveal whether it is a comitant or incomitant misalignment or squint.

Comitant misalignment

A previously strabismic patient can experiment diplopia as the result of a change in the angle of strabismus, or a change in his refractive management or needs (3). The onset of diplopia is often gradual.

A comitant squint with diplopia can be the result of an acute-onset comitant esotropia. The onset of esotropia may be sudden, with a constant comitant esotropia. The vast majority of cases will not be associated with serious underlying neurologic disease. When there is a history of previous strabismus, occlusion therapy, monocular visual loss, or myopia, acquired comitant esotropia is usually benign.

However, if a patient has no apparent cause for acute-onset comitant esotropia, the possibility of an underlying neurologic disorder should at least be considered, especially in pediatric patients. The size of the deviation and the presence or absence of an A or V pattern are especially important in assessing these patients (4).

1. ***Acute-onset comitant esotropia with brain tumors (cerebellum being the most common tumor site) :***

In some cases, the esotropia is initially intermittent and a constant comitant strabismus develops over a few days or weeks. The angle of deviation is often small or even intermittent initially but over time tends to increase. The esotropia presents without any pattern or a small V pattern, and there is a lack of significant motor and sensory fusion (with hand-held prisms or on synoptophore examination), even after appropriate optical and/or surgical treatment. A careful examination for nystagmus and/or papilloedema is of the utmost importance although their absence does not exclude posterior fossa dysfunction. Any evidence of clumsiness or loss or motor skills should prompt thorough investigation for a cerebellar tumor.

2. ***Acute onset comitant esotropia associated with hydrocephalus or Chiari type I malformation :***

This esotropia is generally associated with an A pattern. In the case of hydrocephalus, it often presents with a large angle. It can be a sign of shunt failure. Most of these patients will experience realignment of the ocular axes after restoration of normal intracranial pressure.

In Chiari type I malformation (displacement of the cerebellar tonsils into the upper cervical canal), nystagmus is present in 60 % of the patients.

3. ***Divergence paresis :***

This is a supranuclear paralysis heralded by the sudden onset of esotropia with diplopia. Horizontal versions are normal and the misalignment is usually comitant. At near, there is a small range in which the patient is able to fuse. Fusional divergence amplitude is markedly reduced (normal values : 6-8 D distance, 12-14 D near). Most often, divergence paresis is benign and self limited, but occasional reports describe it with demyelinating disease or tumor in and around the cerebellum (2).

Incomitant ocular misalignment

1. Single ocular motor palsy

An incomitant squint generally reveals an ocular motor palsy. It is possible to establish whether the case is serious and work-up should to be done without delay. Dr Cruysberg's following sentence (completed by two letters in red) will help the ophthalmologist to answer to this question :

« DON'T PPANHIC with ocular motor palsies »

The clinical importance of an ocular motor palsy is determined largely by the presence of accompanying signs and symptoms. Causes for alarm include : papilloedema (raised intracranial pressure); a dilated pupil (oculomotor nerve compression by aneurysm or neoplasm); constricted pupil (sympathetic pathway involvement, Horner's syndrome); acquired nystagmus (pontine or cerebellar damage); visual fields defects (space occupying lesion along the optic pathways); and decreased corneal sensitivity (trigeminal nerve involvement). Ten years ago, an ophthalmologist from Nijmegen (Holland), Dr Cruysberg, published in the Lancet a mnemonic to help remembering the important clinical signs : the PANIC signs (5). I would add another P for Pain in the neck or mandibula (cerebral artery dissection), and H for Horton arteritis clinical signs (age > 55, nocturnal sweating, pyrexia of unknown cause, weight loss, headache, jaw claudication, sensitivity of the scalp, history of polymyalgia rheumatica).

P = Pain in the neck or mandibula
P = Papilloedema
A = Anisocoria
N = Nystagmus
H = Horton
I = Incomplete visual fields
C = Corneal hypo-aesthesia

The presence of one or more alarm signals (PPANHIC signs) makes a serious case very likely. However, if thorough medical examination suggests that a palsy is isolated, the condition is unlikely to be the result of serious intracranial disease. One exception to this rule is an isolated VIth nerve palsy in a patient between 15 and 40 years: Although in many of these patients the problem is benign and remitting, MRI is recommended, followed if negative by a thorough neurologic examination, including a lumbar puncture to exclude such entities as hypertension, collagen vascular disease, multiple sclerosis, Lyme disease, and lues.

An ocular motor palsy with the H sign (Horton arteritis) requires an ESR and CRP evaluation.

An ocular motor palsy with one of the other PPANHIC signs imposes a cerebral MRI (magnetic resonance imaging). Help the radiologist and precise what kind of lesion you want to rule out. MRI must be followed by a lumbar puncture with a measure-

ment of CSF (cerebrospinal fluid) pressure in case of papilloedema without cerebral lesion and without Arnold-Chiari malformation (tonsillar engagement !).

Among the PPANHIC signs, Anisocoria deserves special comments :
Pupillary sparing in isolated third nerve palsy
When there is a third nerve palsy, the relative involvement or sparing of the pupillary light reflex is important to check for the following work up. The pupillo-constrictive fibers are indeed superficially situated in the bulk of the nerve through its route at the base of the skull. Hence, they are injured in 95 % of compressive causes of IIIrd nerve paralysis (2). On the contrary, ischemic causes involving mainly the deep layers of the nerve, the pupillo-constrictive fibers are spared in 80 % of the cases.

The involvement or sparing of the pupillary light reflex is always appreciated relatively to the oculomotor involvement. Hence, if a patient presents with a complete involvement of all the motor components of the IIIrd nerve but with a pupil reacting briskly to light even though 2 mm wider than the other pupil, he is considered to have a relative pupillary sparing. On the contrary, if the pupil slightly under-reacts to light in the presence of an incomplete or partial involvement of the motor components of the IIIrd nerve, there is no relative sparing of the pupil.

The most important challenge presenting to the ophthalmologist dealing with an isolated IIIrd nerve palsy is not to overlook an intracranial aneurysm (6). Aneurysms account for as many as 30 % of cases of isolated third nerve palsy in some series. The estimated rate of subarachnoid hemorrhage from a previously unruptured asymptomatic aneurysm is only 1% to 2% per year, but those that rupture are associated with a mortaliy rate of roughly 50 %. On the contrary, the treatment of an aneurysm before it ruptures is now highly successful and in most cases reasonably safe.

Most of the aneurysms responsible of a IIIrd nerve palsy arise from the posterior communicating artery and disclose an approximate size of 5 mm or more. Catheter angiography has long been considered the only definitive study for detecting cerebral aneurysm, but it is associated with a 1% to 2% risk of neurologic and systemic complications. Refinements in magnetic resonance angiography (MRA), a noninvasive tool capable of imaging the cerebral circulation now offer a tempting alternative to catheter angiography. Actually, it is estimated that properly performed and interpreted MRA will overlook only 1.5 % of aneurysms that cause third cranial nerve palsy and that will go on to rupture during the subsequent 8 years if untreated. This 1.5 % risk of overlooking an aneurysm likely to rupture is nearly equal to the aggregate risk of stroke, myocardial infarction and death associated with catheter angiography. Among elderly patients (>70 years) or in patients suffering from symptomatic atherosclerotic cerebrovascular disease, significant cardiovascular or renal disease, the risk with MRA of overlooking an aneurysm likely to rupture is slightly less than the risk of catheter angiography. However, because of the potentially drastic consequences of overlooking an aneurysm, MRA should be considered the definitive screening test

only among patients with a relatively low likelihood of harboring an aneurysm or a relatively high likelihood of suffering a complication during catheter angiography.

The following table shows the recommended screening neuroimaging procedures for patients with acute neurologically isolated third nerve palsy.

1. Patient < 10 years, any isolated IIIrd nerve palsy regardless of the state of the pupil	MRI and MRA, no conventional angiography (low likelihood of aneurysm)
2. Patient > 10 years, IIIrd nerve palsy involving the pupil	MRI and MRA followed by catheter angiography if the results are normal or compatible with aneurysm
3. Pupil-sparing third nerve palsy and patient between 10 to 50 years	MRI followed by MRA if MRI does not disclose a nonaneurysmal cause to the third nerve palsy *
4. Pupil-sparing complete third nerve palsy in patient ≥ 50 years and vasculopathic risk factors present	Blood pressure evaluation, 2-hour postprandial glucose, daily follow-up during the first week, then after 6 weeks *

* Catheter angiography is required if

- Worsening of extraocular muscle or iris sphincter impairment continues beyond 2 weeks
- Iris sphincter impairment progresses to anisocoria > 1 mm, signs and symptoms of subarachnoid HH
- No recovery of function occurs within 3 months
- Signs of aberrant regeneration develop

N.B. 1) Aberrant regeneration usually occurs following recovery from an acute third nerve palsy due to trauma or a compressive lesion, such as an aneurysm. Aberrant regeneration is presumed to be due to miswiring following a break in the axon cylinder within the third nerve with misdirection of sprouting axons. As a consequence, it can not occur after an ischemic mononeuropathy

2) An acute painless areflectic mydriasis occuring without any oculomotor impairment (and hence without diplopia) is not a third nerve palsy and does not require any angiography. The most common cause of this clinical presentation is an acute tonic pupil (=Adie's pupil).

Horner pupil and ocular motor palsy

The sympathetic postganglionic fibers, after being intimately associated to the wall of the internal carotid plexus, join briefly with the abducens nerve (VI) before entering the orbit with the nasociliary nerve, a branch of the ophthalmic division (V1) of the trigeminal nerve. After reaching the nasociliary nerve, the sympathetic fibers reach the iris dilator muscle as the long ciliary nerves.

Therefore, a Horner pupil associated with an ocular motor palsy on the same side raises the suspicion of an expansive processus in the cavernous sinus region.

2. Multiple unilateral or bilateral ocular motor palsies

In these cases, the condition is more susceptible to be a serious one. The PANIC signs are still useful to determine the possible cause. Papilloedema with a bilateral VIth nerve palsy (raised intracranial pressure); dilated pupils (Botulism, Miller-Fisher syndrome); visual fields defects (space occupying lesion along the optic pathways, pituitary apoplexy, cavernous sinus thrombosis); and decreased corneal sensitivity or severe pain in the trigeminal territory (trigeminal nerve involvement by a space occupying lesion, Tolosa-Hunt syndrome).

Let us precise however that a double isolated non traumatic IVth nerve palsy is generally of tumoral origin, and that, last but not least, another potentially life threatening illness leads also to ocular motor palsies without any PANIC signs : Myasthenia. Any fluctuating diplopia, particularly if associated with variable ptosis, without pain and without any pupillary involvement compels a tensilon or prostigmine test.

