Optic Neuropathy Update

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Disclosures

- Consultant for Santhera

- Most illustrations are from:

  Biousse V, Newman NJ.

  Neuro-Ophthalmology Illustrated.

  Thieme, NY. 2009


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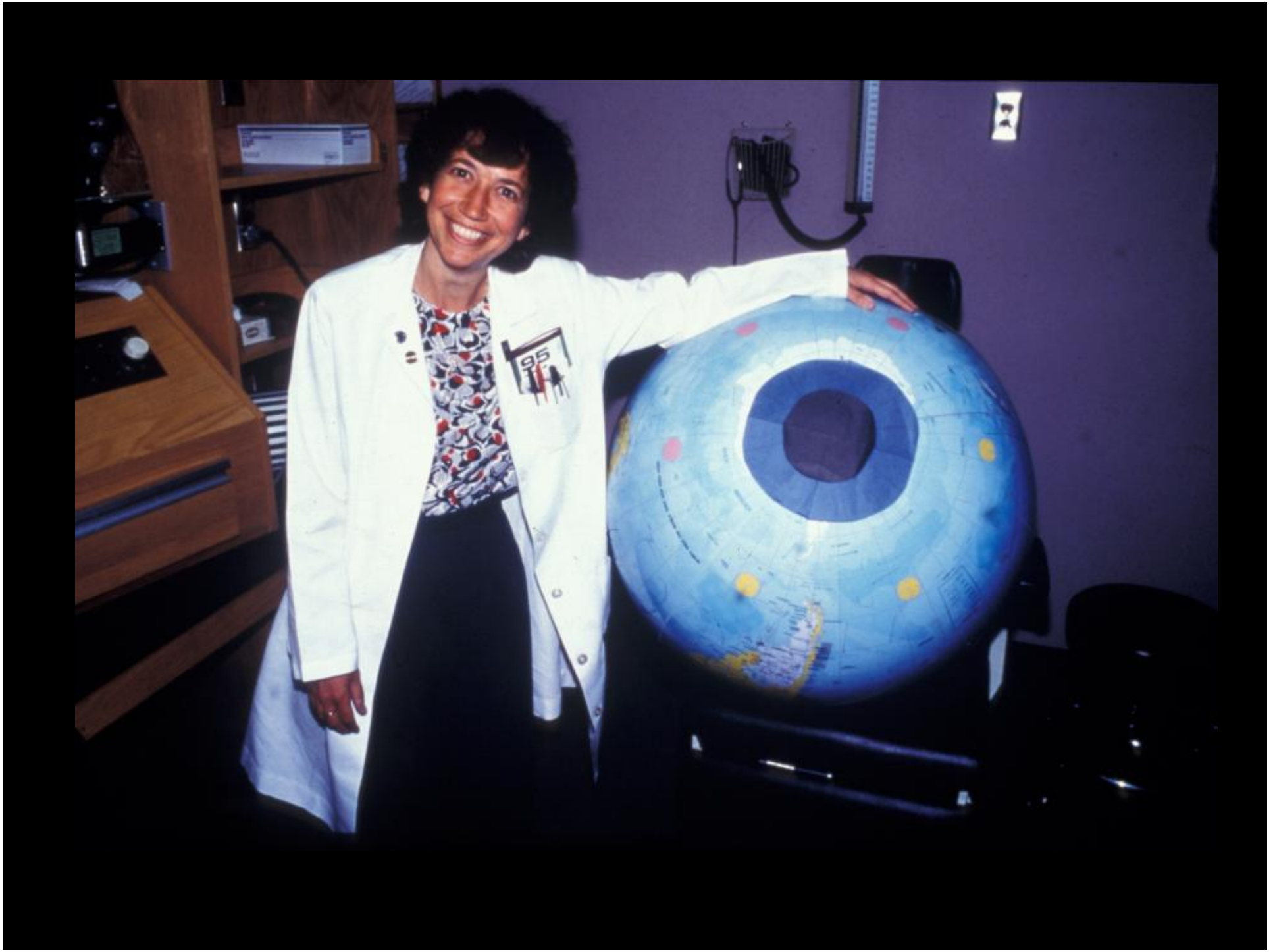
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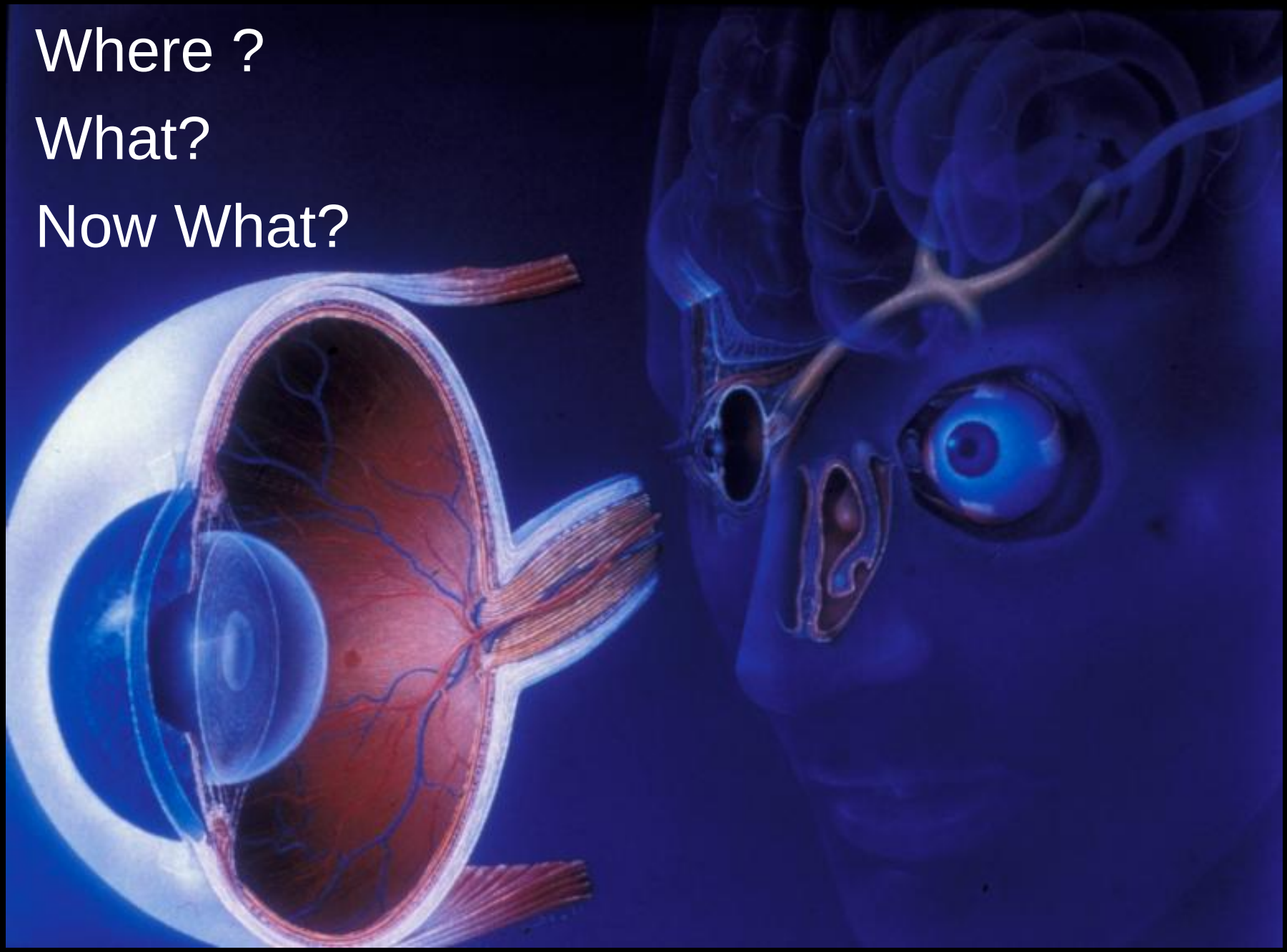
Where ?

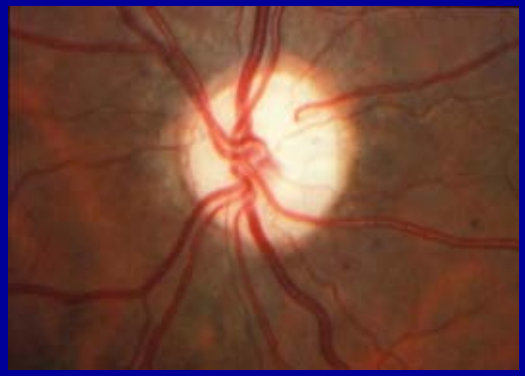
What?

Now What?



Optic Neuropathy

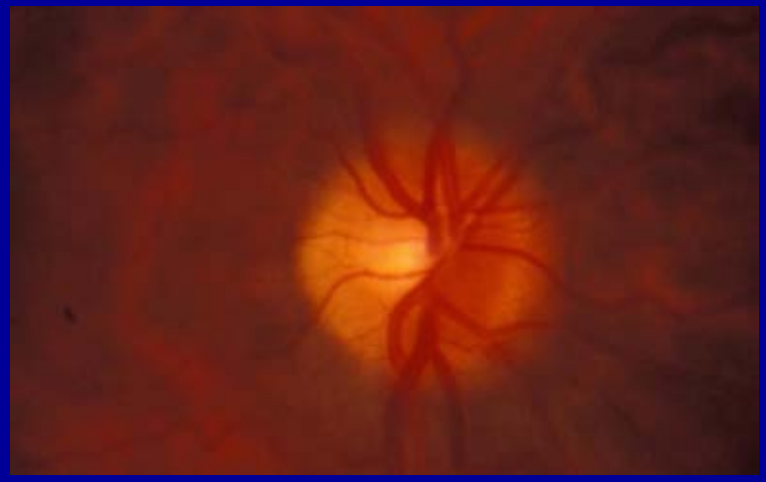
Classic Features

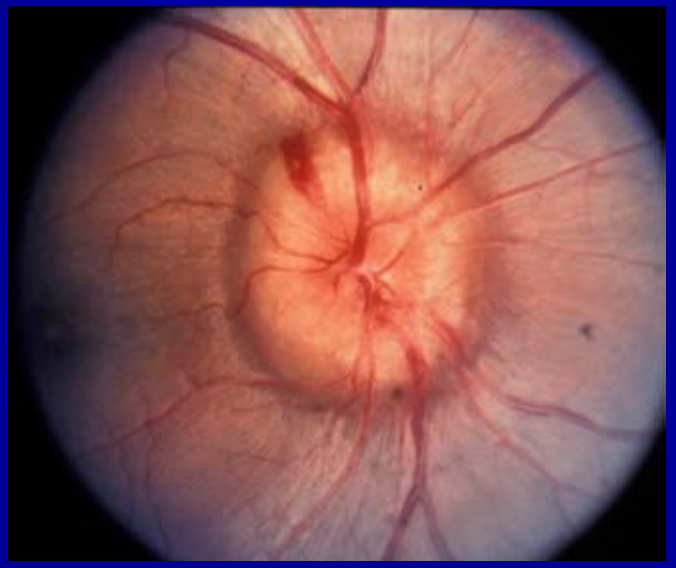


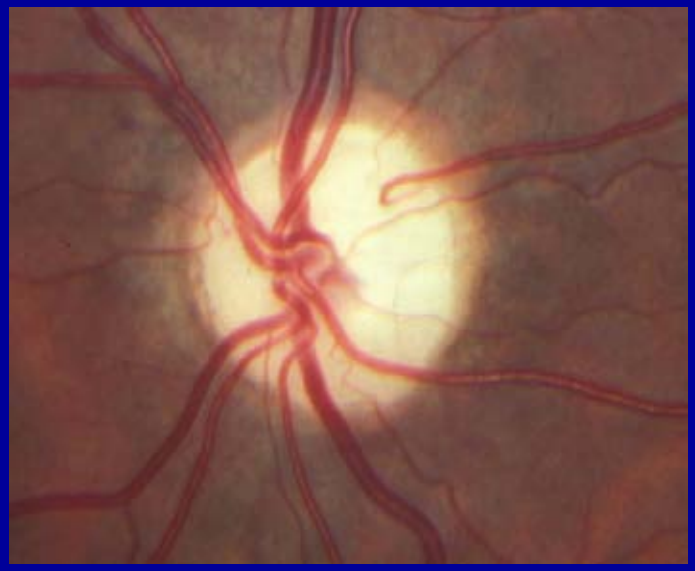
- Decreased visual acuity
- Abnormal visual field
- Relative afferent pupillary defect
- Can see through to the nerve
- Swollen or pale optic nerve