Retinal diplopia

Macular wrinkle and epiretinal membranes can induce a true binocular diplopia but the images seen by each eye are slightly dissimilar. In spite of good visual acuity, there is a distortion or illusory image movement when monocularly fixating with the involved eye. The clues to retinal diplopia are the following :

- Diplopia worse in daylight or normal room illumination, symptoms improve with room lights extinguished
- Mismatched objective and subjective findings (vertical diplopia in the absence of a vertical strabismus, vertical diplopia of a larger magnitude than the misalignment, full ocular rotations)
- Good stereo-acuity, but poor sensory fusion
- Vertical fusional amplitudes may be normal
- Unability to achieve stable fusion in free space with prism

Pathophysiologically, the macular traction causes a spreading or bunching of macular retinal elements that induces a shift in foveal visuomotor localization relative to retinal periphery and relative to the fovea of the fellow eye. Under photopic conditions, foveal and peripheral fusion are out of phase but macula has spatial visual superiority while peripheral retina drives motor fusion inducing a vicious circle. The foveal diplopia induces foveal fusion, the foveal fusion induces a peripheral image disparity that induces an activation of the vergence system, the peripheral fusion is then restored, inducing again foveal diplopia (7).

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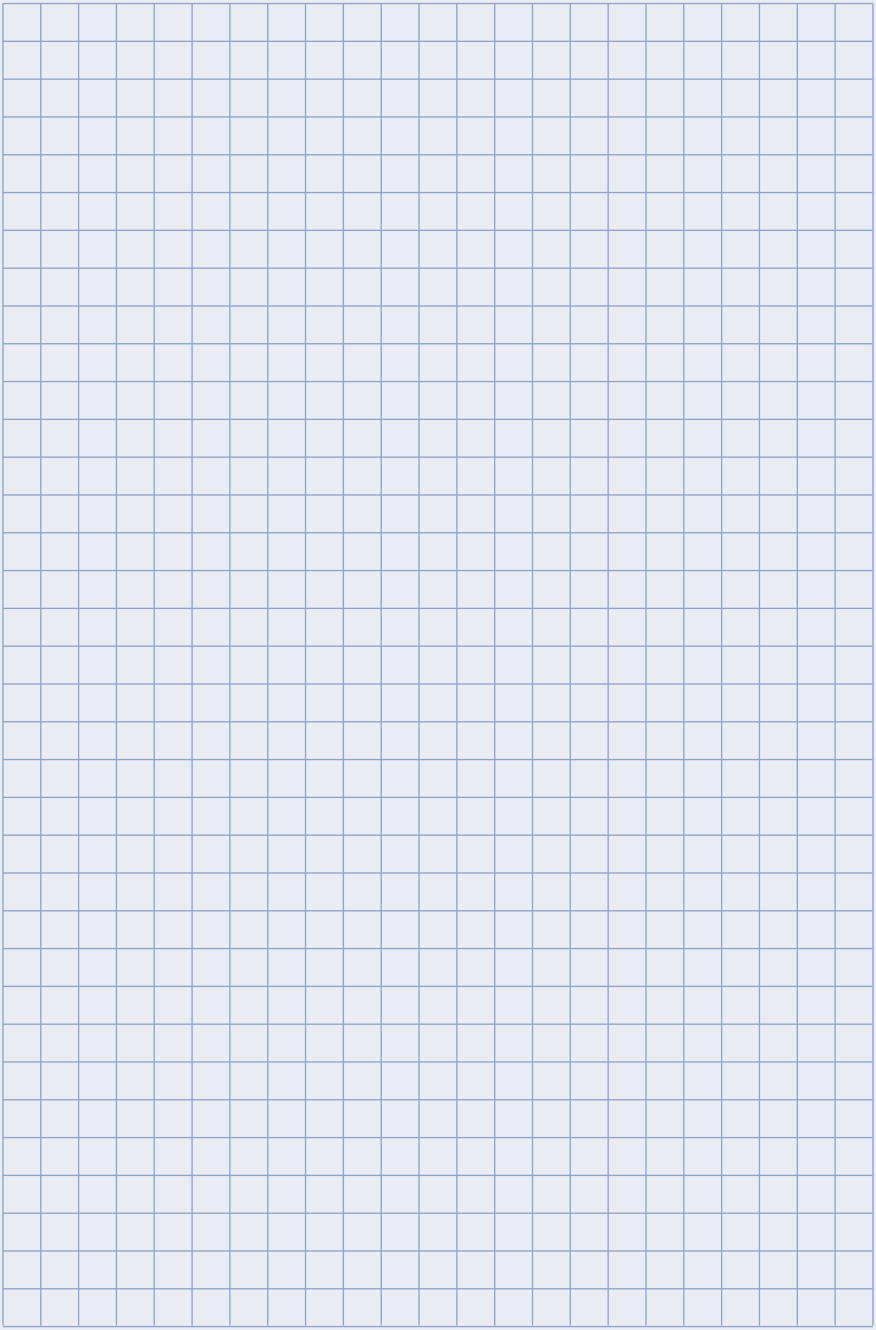


Convergence and Divergence Palsy – Real or Imagined?

| John S Elston, Oxford, United Kingdom |

Paediatrics/Neuro-ophthalmology - Oxford Eye Hospital, John Radcliffe Hospital, UK

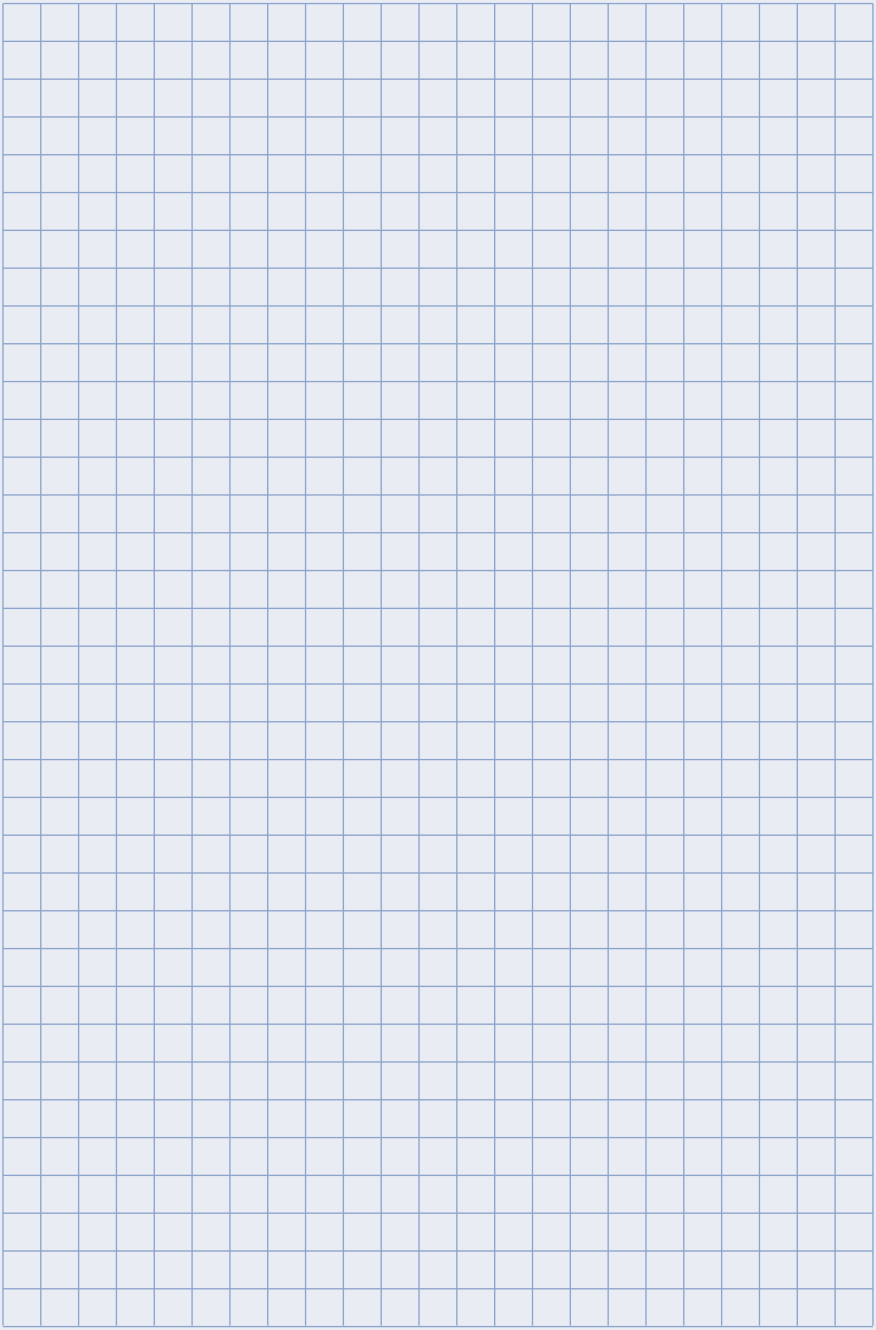
The development of normal binocular single vision (BSV) is dependent on a symmetric visual input from each eye integrated with ocularmotor functions, including accommodation. The vergence system co-ordinates accommodation with afferent and efferent components, allowing dynamic maintenance of BSV at different distances and eccentricities.

The presentation will outline:

1. The relevant neuro-anatomy, including the cortical basis of binocularity and the supra and internuclear motor networks.
2. The development of normal ocular alignment, binocularity, accommodation and vergence in childhood.
3. Disorders of accommodation/convergence – recognition and management.

20

- Convergence Excess Esotropia
- Convergence Insufficiency
- Convergence Spasm
- Convergence/Retraction Nystagmus
- Near Exotropia
- Internuclear Ophthalmoplegia with Preserved Convergence



Diagnosis and management of infantile nystagmus

| Irene Gottlob, Leicester, United Kingdom |

Pathological nystagmus consists of rhythmic involuntary oscillation of the eyes. The types nystagmus are very diverse due to different time of onset, possible association with other diseases and appearance of the eye movements.

The onset of infantile nystagmus forms is usually in the first months of live. They recently have been grouped together in a classification of the NIH as "infantile nystagmus syndromes". Infantile nystagmus can be idiopathic or associated with other ocular diseases or neurological syndromes. Acquired nystagmus occurs later in life and is caused by neurological diseases. It occurs for example in multiple sclerosis, cerebellar diseases, tumors and strokes. Infantile nystagmus and acquired nystagmus differ in that patients with acquired nystagmus typically experience oscillopsia, the perception that the world is in motion. This can be extremely disabling causing patients with acquired nystagmus to have worse visual function than even patients treated in low vision services or people with age-related macular degeneration. Nystagmus leads to deterioration in visual acuity mainly because of deterioration in foveal vision when images move across the retina rapidly. The constant motion can also lead to reduced motion sensitivity. Nystagmus can have a significant psychological and social impact.

Nystagmus can be described according to many characteristics such as amplitude, frequency, intensity (amplitude multiplied by frequency), its plane (horizontal, vertical, torsional or combinations of these), waveform (pendular or jerk), conjugacy between both eyes and foveation (periods where the eyes move at a lower velocity allowing high acuity vision) (Figure 1A). Nystagmus can also change with time (Figure 1B).