Optic Neuropathy

Disc Alternatives







Optic Neuropathy

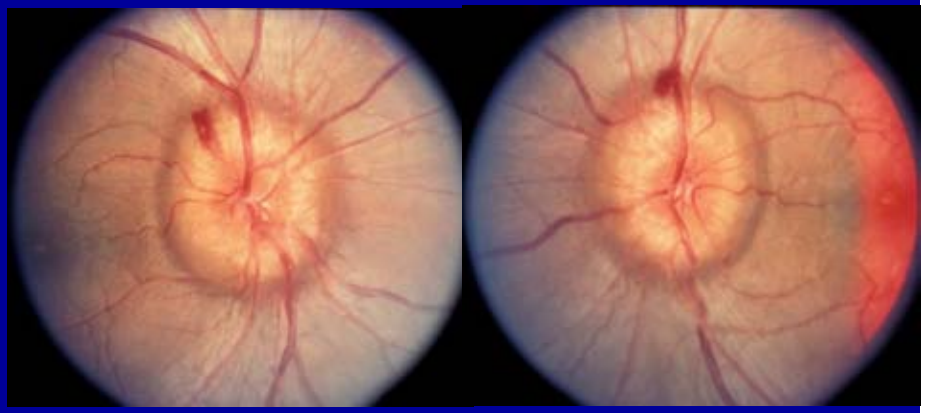
Causes

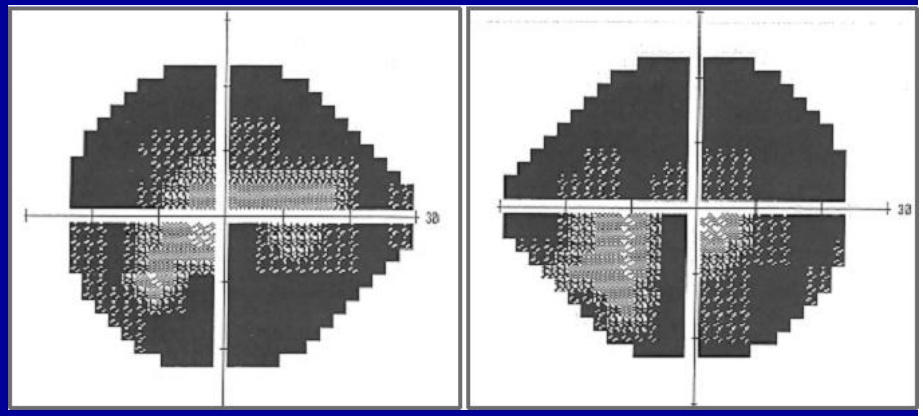
- Inflammatory
- Vascular
- Compressive/Infiltrative
- Toxic/Nutritional
- Hereditary
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure

Optic Neuropathy

Papilledema

- Disc swelling from ↑ intracranial pressure
- Any age
- Painless
- Bilateral
- Spares visual acuity
- Constriction of visual field

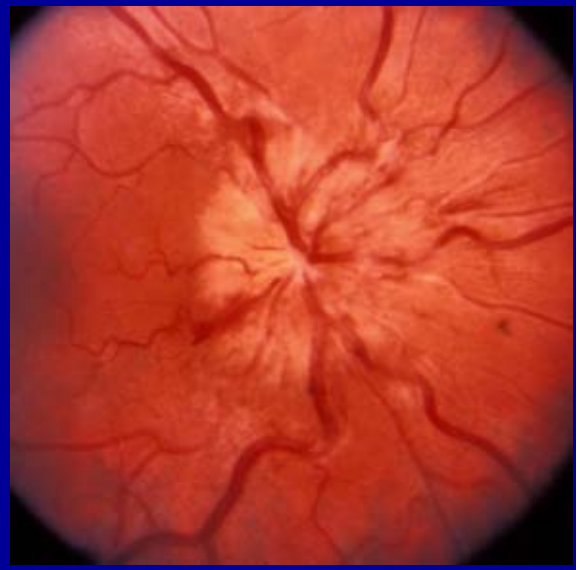




Papilledema

Causes

- Intracranial mass lesions
- Hydrocephalus
- Meningeal processes
- Cerebral venous thrombosis
- Idiopathic intracranial hypertension (pseudotumor cerebri)



Optic Neuropathy

Causes

- Inflammatory
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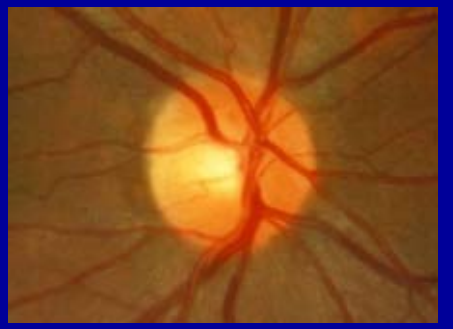
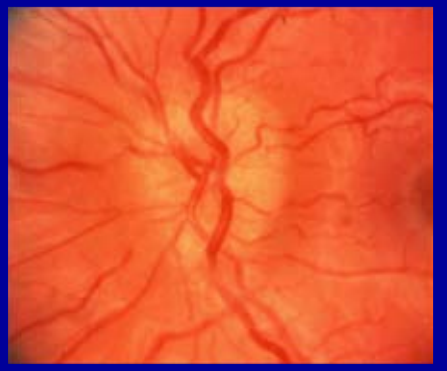
- Toxic/Nutritional
- Hereditary
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure

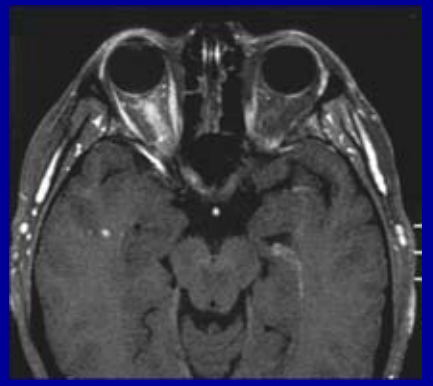
Optic Neuropathy

Typical Optic Neuritis

- Inflammation of the optic nerve
- F:M 3:1
- Age: 15-45
- Pain on eye movement
- Normal or swollen disc
- Spontaneous improvement
- Associated with multiple sclerosis



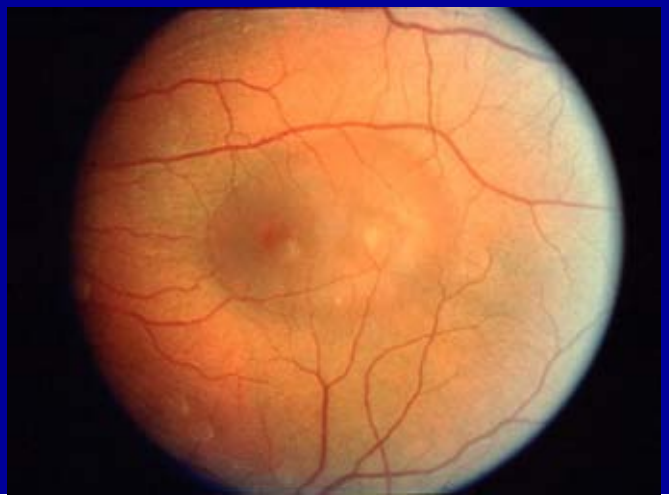




Differential Diagnosis

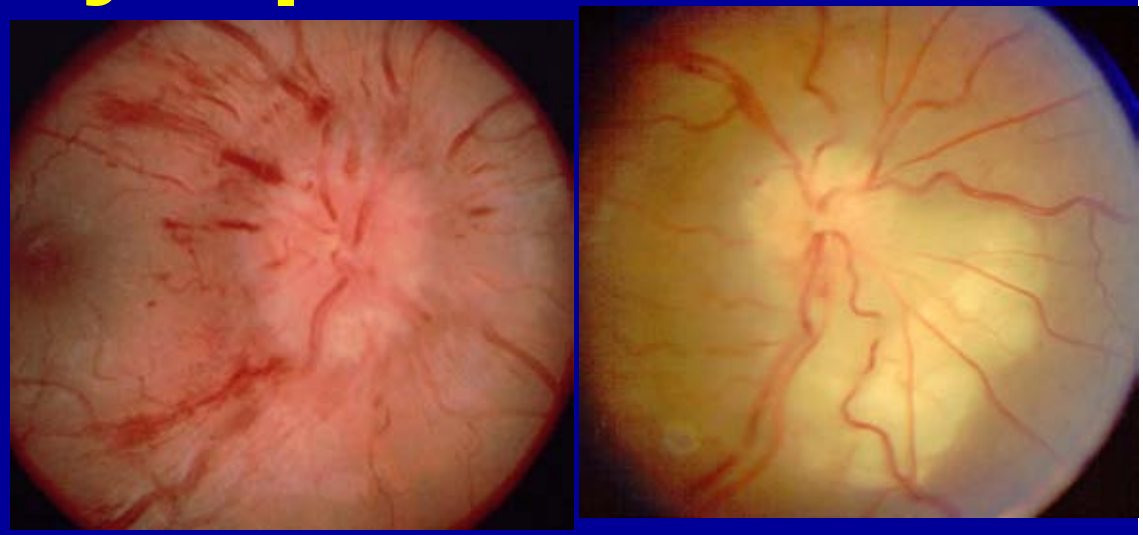
- Macular disease
- Anterior ischemic optic neuropathy
- Leber hereditary optic neuropathy
- Systemic disease (sarcoidosis)
- Infectious

	Optic Neuritis	Maculopathy
Sex	Female	Male
Pain	Yes	No
Field	Central	Central
Pupil	RAPD	No RAPD
Fundus	Nerve nl or edema	Blister