Figure 1: Characterisation of Nystagmus: Nystagmus can be described using (A) eye movement intensity (amplitude x frequency), plane of oscillation, waveform, conjugacy between right (R) and left (L) eyes, and duration and position of periods when the velocity of eye movements is slow enough to allow useful foveal vision (foveation). (B) Some of these characteristics can also vary with time, occlusion of one eye, convergence and eccentricity of eye position.

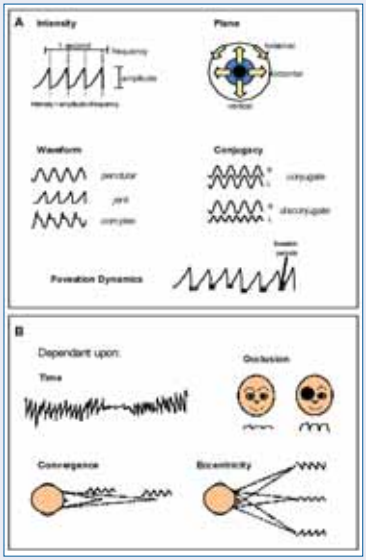


Figure 1: Characterisation of Nystagmus: Nystagmus can be described using (A) eye movement intensity (amplitude x frequency), plane of oscillation, waveform, conjugacy between right (R) and left (L) eyes, and duration and position of periods when the velocity of eye movements is slow enough to allow useful foveal vision (foveation). (B) Some of these characteristics can also vary with time, occlusion of one eye, convergence and eccentricity of eye position.

The prevalence of nystagmus has previously been estimated to be 1 in 1000. Recently we have found a higher prevalence in the "Leicestershire Nystagmus Survey" of 2.4 per 1000. We investigated the type of nystagmus in 357 patients who presented in clinics in Leicestershire. We found that approximately 70% had infantile nystagmus forms and 30% acquired nystagmus. Infantile nystagmus was further divided into idiopathic infantile nystagmus, albinism, nystagmus secondary to retinal disease and low vision, manifest latent nystagmus and other congenital nystagmus forms (i.e. spasmus nutans, nystagmus due to neurological syndromes such as Down syndrome, Joubert syndrome, Pelizaeus-Merzbacher syndrome, foetal alcohol syndrome and Cockayne's syndrome) (Figure 1).

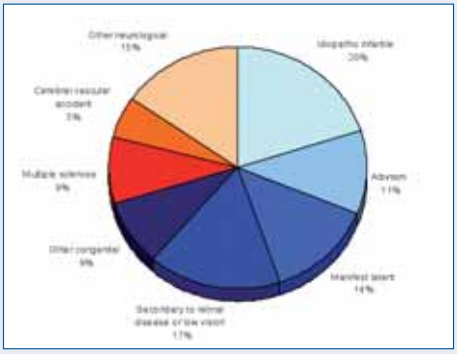


Figure 1:Breakdown of causes of nystagmus (taken from 357 patients attending clinics in Leicester Royal Infirmary, UK between February 2002 and October 2007). Infantile nystagmus types are shown in blue colours and acquired types in red colours.

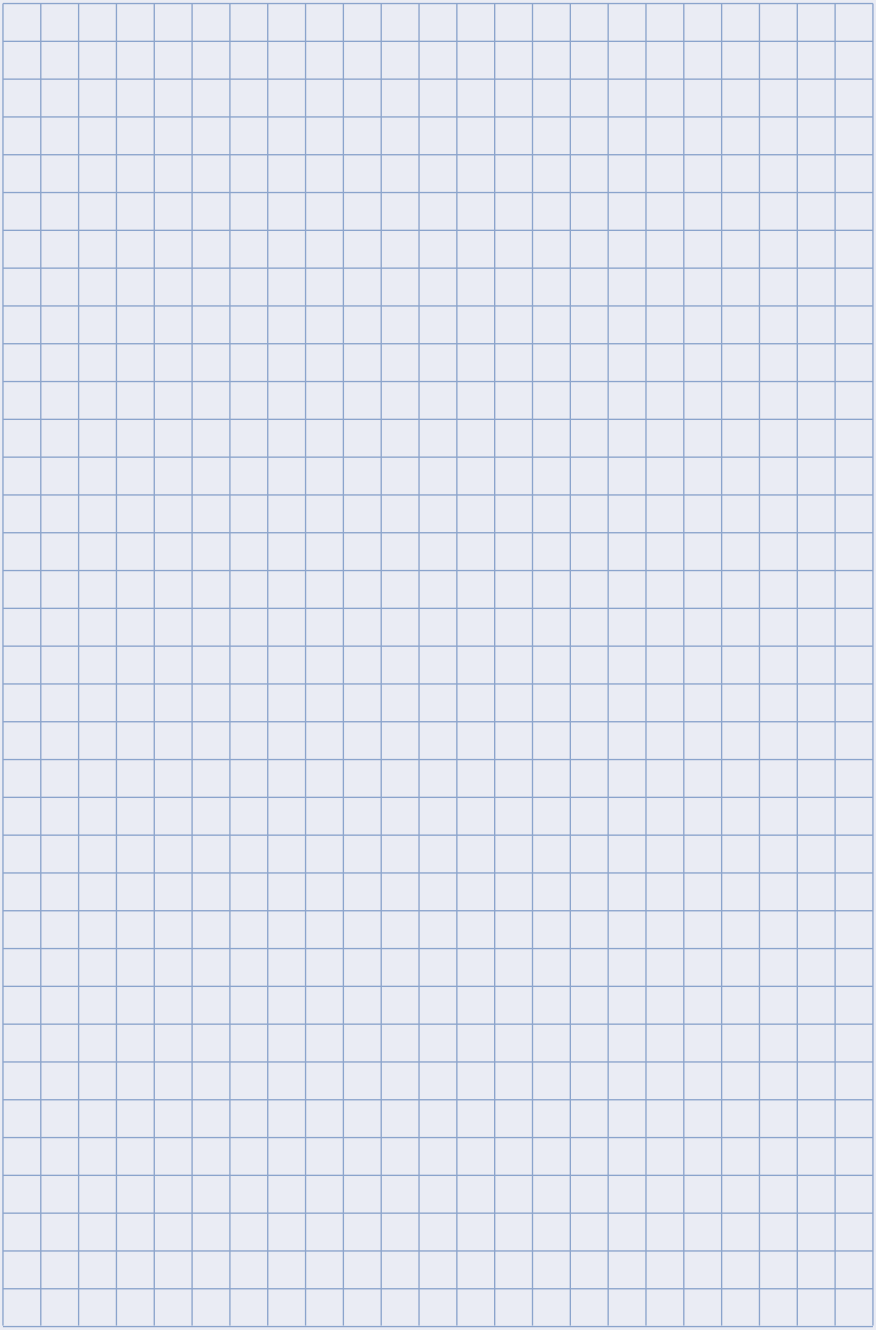
Examination of nystagmus patients

To classify nystagmus it is essential to establish whether the presentation corresponds to the typical pattern of idiopathic nystagmus or any other associated problem can be detected. A thorough history including family history, possible consanguinity of parents, any possible teratogenic events during pregnancy or perinatal problems, the time of onset of nystagmus, changes of nystagmus over time, visual development and oscillopsia need to be determined. Usually parents of patients with idiopathic nystagmus can see a clear improvement of the visual development of their children some months after the onset of nystagmus. Although oscillopsia often indicates acquired nystagmus some patients with idiopathic nystagmus have mild oscillopsia especially if they are looking in directions of gaze away from their null point. It is important to ask the patients or their parents about light sensitivity and night vision, abnormalities of which would point to retinal diseases. Light sensitivity is very pronounced in achromatopsia and sometimes present in albinism but usually milder. Problems of vision in the dark would hint that the patients have congenital stationary night blindness or other diseases affecting rods.

Examination of patients should include visual acuity, thorough slit lamp examination and fundus examination. Since albinism is commonly associated with nystagmus and patients are often not aware of having albinism it is very important to look for iris transillumination to identify albinism. This is best performed in a completely dark room with the beam of the slit lamp directed straight at the fundus to visualize the red reflex. Iris transillumination is usually seen to various degrees and since it can be very subtle its examination needs to be very thorough. Examination of parents or siblings can be helpful because it sometimes shows iris transillumination although they do not have nystagmus. Optical coherence tomography has been shown to detect foveal hypoplasia in albinism. Electrophysiology following the standards of the International Society of Electrophysiology of Vision (ISCEV) should be performed in all patients with nystagmus including visual evoked potential (VEPs) and electroretinograms (ERGs). Asymmetries in VEPs are a strong indicator for albinism. Abnormal ERGs are seen in retinal diseases. If the patients reports problems with night vision a dark adaptometry can be performed to confirm this and see to what amount they are affected.

Idiopathic infantile nystagmus (IIN) can be sporadic or inherited. The most common mode of inheritance is due to X-linked mutations. Recently, we localised IIN associated with a frequently occurring autosomal X-linked recessive inheritance to various mutations on a single gene called FRMD7 (Xq26.2) (NYS1). Although the exact function of this gene is still unknown it is expressed in the retina, cerebellum and lateral ventricles during development. The FRMD7 protein shows a close homology to the amino acid sequence of FARP1 and FARP2 proteins. These appear to modulate the length and degree of neurite outgrowth in the developing rat cortex.

Several drugs such as baclofen, gabapentin, memantine, cannabis, and sodium or potassium channel blockers have been used to reduce acquired nystagmus. Recently we have shown in a case series and a randomised placebo controlled study that gabapentin and memantine can reduce nystagmus intensity and improve visual acuity in congenital nystagmus forms.



Louis émile JAVAL (1839-1907), yesterday and today. Statics and dynamics of the ocular globe — An historical vignette —

| André Roth, Geneva, Switzerland |

"Louis émile Javal (1839-1907) ….must always be regarded as the father of modern ideas on the nature and treatment of squint on rational lines. By recognizing the central anomaly in the development of squint and introducing the partnership of functional education and operative aid in its treatment, he revolutionized and set on a firm basis our knowledge of this subject." [Duke-Elder S., System of Ophthalmology, vol. VI (1973), p. 421].

Javal was initially a coal-mining engineer. The squint of his father and of his sister "led him to study medicine in Paris" (op. cit.). He developed his activity as the first director of the Laboratory of Ophthalmology in the department of Physiology at the School of Higher Studies in Paris. He published the "Manuel du Strabisme" in 1896 at 57 years of age. Five years later he "became completely blind from glaucoma" (op. cit.). All strabismologists of the XXth and XXIst centuries are, consciously or not, the heirs and the continuators of this great predecessor.

The name of Javal is well known to every ophthalmologist because of his clinical keratometer. He translated Helmholtz's "Handbuch der physiologischen Optik" into French. His work greatly surpasses, however, the refraction of the eye alone. In reading his "Manuel du Strabisme" we are constantly impressed by his clear-sighted thinking.