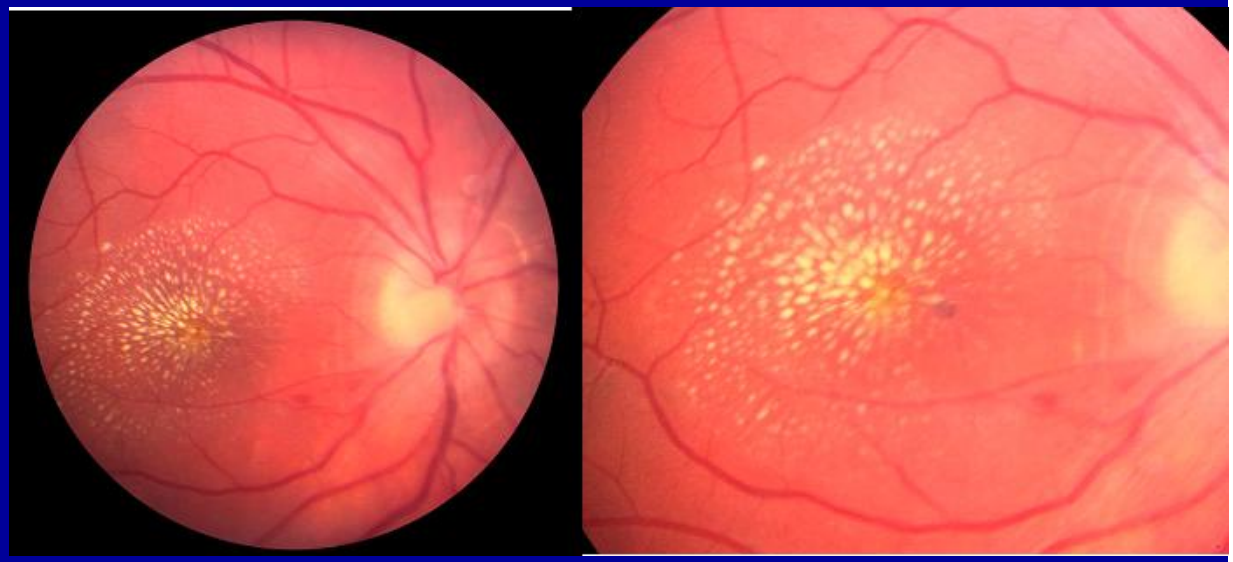


Inflammatory Optic Neuritis

- Bilateral
- Intra-ocular cells
- Disc swelling
- Hemorrhages
- Exudates (“star”)

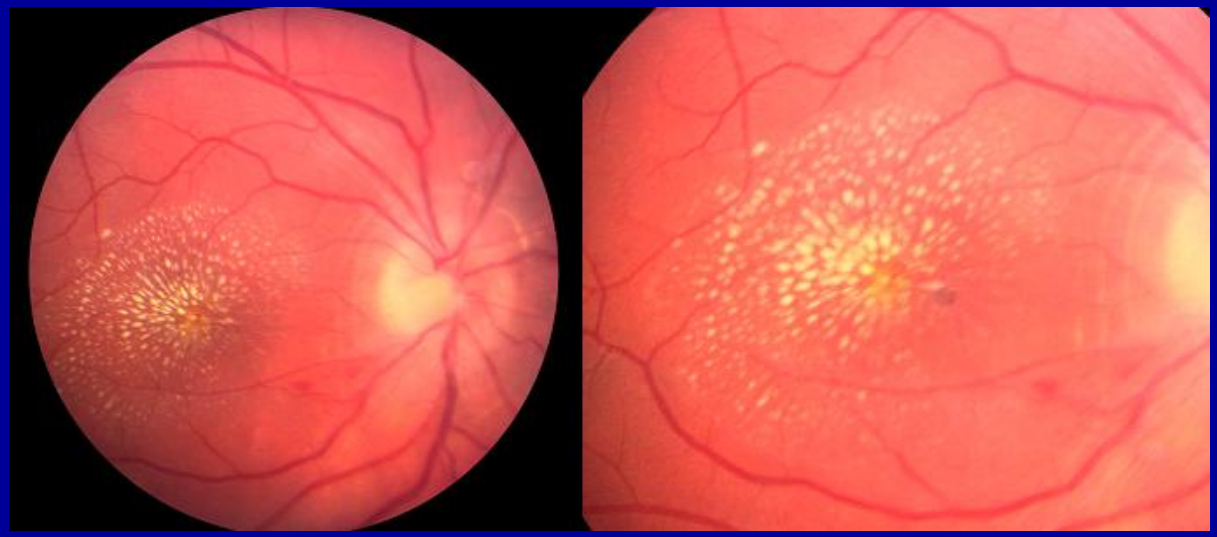


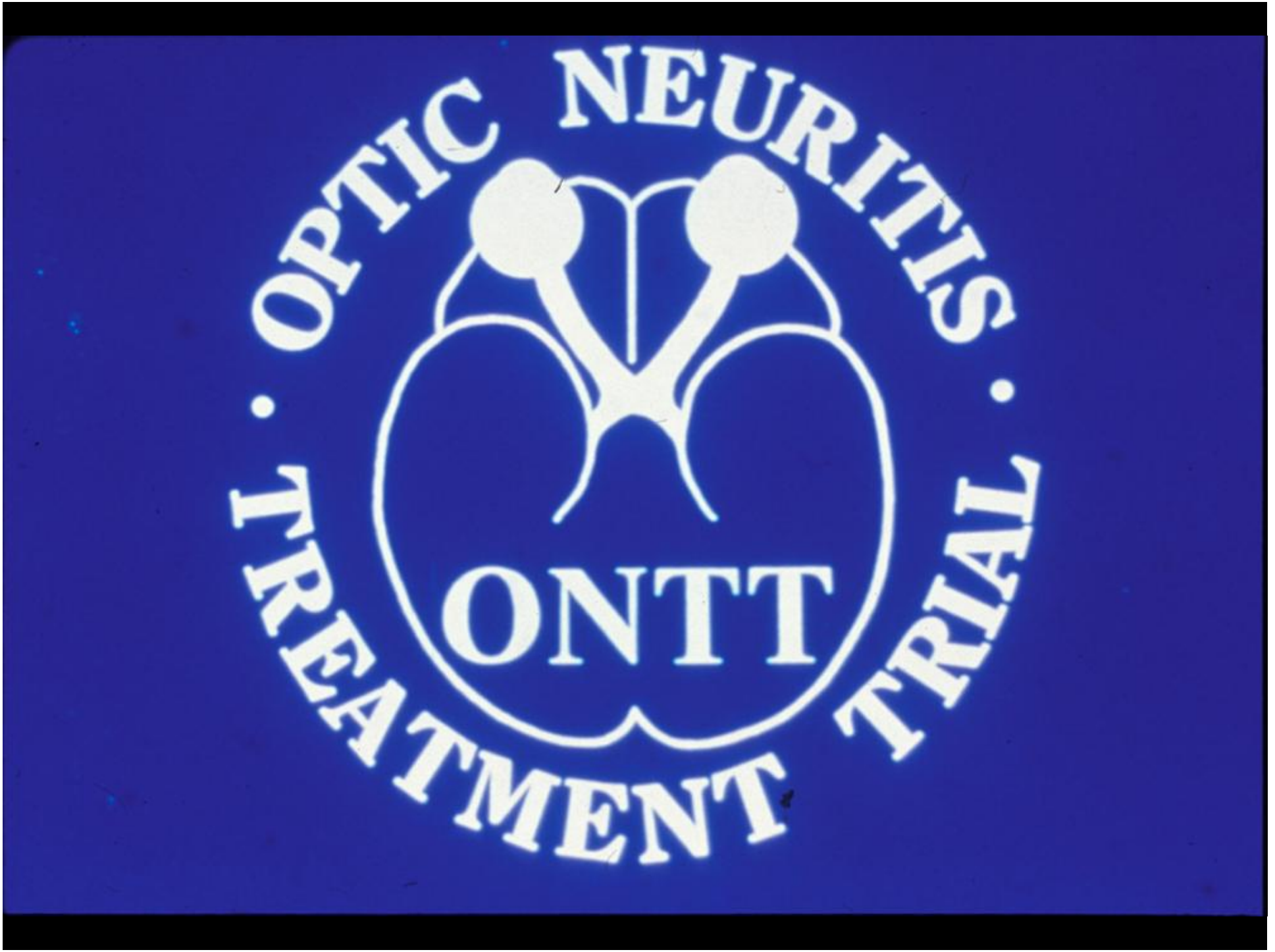
- Sarcoidosis
- Bartonella
- Syphilis
- Tuberculosis
- Viral



Neuroretinitis

- Optic neuritis with retinal changes (exudates forming a macular star)
- Cat scratch, syphilis, sarcoidosis
- NOT associated with multiple sclerosis




OPTIC NEURITIS
TREATMENT TRIAL
ONTT

ONTT

Treatment Groups

- Oral prednisone (1 mg/kg/day for 14 days)
- Oral placebo (for 14 days)
- IV methylprednisolone (250 mg q6h x 3 days) then oral prednisone (1 mg/kg/d for 11 days)

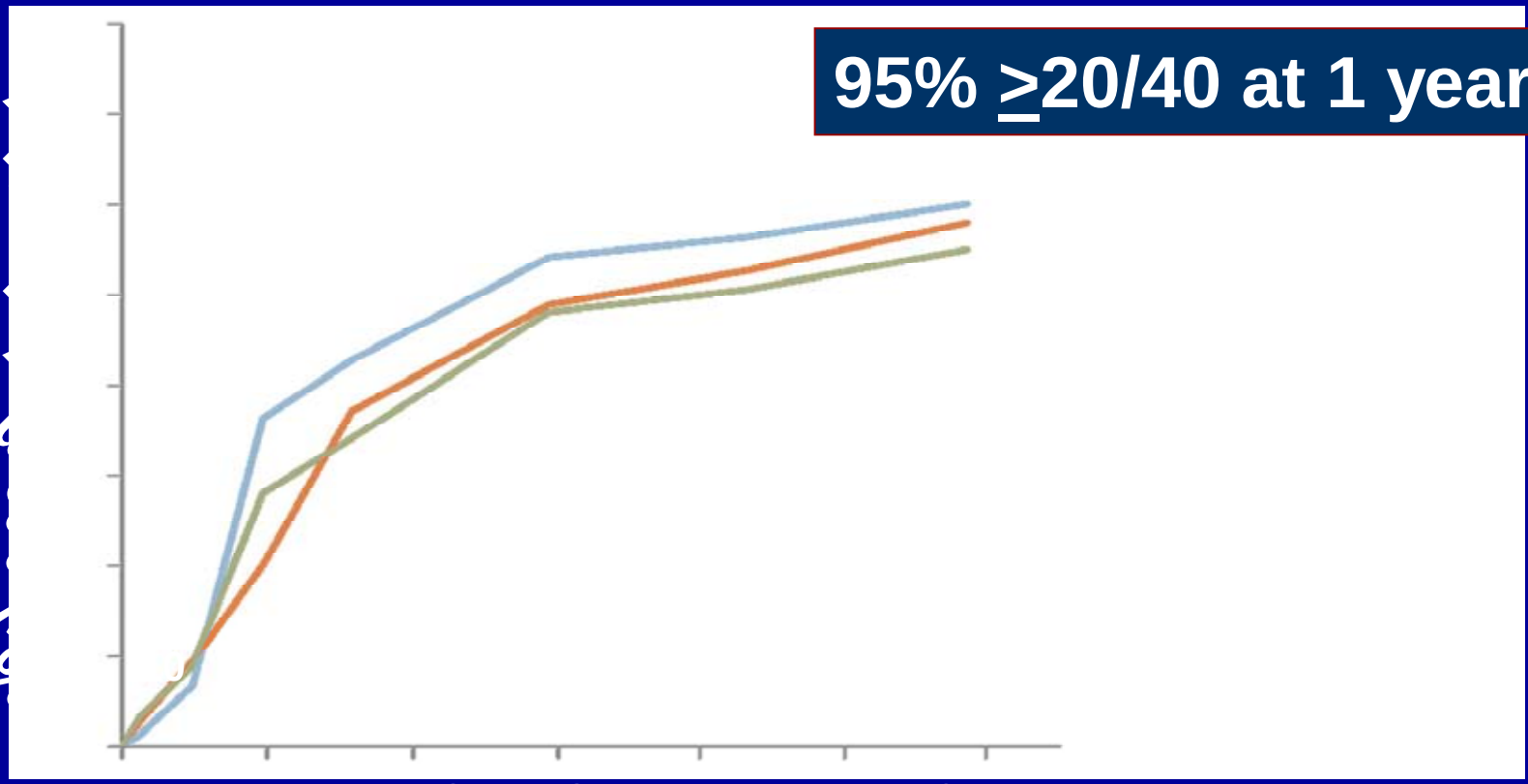
Each oral regimen followed by a 4-day taper