Taking into consideration, among many others, the motor aspect of concomitant strabismus, one of the methods used by Javal to examine the deviation of the visual axis was already, more than hundred years ago, a translucent occluder. He observed that the deviation in concomitant strabismus may vary according to the distance of fixation, the fixing eye, or the direction of gaze. In other words, that incomitance may be associated with concomitant strabismus. It was his opinion that a fixed part of the deviation should be differentiated from a variable one, and that the former requires surgical correction while the latter may, in most cases, be treated by optical means. He also noted that a convergent deviation may disappear under general anaesthesia.

The need to define a reference angle to calculate the amount of surgery lead, through Bielschowsky, to the concept of a basic angle (Basiswinkel), i.e. that measured with prisms and alternate cover test. The fact that the deviation of a concomitant squint is variable, and that the "fixed" and "variable" parts should be treated differently,

received new impact, especially through the work of Cüppers. Different terms were used to denote these "parts", in particular "static" and "dynamic" angle. Combining the two notions of variability and basic angle, C. Speeg-Schatz and I (Eye Muscle Surgery, 1995) proposed, along the lines of Javal, the terms of minimum and maximum angle and angle variability, which are purely descriptive. Thus, as shown in Figs. 1 and 2, the horizontal angle is, at any moment, the sum of the basic angle plus or minus the variability factors:

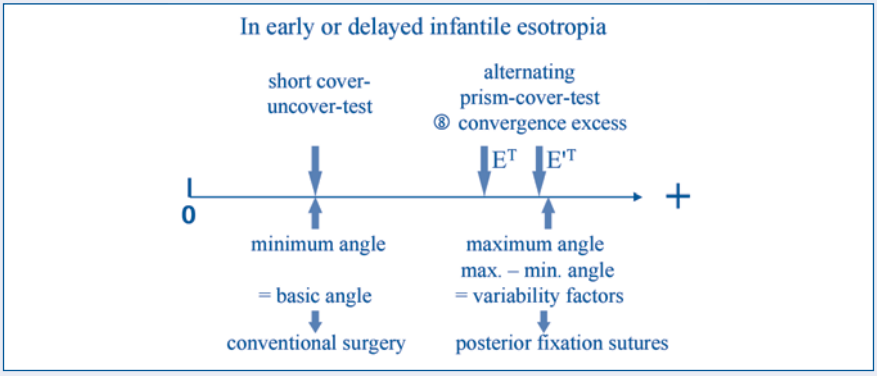


Fig. 1 : In esotropia the basic angle corresponds to the minimal angle, and the difference between the maximal and the minimal angle to convergence excess or angle variability.

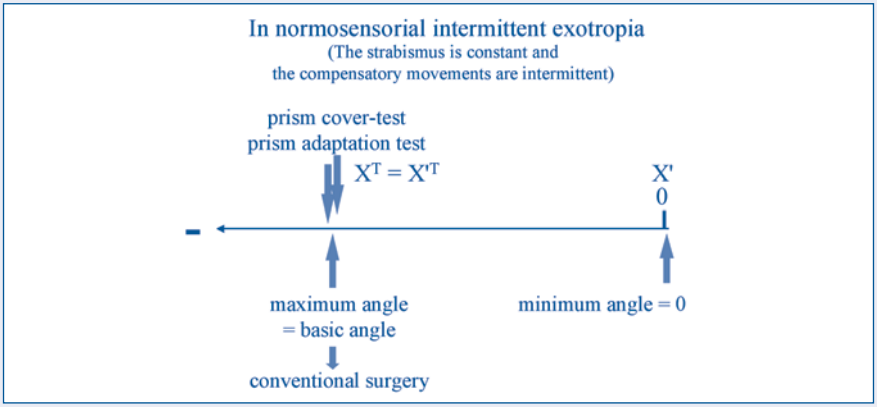


Fig. 2 : In intermittent normosensorial exotropia the basic angle corresponds to the maximal angle, while the difference between the maximal and the minimal angle is due to compensatory movements as according to Bielschowsky, or to angle variability (the minimum angle equals 0 in the case of intermittent exotropia).

According to the type of concomitant strabismus the basic angle corresponds either to the minimum or to the maximum angle.

This example shows the real topicality of Javal's heredity.

The management of congenital and acquired fourth nerve palsies

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Diagnostic considerations and tips:

Before talking about proper management, a proper diagnosis has to be established!

Use the three-step test according to Parks[1], based on Bielschowsky head tilt phenomenon[2]:

First step:	Determine which eye is hypertropic (R/L or L/R, +VD or –VD)?
Second step:	Is the vertical deviation larger in right gaze or in left gaze?
Third step:	Is the vertical deviation larger in right tilt or in left tilt?

While this test is very useful in nailing down the diagnosis of a fourth nerve palsy, patients unfortunately do not enter your office posing the question: "Doctor, which one of my eight cyclovertical muscles does not work?" It is therefore mandatory to consider other causes of vertical strabismus when interpreting the result of Parks' three step test[3]. In a busy clinic, a single diagram may be used to analyze cyclovertical muscle palsies[4]. The **right eye** of the examiner is projected onto a plane of paper, with muscles shown in their respective fields of action:

Inferior Oblique	Superior Rectus
Superior Oblique	Inferior Rectus

Three lines are then drawn according to the results of the three step test: The first line represents the first step, the second line represents the second step and the third line represents the third step.

- In a case of a right hypertropia a horizontal line is drawn to indicate involvement of the two depressors: SO and IR

- If right hypertropia increases in left gaze, a vertical line is drawn on the left side, going through IO and SO
- If right hypertropia increases in tilt to right, a diagonal line is drawn, going through the SO and SR.

As a result, all three lines intersect in the field of SO, thus the **right superior oblique muscle** is paretic. If no lines intersect in one square then the paretic muscle is the respective muscle in the **left** eye.

Anatomic considerations of the trochlear nerve[5]:

- Cranial nerve with the longest intracranial course (75 mm), thin and vulnerable
- The only cranial nerve exiting dorsally from the brainstem, at the level of the inferior colliculi
- The short fascicles cross in the floor of the fourth ventricle, thus innervating the contralateral superior oblique muscle

Congenital trochlear nerve palsy ("decompensated Strabismus sursoadductorius"):

- Very common
- May present in late adulthood! Perform the F.A.T. scan before the C.A.T. scan!
- Typical features are: Large vertical fusional ability, extensive overaction of the ipsilateral inferior oblique muscle with vertical deviation at least as large in adducted upgaze as in adducted downgaze
- Management: Weakening of the ipsilateral Inferior Oblique is usually the first and only step. In extreme cases a combination with weakening of the contralateral inferior rectus may be advisable. Avoid overcorrections: Patients may be able to fuse a large vertical deviation preoperatively, but not even a small vertical deviation in the opposite direction postoperatively

Acquired trochlear nerve palsy:

- 10-20-30-40 rule (Kline & Bajandas): 10% compressive, 20% ischemic, 30% undetermined or miscellaneous, 40% trauma
- Is the paresis isolated? Associated neurological signs indicate site of lesion
- Isolated acquired trochlear nerve palsy induces torsional vertical diplopia worst on down gaze, while motility is almost normal
- Stable quantitative measurements of deviation in all directions of gaze are mandatory before surgery is performed
- Always look for bilateral involvement (the excyclotorsion is very large, vertical deviation may be small, pronounced V-pattern, switching from R/L to L/R with Bielschowsky head tilt test and with side gaze). In bilateral palsy, aim surgical approach for both palsies, in asymmetrical involvement adjust the amount of surgery accordingly
- In traumatic cases, wait one year before surgery (includes surgical trauma after neurosurgical interventions)

- Surgical management requires strengthening of the paretic superior oblique muscle, with or without weakening of the ipsilateral inferior oblique

General considerations:

- "Many roads lead to Rome", every strabismus expert develops his or her patterns of surgical approach over the years...[6-11]
- For those interested in research dealing with consequences of trochlear nerve palsy on the oculomotor plant and ways to examine them, see selected references[12-14]

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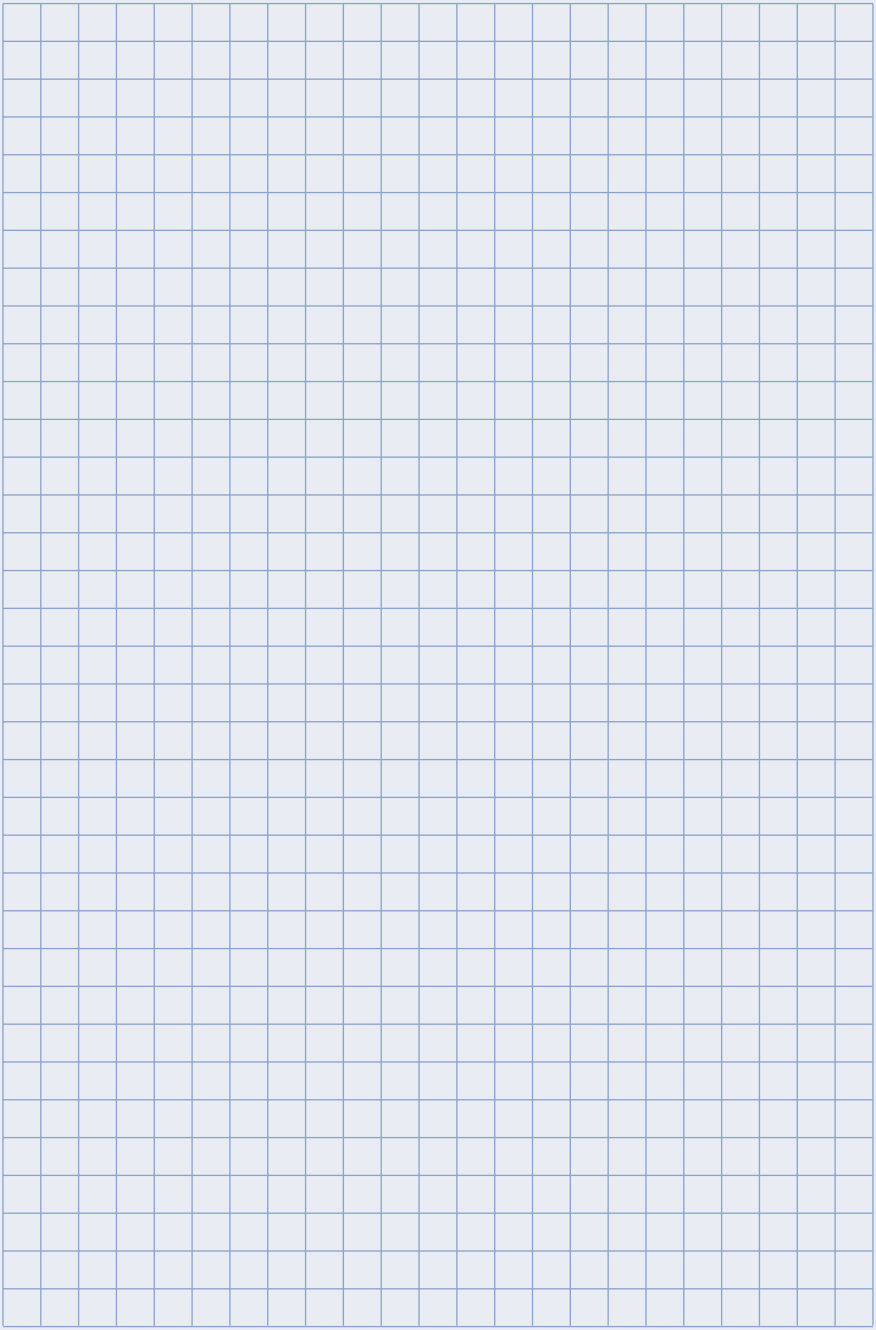

Timely management of infantile strabismus

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Infantile esotropia has been defined as an esotropia with an onset before the age of 6 months, with a large angle of strabismus, no or mild amblyopia, small to moderate hyperopia, latent nystagmus, dissociated vertical deviation, limitation of abduction and absent or reduced binocular vision, in the absence of nervous system disorders (Costenbader, 1961; von Noorden, 1988). Infantile esotropia affects 0.2 – 0.35 % of the population (Mohney et al., 1998). A larger prevalence was found in earlier studies, but in a recent population-based incidence study (Greenberg et al., 2007) a strict distinction was made between esotropia with and without an abnormal central nervous system, and in that study a conspicuously low prevalence of pure infantile esotropia was found. Minimal brain damage can easily result from prematurity, low birth weight and low Apgar scores, and these are significant risk factors for infantile esotropia (Mohney et al., 1998).

Strabismus surgery has been the principal means of treatment. The optimal age for surgery for infantile esotropia is debated. Proponents of early surgery believe that further loss of binocular vision can be prevented by early surgery, a minority believes that binocular vision can be restored by early surgery.

In the past years, we are becoming increasingly aware that infantile esotropia is a collection of disorders with different causes: If the strabismus is caused by a pure motor disorder like a congenital palsy, it is similar to surgically-induced strabismus in macaque monkeys (Wong et al., 2003), and early surgery works. If it is caused by a brain disorder, early surgery is of no use (Charles & Moore, 1992). On can differentiate between the Chavasse (1939) type of infantile strabismus: "most infants with congenital squint are capable of developing fusion if the deviation is fully corrected before the age of two years" and the Worth (1903) type of infantile strabismus: "the cause of strabismus is a retarded, insufficient or absent development of the ability to fuse the images of both eyes".

There has been no shortage of clinical studies advocating early surgery (Ing et al., 1966; Ing, 1995; Wright et al., 1994). None of these studies had a control group with late surgery, however, and it seems possible that the strabismus could have resolved spontaneously in some of the cases. Spontaneous resolution of infantile strabismus or reduction to a small-angle microstrabismus does occur (Clarke & Noel, 1982; Pediatric Eye Disease Investigator Group study, 2002). The difficulty of establishing the diagnosis of strabismus in early life has been emphasized by Horwood & Williams

(2001): Frequent squinting in the neonatal period trebled the chances of developing a significant esodeviation or refractive error, but the incidence of the abnormality still did not exceed 9%.

The first prospective study of surgery for infantile esotropia (Birch et al., 1990) reported 35% gross random dot stereopsis (disparity equal or better than 400") among 84 children first operated at 8.5 months of age, on average. In a retrospective study (Birch et al., 1995), children were divided into three groups according to the age at which alignment within 8 prism diopters had been reached. In the group that reached alignment at 5-8 months of age, stereopsis better than 200" was reached by 18.8%, at 9-12 months by 26.4% and at 13-16 months by none. Children who did not reach alignment within 8 prism diopters had been excluded, however. For comparison, in the Early vs Late Infantile Strabismus Surgery Study, that compared early with late surgery in 58 university clinics in Europe, 35% of the 405 children in both the early-surgery and the late-surgery groups who completed the study were not aligned within 0 - 10 degrees at age six (Simonsz et al., 2005).

In that European study, 231 children had been recruited at the age of 11.1 SD 3.7 months for early surgery and 301 at the age of 10.9 SD 3.7 months for late surgery. At age six, 13.5 % of the early vs. 3.9 % of the late group had gross stereopsis (Titmus Housefly). This clear advantage for early surgery was not found for fine stereopsis beyond Titmus Housfly.

The number of operations was 1.18 SD 0.67 in the early-operated children and 0.99 SD 0.64 in the late-operated children.

Children scheduled for early surgery had first been operated at 20 SD 8.4 months, but 8.2 % had not been operated at age six. Likewise, children scheduled for late surgery had been operated at 49.1 SD 12.7 months, but 20.1 % had not been operated at age six. In a majority of these, a spontaneous reduction of the esotropia to microstrabismus had occurred. The question is whether such resolution of strabismus can be predicted and, hence, unnecessary operations can be avoided.

In a random-effects-model study (Simonsz & Eijkemans 2007), baseline characteristics of these children at 11 SD 3.7 months (angle, refraction, reported time of onset, degree of amblyopia and limitation of abduction) were related to whether they had been operated at age six or not. It was found that the chance of a spontaneous reduction of the esotropia to microstrabismus was large when an angle of strabismus less than 15° is found repeatedly at the age of 1 or 2. The fact that spontaneous reduction of esotropia occurs so frequently even when recruiting at 11 SD 3.7 months puts all studies without a control group, especially studies that recruit at a younger age, under pressure.

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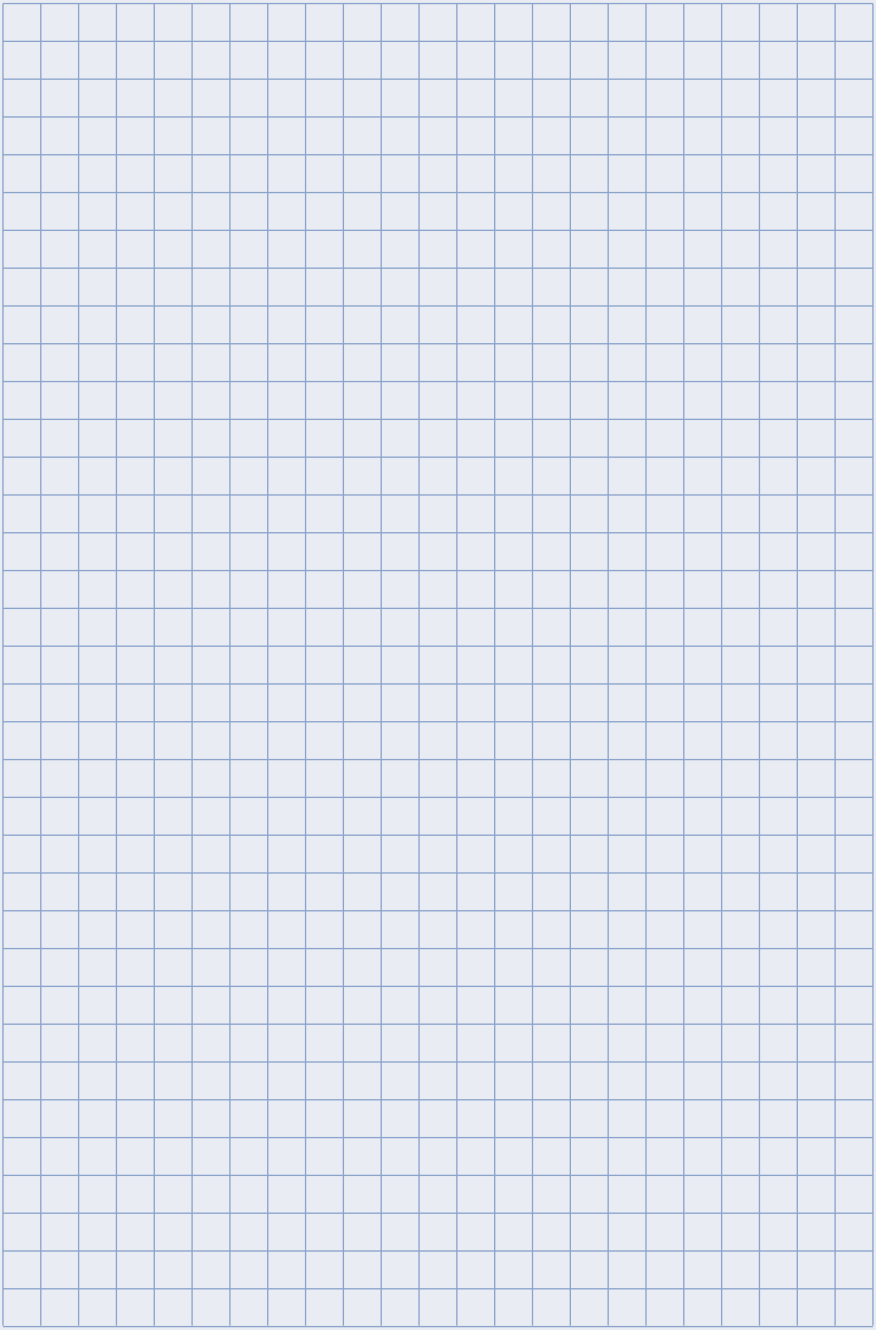

Does infantile esotropia arise from a dissociated deviation?

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Tonus refers to the effects of baseline innervation on musculature in the awake, alert state.[1] Since the normal anatomical resting position of the eyes is one of exodeviation, extraocular muscle tonus plays a vital physiologic role in establishing ocular alignment. Under normal conditions, binocular esotonus is superimposed on the baseline anatomical position of rest to maintain approximate ocular alignment, save for a minimal exophoria that is easily overcome by active convergence. When binocular visual input is preempted early in life, monocular fixation may give rise to a larger dissociated esotonus that gradually drives the 2 eyes into a "convergent" position, resulting in infantile esotropia.[2]

In our companion article,[2] we examine clinical and evolutionary evidence for the proposition that dissociated horizontal deviation is a clinical expression of dissociated esotonus. When superimposed on a baseline orthoposition, dissociated esotonus manifests as an intermittent esotropia that is asymmetrical or unilateral.[3] More commonly, dissociated esotonus is superimposed on a baseline exodeviation, producing an intermittent exodeviation that is asymmetrical, unilateral, or associated with a paradoxical esodeviation when the nonpreferred eye is used for fixation.[4-11]

Although the term dissociated has historically been restricted to the description of vergence eye movements,[12-14] in a more general sense it describes any ocular movements that result from a change in the relative balance of visual input from the 2 eyes.[15] These movements arise almost exclusively in the setting of infantile strabismus,[16] which has a strong predilection for esotropia over exotropia. It is held that infantile esotropia disrupts binocular control mechanisms and thereby engenders these dissociated eye movements.[16] This time-honored notion assumes a distinct and unrelated pathogenesis for infantile esotropia.