ONTT

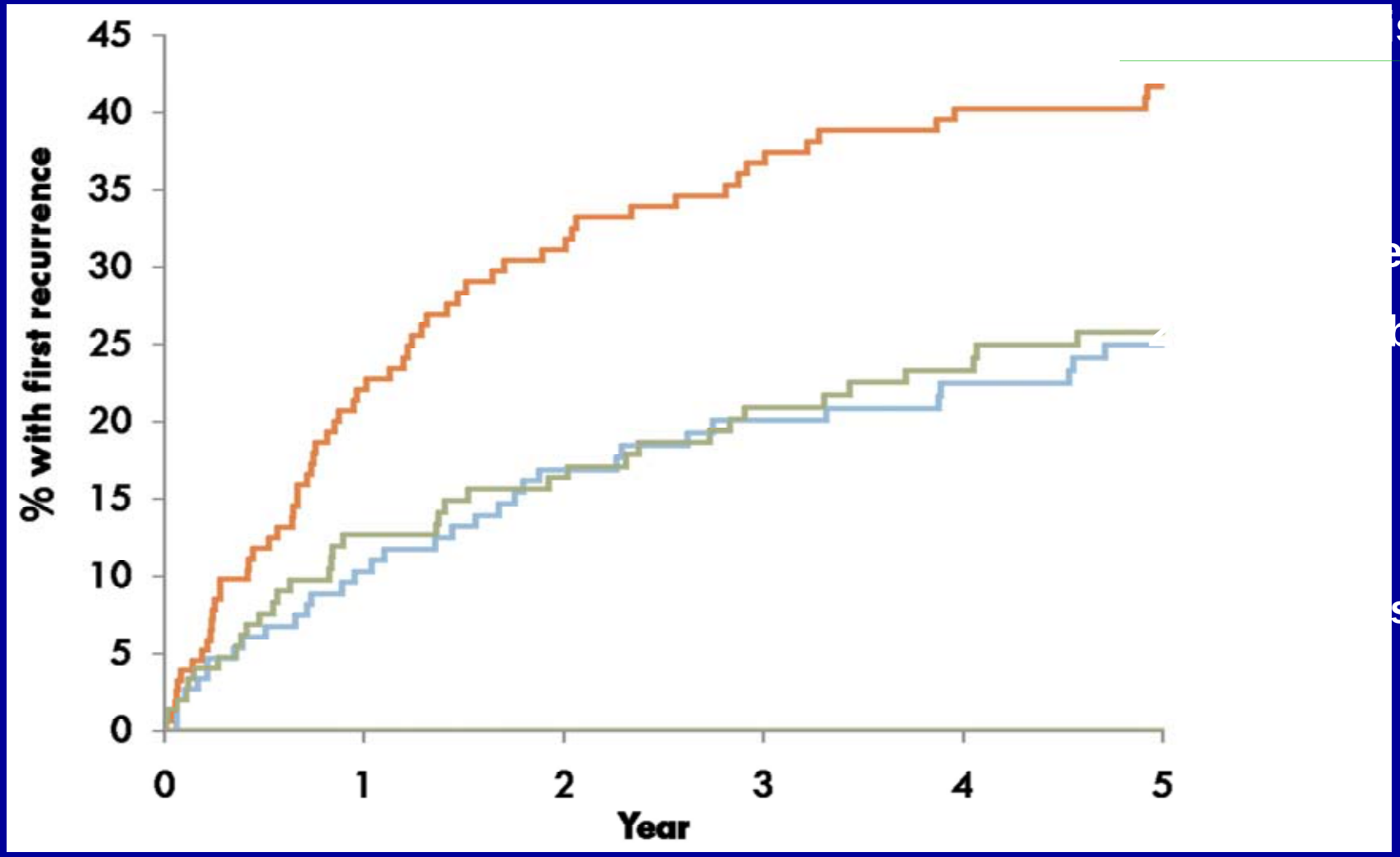
- No difference in visual acuity between steroid and placebo groups at 6 months.
- I.V. steroids may accelerate recovery by 2 to 3 weeks.

(NEJM 326:581, 1992)