The purpose of this analysis is to raise an unexamined question regarding the pathogenesis of infantile esotropia. Since dissociated deviations almost uniquely accompany infantile strabismus, could infantile esotropia arise from a dissociated deviation? Our findings raise the possibility that dissociated esotonus could be the proximate cause of infantile esotropia.

Contrary to the stereotype of "congenital" esotropia as a large-angle deviation that is present at birth, most cases are acquired (ie, "infantile" in origin).[17,18] Furthermore, the eyes do not simply snap in to their final esotropic position. Before 12 weeks of age, nascent infantile esotropia is an intermittent, variable esodeviation that gradually becomes constant after building in intensity to a large fixed angle of horizontal mis-

alignment.[17,18] Ing[19] has noted that 50% of patients with infantile esotropia show an increase in the measured angle between the time of first examination and the date of surgery. Clearly, unequal visual input in infancy must produce a gradual and progressive increase in the angle of esotropia. That this esodeviation appears during the early period when stereopsis is developing, but before macular anatomy has matured sufficiently to provide high-resolution acuity,[20] suggests that it is actively driven primarily by an imbalance in peripheral visual input.

In a recent hypothesis, Guyton[21] has invoked vergence adaptation and muscle length adaptation to explain how a small innervational bias (such as the convergence produced by increased accommodative effort in the presbyope) can build slowly over time into a large constant deviation. *Vergence adaptation* refers to the tonus levels that normally operate to maintain a baseline ocular alignment and thereby minimize retinal image disparity. According to Guyton, vergence adaptation can allow primitive ocular motor biases to gradually amplify and create strabismic deviations under pathological conditions.[21] *Muscle length adaptation* refers to the change in extraocular muscle length due to gain or loss of sarcomeres. Muscle length adaption is driven in part by the physiologic effects of vergence adaptation.

Our results suggest that dissociated esotonus could provide the sensorimotor substrate for vergence adaptation when binocular cortical control mechanisms fail to take hold. The finding of a positive Bielschowsky phenomenon in dissociated horizontal deviation[5,8] shows that peripheral luminance reflexes are retained, as in dissociated vertical divergence.[22] In this setting, both peripheral (luminance and optokinetic) and central (fixational) reflexes augment dissociated esotonus and lead over time to infantile esotropia. Subcortical visual reflexes would provide the default system through which dissociated esotonus operates to reestablish the baseline horizontal eye position. This process can ultimately lead to loss of sarcomeres and secondary shortening of the medial rectus muscles. The fact that the eyes straighten to an almost normal baseline position under general anesthesia,[23-27] however, suggests that esotonus is the driving force for infantile esotropia and that mechanical effects play a secondary role in its pathogenesis. It is therefore possible that the stable large-angle esodeviation that we recognize as infantile esotropia simply represents the final stage of dissociated esotonus. As with many other forms of ocular misalignment, the constant esodeviation that develops over time may eventually obscure the pathogenesis.

Early monocular visual loss is known to generate esotonus and reproduce the same constellation of dissociated eye movements that accompany infantile esotropia.[25] Patients with unilateral congenital cataract often develop large-angle esotropia, latent nystagmus, dissociated vertical divergence, and a head turn to fixate in adduction with the preferred eye.[25] By contrast, early infantile esotropia is often characterized by similar visual acuity in the 2 eyes, with alternating suppression of the nonfixating eye. So perhaps dissociated horizontal deviation is not an epiphenomenon of infantile esotropia but a "footprint in the snow" of the dissociated esotonus that is responsible for its inception.

There remains the unfortunate tendency in the strabismus literature to conflate esotonus of the eyes as a baseline innervation with convergence of the eyes as an active function. Jampolsky[28,29] has emphasized the mechanistic importance of distinguishing between convergence as an active binocular function and esotonus as a baseline innervational state that is centrally driven by unequal visual input to the 2 eyes. The importance of this distinction lies in understanding that convergence implies a deviation from baseline under normal conditions of sensory input, whereas tonus implies a return to baseline under altered conditions of sensory input. The distinction between convergence (the effect) and monocular esotonus (the cause) lies at the heart of understanding infantile esotropia. Horwood and colleagues have recently shown that normal infants display fleeting large-angle convergence eye movements during the

first 2 months of life and that these spontaneous convergence movements are ultimately predictive of normal binocular alignment.[30] By contrast, infantile esotropia tends to increase over the period when this excessive convergence is disappearing in normal infants.[31] This time course challenges the dubious assumption that infantile esotropia arises from excessive convergence output. The evidence for dissociated esotonus suggests that we retain a primitive tonus system, independent of convergence output, that can operate under conditions of unequal visual input to reset eye position to a new baseline "convergent" position. This mechanism would explain why infantile esotropia is so much more common than infantile exotropia.

If the dissociated esotonus that manifests as dissociated horizontal deviation gives rise to infantile esotropia, why does dissociated horizontal deviation manifest as an intermittent exotropia? Although we use the term intermittent exotropia diagnostically, it is ultimately a descriptive term comprising a variety of conditions with different diagnostic implications. The intermittent exodeviation caused by dissociated horizontal deviation simply constitutes one distinct form of intermittent exotropia with its own unique pathophysiology.

Many clinicians apply the hybrid term intermittent exotropia/ dissociated horizontal deviation, implying that the 2 conditions often coexist, and perhaps acknowledging some diagnostic ambiguity.[5-10] So what are the innervational substrates for these distinct but overlapping categories of intermittent exotropia? Although Burian[32] believed intermittent exotropia to be caused by an active divergence mechanism, independent studies have found that these patients are approximately 30 prism diopters more exotropic when deeply anesthetized than in the awake state,[26,27] suggesting that intermittent exotropia actually results from intermittent fusional control of a large baseline exodeviation.[33,34]

When intermittent exotropia is associated with dissociated horizontal deviation, fixation with either eye superimposes dissociated esotonus on the baseline exodeviation to produce a variable intermittent exodeviation.[2] The distinction between nondissociated intermittent exotropia and dissociated horizontal deviation lies primarily in the relative activation of binocular fusion (which behaves as an all-or-nothing phe-

nomenon in most forms of intermittent exotropia) vs dissociated esotonus (which functions as an open-loop process without reference to ultimate binocular alignment in dissociated horizontal deviation). Because fixation with the nonpreferred eye exerts greater esotonus,[2] the baseline exodeviation can be unilateral, asymmetrical, or associated with a paradoxical esotropia when the nonpreferred eye is used for fixation.

Infantile esotropia and intermittent exotropia are universally regarded as distinct forms of strabismus that occupy opposite points on a clinical spectrum. In contrast to infantile esotropia, intermittent exotropia usually has a later onset and is rarely associated with prominent dissociated eye movements (although small degrees of dissociated vertical divergence can be detected).[35] At first glance, it is difficult to imagine how these diametrical forms of horizontal misalignment are not mutually exclusive.

The beauty of dissociated horizontal deviation is that it allows us to recast horizontal strabismus as the relative balance of mechanical and innervational forces, without regard to final eye position. Dissociated esotonus can still be expressed from an exodeviated position, because it is generated by unbalanced binocular input that exerts its influence on any baseline deviation. Consequently, intermittent exotropia is a common clinical manifestation of dissociated esotonus. Mechanistically, there is nothing sacred about orthotropia as a clinical demarcation and nothing signatory about the direction of horizontal misalignment.

In this light, dissociated horizontal deviation is transformed from a clinical curiosity to a fundamental piece of the puzzle for understanding horizontal strabismus. The exotropic form of dissociated horizontal deviation uniquely embodies the coexistence of the mechanical exodeviating forces that give rise to intermittent exotropia and the dissociated esotonus that may give rise to infantile esotropia. For example, infantile exotropia is often accompanied by dissociated eye movements such as latent nystagmus and dissociated vertical divergence.[36,37] Some infants exhibit an intermittent form of exotropia with other dissociated eye movements,[38] suggesting a component of dissociated horizontal deviation. Patients with primary dissociated horizontal deviation also display an intermittent exodeviation of one or both eyes with other signs of dissociation.[6]

All of these conditions share a common pathophysiology wherein dissociated esotonus is superimposed on a baseline exodeviation to produce an intermittent exodeviation that varies in size depending on which eye is used for fixation. In patients without binocular fusion, dissociated esotonus can cause a constant exodeviation to appear intermittent. In patients who retain binocular fusion, it can produce a combined clinical picture of intermittent exotropia (with intermittent fusion), an asymmetrical exodeviation of the 2 eyes, or an exodeviation of the nonpreferred eye with a paradoxical esodeviation of the preferred eye. In classifying these disorders pathogenetically, it is critically important to distinguish sensorimotor factors from the different forms of ocular misalignment that they ultimately produce. Dissociated horizontal deviation shows us how it is only the resultant horizontal deviations, and not the underlying conditions, that are diametrically opposed.

In conclusion, our findings raise the intriguing possibility that dissociated esotonus, an unrecognized dissociated eye movement, may be the cause, rather than the effect, of infantile esotropia. If this proves to be the case, then the prevailing concept of infantile esotropia as the proximate cause of dissociated deviations may need to be revised.

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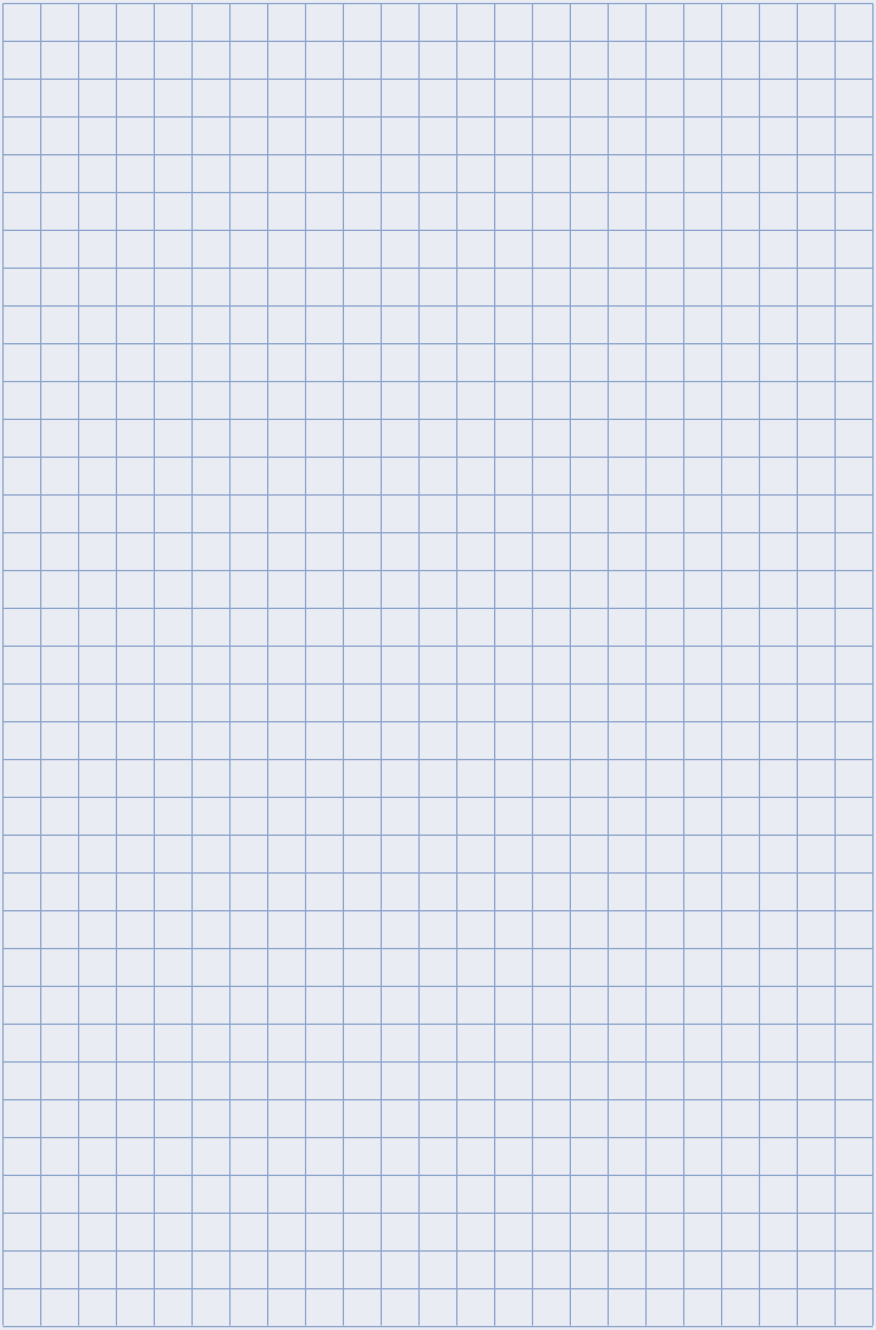

Congenital dysinnervation syndromes: new understanding of clinical manifestations

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The congenital ophthalmoplegic syndromes include a group of disorders with abnormal motility of the eyes and eyelids. Although these disorders were previously referred to in the literature under various terms, including 'congenital fibrosis syndromes', it has been suggested to refer to them as the 'congenital cranial dysinnervation disorders' or CCDDs, because these disorders result from developmental errors in innervation of the ocular and facial muscles [Gutowski et al., 2003].

The aim of this presentation is to give an overview of the spectrum of congenital ophthalmoplegic syndromes. Clinical manifestations and genetic data were collected from the literature and from my own clinical experience.

The differential diagnosis of congenital dysinnervation syndromes includes several different conditions, such as Duane syndrome, Möbius syndrome, congenital fibrosis of extraocular muscles (CFEM), horizontal gaze palsy, and other disorders.

Duane syndrome

Duane syndrome is characterized by a congenital limitation of horizontal ocular motility and some retraction of the eye into the orbit on attempted adduction as a result of aberrant innervation. Duane syndrome is the most common congenital ophthalmoplegic syndrome and is a developmental error in innervation of the lateral rectus muscle. Abducens motor neurons may be reduced or absent, with aberrant innervation of the lateral rectus muscle by the inferior branch of the oculomotor nerve [Hotchkiss et al., 1980; Miller et al., 1982]. The disorder is attributed to a teratogenic disturbance in the second month of pregnancy [Pfaffenbach et al., 1972]. However, in more recent years genetic loci have been defined in a number of cases.

Major clinical characteristics of Duane syndrome:
- congenital limitation of horizontal ocular motility;
- limitation of abduction, with variable limitation of adduction [Duane 1905];
- retraction of the globe on attempted adduction, caused by co-contraction of the extraocular muscles, resulting in narrowing of the palpebral fissures [Duane 1905];
- in cases of unilateral Duane syndrome, the left eye is more often involved than the right eye;

- other associated congenital anomalies may occur [Pfaffenbach et al., 1972];
- lack of diplopia (suppression) in de paretic direction of gaze; binocular single vision if eyes are kept parallel with torticollis.

Types of Duane syndrome

Four types of Duane syndrome have been defined:
- Duane type 1: limited abduction;
- Duane type 2: limited adduction;
- Duane type 3: limited abduction + limited adduction;
- Duane type 4: limited adduction + abduction on attempted adduction (synergistic divergence); [Cruysberg et al., 1989; Cruysberg & Huygen, 1990].

Congenital anomalies associated with Duane syndrome

Duane syndrome may associated with many other congenital anomalies or syndromes:

- Möbius syndrome (congenital palsies of facial and abducens nerves) [Verzijl et al., 2003];
- Goldenhar syndrome (facio-auriculo-vertebral sequence: hemifacial microsomy, epibulbar dermoids, eyelid coloboma, ear anomalies, vertebral anomalies) + Duane type 1/3 [Mansour et al., 1985];
- Klippel-Feil anomaly (fused cervical vertebrae);
- Wildervanck syndrome (Duane syndrome, Klippel-Feil anomaly, deafness);
- 'congenital crocodile tears'-phenomenon (aberrant innervation of lacrimal gland) + Duane type 1 [Ramsay & Taylor, 1980];
- optic nerve hypoplasia + Duane type 1 [Denslow & Sims, 1980];
- congenital panhypopituitarism + bilateral Duane type 3 [Cruysberg et al., 1986].
- Kallmann syndrome (hypogonadotropic hypogonadism + anosmia) + Duane type 3 [Cordonnier et al., 1992];
- congenital arthrogryposis + Duane type 4 [Cruysberg et al., 1989];
- Okihiro syndrome (Duane-radial-ray-syndrome) [Okihiro et al, 1977];
- BOR-syndrome (branchio-oto-renal syndrome);
- Duane + congenital urogenital abnormalities;
- Duane + ocular associations (e.g. congenital glaucoma);
- Duane + congenital cardiac abnormalities.

Möbius syndrome

Möbius syndrome is characterized by the combination of:
- congenital facial weakness;
- congenital ocular abduction deficit;
- frequently accompanied by lingual and/or pharyngeal dysfunction at birth, craniofacial dysmorphisms, and limb malformations. Möbius syndrome is associated with Poland anomaly: absence of pectoral muscle.

Further analysis of ocular motility [Verzijl et al., 2003] showed that the ocular abduction deficit in Möbius syndrome is caused by one of the following:
- conjugated horizontal gaze paresis;
- Duane retraction syndrome;
- (simple) abducens nerve palsy;
- congenital fibrosis of extraocular muscles (CFEOM).

Congenital fibrosis of extraocular muscles

'Congenital fibrosis of extraocular muscles' (CFEOM) is characterized by congenital, non-progressive, restrictive ophthalmoplegia caused by absence of the superior division of cranial nerve III. The patients show vertical ophthalmoplegia with ptosis and torticollis (chin up). In contrast to Duane syndrome and Möbius-syndrome, CFEOM is a genetic disorder, with autosomal dominant or autosomal recessive inheritance:

- CFEOM1 is caused by absence of the superior division of the oculomotor nerve (CN III), characterized by 'infraducted eyes' due to ophthalmoplegia of the superior rectus muscle (torticollis with chin up) and palpebral levator muscle (ptosis), with autosomal dominant inheritance; chromosome 12 (12p11.2-q12) [Engle et al, 1994, 1995, 1997].
- CFEOM2 is characterized by bilateral ptosis, exotropic ophthalmoplegia (strabismus divergens fixus), and autosomal recessive inheritance; chromosome 11 (11q13) [Wang et al, 1998; Nakano et al., 2001].
- CFEOM3 is characterized by a variable phenotype (e.g. unilateral) and autosomal dominant inheritance; chromosome 16 (16q24.2-q24.3) [Doherty et al., 1999].

Other ophthalmoplegic syndromes

Ophthalmoplegic syndromes which are so far not part of the CCDD's include other types of mechanical strabismus (i.e. Brown syndrome, craniosynostosis), after birth trauma, and other disorders.

Brown syndrome

Brown (tendon sheath syndrome) is characterized by a marked limitation of ocular elevation in adduction. The mechanism is supposed to be a mechanical obstruction of the superior oblique muscle tendon [Brown, 1950]. Usually it is a congenital disorder, but the ophthalmoplegia is also seen with a local inflammation of the trochlea [Wang et al., 1984]. Classical Brown syndrome shows:

- mechanical limitation of elevation in adduction;
- normal elevation of the eye in abduction;
- pseudo inferior oblique muscle paresis;
- congenital and stabile presentation;
- bilaterality in 10% of cases.

Crouzon syndrome and Apert syndrome

Limited ocular motility can be caused by abnormal anatomy of the orbits. There is a high prevalence of strabismus in children with congenital craniosynostosis, i.e:
- Plagiocephaly [Robb & Boger, 1983];
- Crouzon syndrome (shallow orbits);
- Apert syndrome (deformity of hands and feet) [Cuttone et al., 1979].

Strabismus is attributed to a partial rotation of the orbit and its contents [Morax, 1984]. In some patients with craniofacial synostosis, absence of extraocular muscles has been reported [Weinstock & Hardesty, 1965; Cuttone et al., 1979; Diamond et al., 1980]. Clinical manifestations of craniosynostosis are:
- shallow orbits with proptosis;
- V-pattern exotropia;
- inferior oblique muscle overactions.

Ophthalmoplegia caused by birth trauma

Birth trauma may cause ophthalmoplegia in the newborn child (de Grauw et al., 1983). Congenital traumatic ophthalmoplegia may be followed by spontaneous recovery or aberrant regeneration.

Congenital oculomotor apraxia (Cogan)

Congenital oculomotor apraxia is characterized by:
- inability to generate horizontal saccades;
- compensatory overshoot of the head in lateral gaze;
- intact vertical saccades;
- intact smooth pursuit of the eyes;
- abnormal brain (MRI);
- more in men, sometimes familial.

Conclusions

- Well known congenital ophthalmoplegic syndromes, including Duane syndrome, Möbius syndrome, CFEOM, are considered to be developmental errors in innervation.
- Nowadays, these congenital ophthalmoplegic syndromes are included in the so called 'congenital cranial dysinnervation disorders' (CCDDs).
- There is overlap in the clinical spectrum of congenital dysinnervation syndromes.
- Duane syndrome is the most common congenital dysinnervation syndrome.
- Congenital dysinnervation syndromes with abnormal motility of the eyes and eyelids are frequently associated with congenital anomalies of the ears and hands.
- Although various genetic loci and genes have been defined, the vast majority of patients with congenital dysinnervation syndromes are isolated cases.

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Diagnosis and management of restrictive myopathies

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Restrictive myopathies are caused by structural anomalies of the extra-ocular muscles or adjacent tissues.

The differential diagnosis is challenging and should include congenital as well as acquired disorders.

Between the congenital pathology we should considered: Duane syndrome (or retraction syndrome), Brown syndrome, adherence syndrome, Chronic Progressive External Ophthalmoplegia (Mitochondrial dis., Myotonic dystrophy,oculopharyngial dystrophy…)

The acquired disorders resulting in a restrictive myopathy, the most frequent one in adult, is certainly Graves or Thyroid orbitopathy (TO), but the differential diagnosis should also considered traumatic myopathy (blow-out floor orbital fracture, sinus surgery, post retinal detachment or cataract surgery), inflammatory orbital pseudotumor (idiopathic myosistis), infective myositis, orbital tumor or metastasis, carotid cavernous sinus fistula…

As first diagnosis approach a systematic ocular examination including an extensive evaluation of each oculomotor subsystem is mandatory.

1. General features: Look for abnormal head postures (head turn, abnl eye-head coordination, hd tremor)
   Look for abnormalities of eyelids (ptosis, retraction, synkinesia…)
2. Examination of vision: VA, VF, Color V, Stereopsis, and Pupillary reflex..
3. Range of eye movement (duction and version) and alignment of the visual axes (test ocular misalignment, subjective test red glass+/- Maddox rod, Cover-test measure deviation in 9 positions of gaze, Bielschowsky test, Primary and secondary deviation)
4. Evaluated Fixation (in primary position, in eccentric gaze)
5. Saccades (spontaneous, assess quick phase)
6. Smooth pursuit (track a small moving target, OKN drum)
7. Eye-head coordination
8. Vergence
9. Forced ductions (to confirm and assess the degree of restriction myopathy)
10. Forced generation test (to evaluated the paretic component)
11. Inspection of surrounding tissue (inspection for a conjunctival scarring, previous orbital or eye muscle surgery, or bony orbital changes).

Ocular motor signs should be interpreted in the context of the history and full examination (laboratory test, imaging).

Surgical concepts

The most important information needed to plan the surgical intervention is the amount of restriction. This should be performed with forced duction test to determine the amount of limitation in both directions for each muscle involved.

Forced generation test is very helpful to evaluate the paretic component of eye movement defect. Inspection of surrounding tissue is necessary to identify any factors contributing to the ocular rotation defect.

Muscle-weakening procedures are generally necessary to treat restrictive strabismus. These include muscle recession, fadenoperation, myectomy, myotomy, and tenotomy. The most successful surgical strategy is one that maximally improves the motility defect while minimally inducing new strabismus in other gaze positions. This usually requires surgery in multiple muscles involving both eyes. In some circumstance, it is necessary to create a matching limitation of the yoke muscle in the fellow eye, which will produce a conjugate gaze paresis.

Many motility disturbances that are classified as restrictive are really a combination of restriction and paresis. Such situation is encountered in Thyroid orbitopathy, blowout fractures, or post cataract strabismus. Then, the surgical approach should be adapted: if the restriction should be relieved, some additional procedure should be performed to weaken the yoke muscle on the other eye, to avoid diplopia in other gaze positions.

We will discuss the most frequent acquired restrictive disorders in adult :

- **Thyroid Orbitopathy** (TO) is a autoimmune disorder related in the majority of patient with Graves' disease. The onset of diplopia usually begins slowly, in relation with the inflammation of the extraocular muscles. The most frequently affected muscle is the inferior rectus, followed by the medial rectus. As the process continues, all the extraocular muscles may become infiltrated, resulting in bizarre motility patterns. The course of the extraocular muscle involvement varies among patients. Some have a motility disturbance that lasts from 3 to 12 month and then slowly resolves. But, if the disorder progresses to the fibrotic stage, persistent diplopia often results.

Surgical intervention should be considered if the TO is inactive and the motility measurements have been stable for at least 4 to 6 months. If orbital surgery is necessary, it should be performed before strabismus surgery.

Patients should be informed that the goal of the surgery is to minimize diplopia in the primary and reading positions (down gaze). Because of the restrictive myopathy of TAO, recessions rather then resections are predominantly performed. For several authors adjustable sutures are very helpful, because the normal dose-response curves are difficult to generalize to this patient population.

Intraoperative forced duction testing must be performed in every case, before and after muscle desinserted, for the most suitable surgical protocol.

Hypotropia with limited elevation is the most common motility abnormality. Inferior rectus recession will be required to correct the vertical deviation. If it may decrease the upper eyelid retraction, it often results in lower lid retraction; special care must be exercised to dissection of the lower eyelid retractor. When horizontal strabismus, usually esotropia, is also present, it should be corrected at same time. It should be emphasize that larger then normal recessions are usually necessary for small deviations, and smaller than normal recessions are advisable for large deviations.

- **Orbital wall fractures** can occur from a variety of traumatic injuries to the face. The most frequent one being the orbital floor fracture or blowout fracture, due to elevation of intraorbital pressure from a ball or fist strikes on the orbital rim.

A wide variety of strabismus patterns can be seen after trauma of the orbit due to a combination of restrictive and paralytic factors. Typically, a blowout fracture involves the floor of the orbit, with the orbital contents displacing inferiorly into the maxillary sinus. This often results in a hypotropia, with limitation of elevation of the involved eye. A medial wall fracture can occur in combination with a floor fracture or as an isolated phenomenon. In this circumstance, the medial rectus or its surrounding tissue becomes trapped in the ethmoid bone fracture. This result in an esotropia that worsens on attempted abduction.

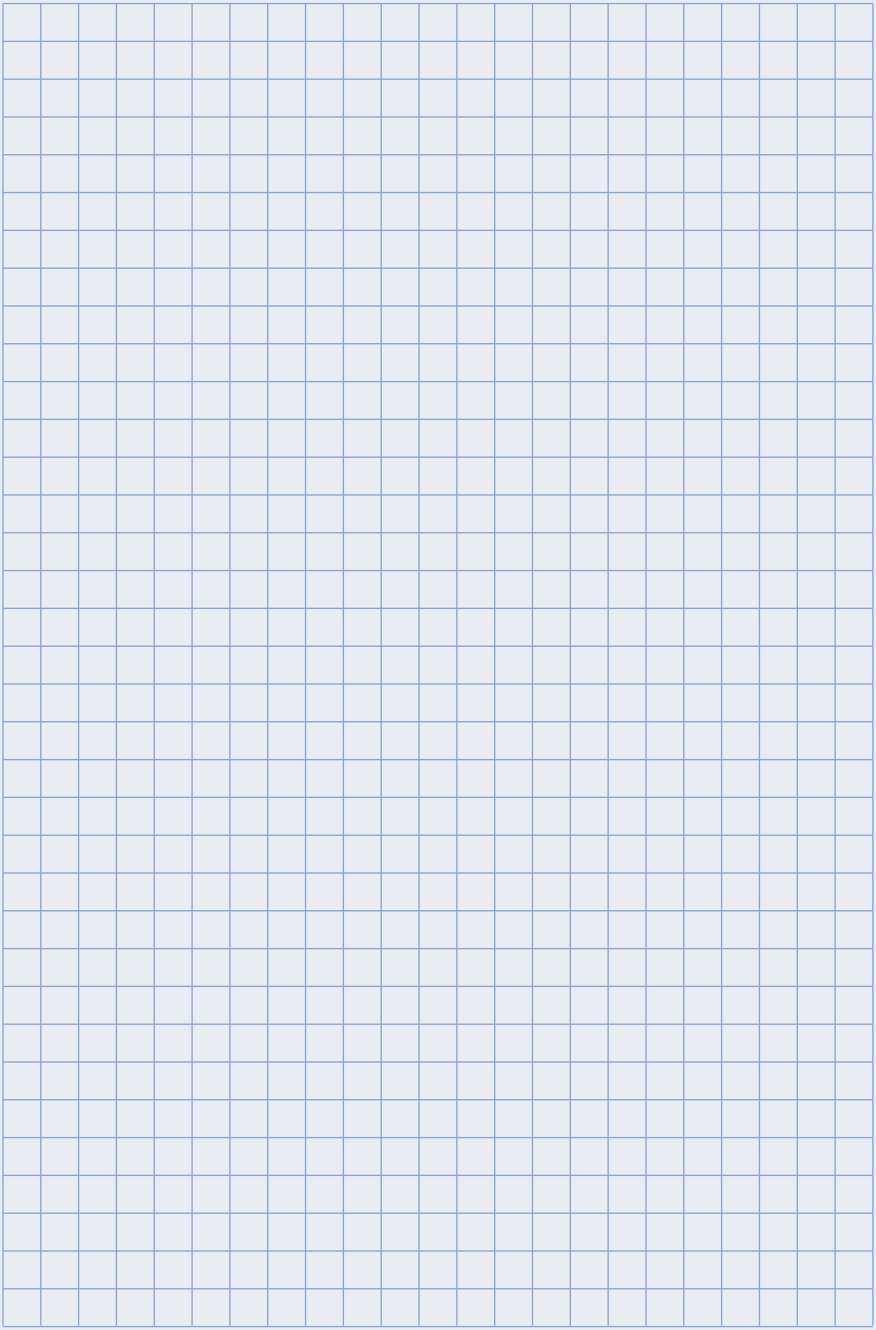
The major concern in the evaluation of strabismus secondary to a blowout fracture is whether the motility limitation is due to restriction or paresis. This requires an analysis of forced ductions and forced generation. Particularly important is the range of movement the eye can make before the restriction limits movement.

Neuroimaging with CT scan is very helpful in delineating the extent of an orbital fracture and the degree of entrapment of ocular tissues.

Surgical treatment: If CTscan reveals no enophtalmos or obvious entrapment, orbital surgery for diplopia is not indicated. In the vast majority of patient in this category, diplopia will resolve spontaneously in 3 to4 weeks.

If there is clear CT evidence of EOM entrapment, orbital surgery should be considered in the first 2 weeks after trauma.

- **Cataract Surgery** After cataract surgery, motility disturbances could relate to contracture, overaction, and paresis. A restrictive strabismus can occur after surgery and is currently thought to be caused by myotoxicity of focal anesthetic agents. Most patients present a vertical deviation and, regardless of the cause (contraction or overaction), the treatment is the same. Single muscle surgical recessions are generally used combined or not with adjustable suture.



Historical vignette : the Bielschowsky legacy

| H.J. Simonsz, Rotterdam, The Netherlands |

Abstract not received

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1. Barnebey HS et al. The Safety and Efficacy of Travoprost 0.004%/Timolol 0.5% Fixed Combination Ophthalmic Solution. Am J Ophthalmol. 2005;140:1-7
2. Topouzis F et al. A 1-year study to compare the efficacy and safety of once-daily travoprost 0.004%/timolol 0.5% to once-daily latanoprost 0.005%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: Eur J Ophthalmol. 2007 Mar-Apr;17(2):183-90

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