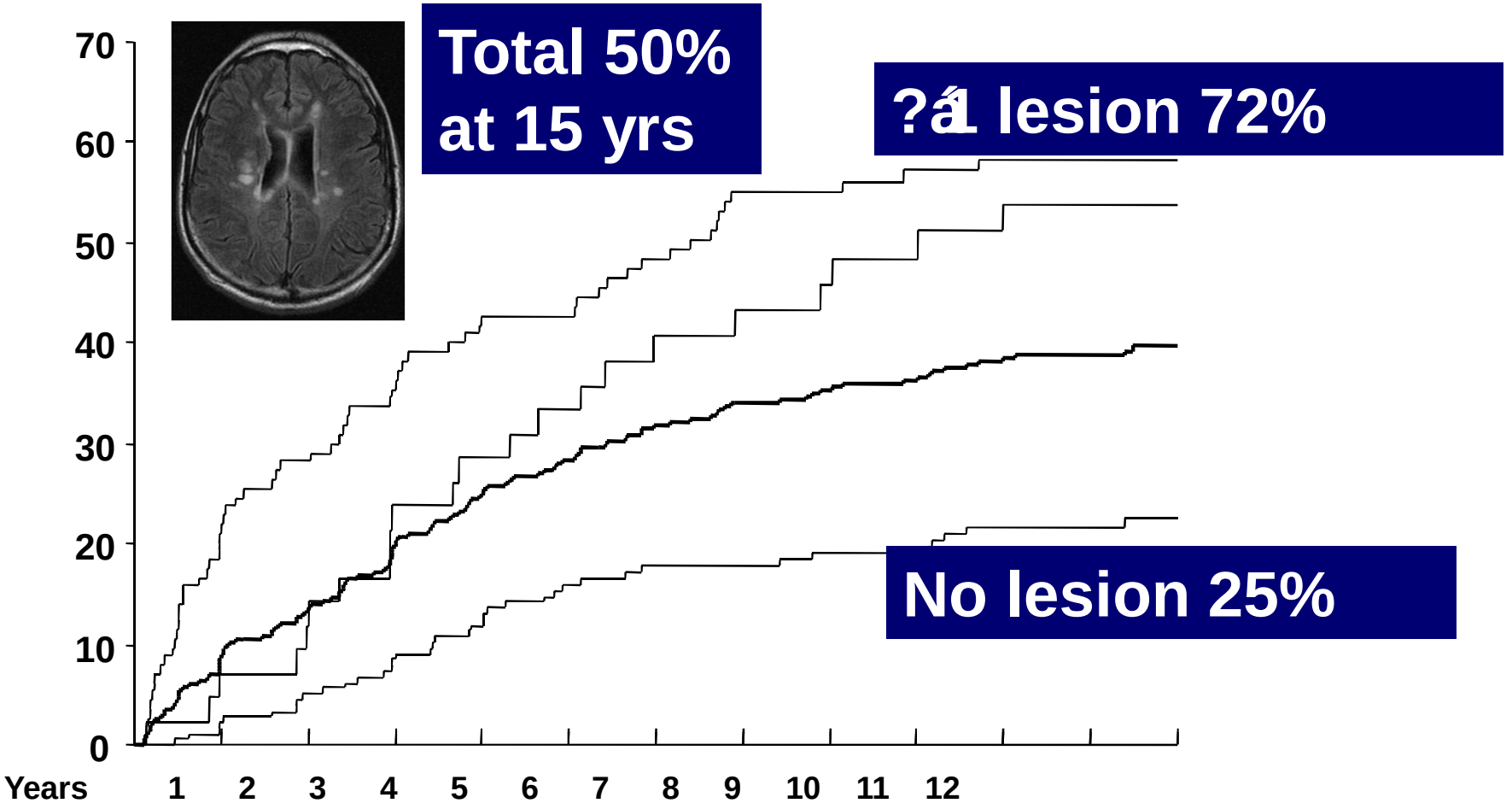
ONTT: Visual Prognosis



ONTT: Recurrent Optic Neuritis



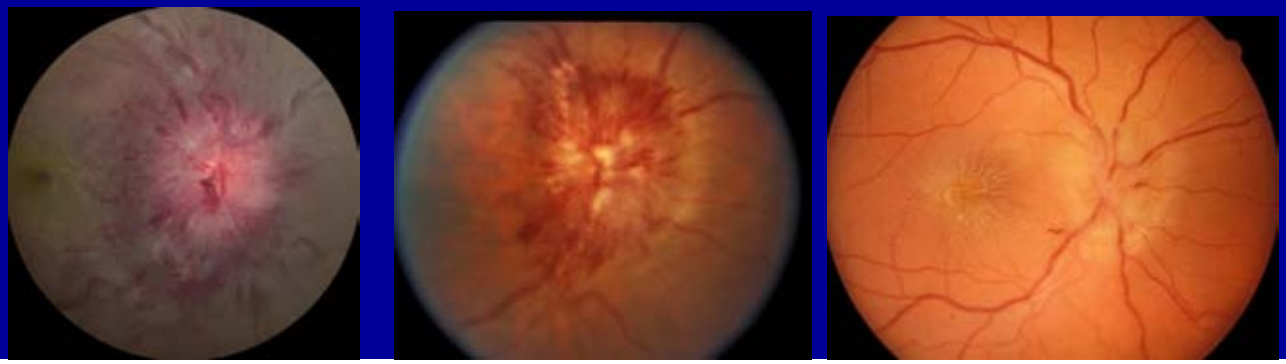
ONTT: MRI predicts the risk of MS



Clinical Features of Optic Neuritis with Low Risk of CDMS in Patients with No Brain MRI Lesions

No cases of CDMS have developed when any one of the following clinical features* was present:

- Severe Disc Swelling (21 patients)
- Hemorrhage, disk or peripapillary (16 patients)
- Macular Exudates (8 patients)
- Painless (19 patients)
- No Light Perception (7 patients)



Monosymptomatic Pts and Delay to CDMS

- CHAMPS: IFN?½1a (Avonex®)
  - 30 ?g IM qwk X 2 yrs (35% vs 50%)
- ETOMS: IFN?A1a (Rebif®)
  - 22 ?g SC qwk X 2 yrs (34% vs 45%)
- BENEFIT: IFN?CH1b (Betaseron®)
  - 250 ?g SC qod X 2 yrs (28% vs 45%)
- PreCISe:Glatiramer acetate (Copaxone®)
  - 20 mg SC qd X 2 yrs (25% vs 43%)

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Management of optic neuritis and impact of clinical trials: An international survey

Valérie Biousse [a,b,*], Olivier Calvetti [a], Carolyn D. Drews-Botsch [d], Edward J. Atkins [e], Busaba Sathornsumetee [f], Nancy J. Newman [a,b,c] for the Optic Neuritis Survey Group [1]

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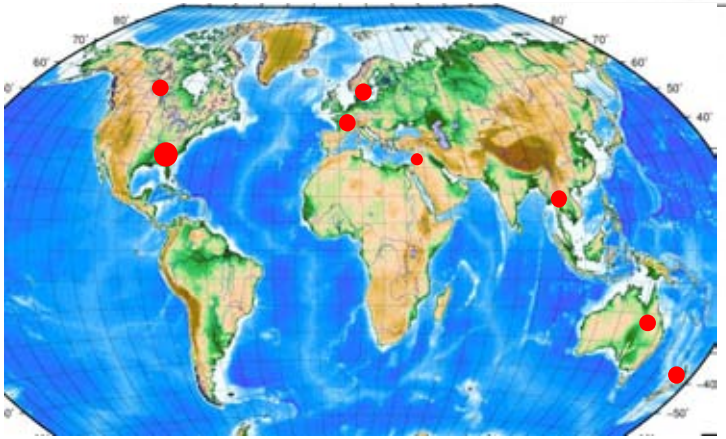
[e] University of Saskatchewan, Saskatoon, SK, Canada
[f] Mettapracharak Hospital, Nakornpathom, Thailand

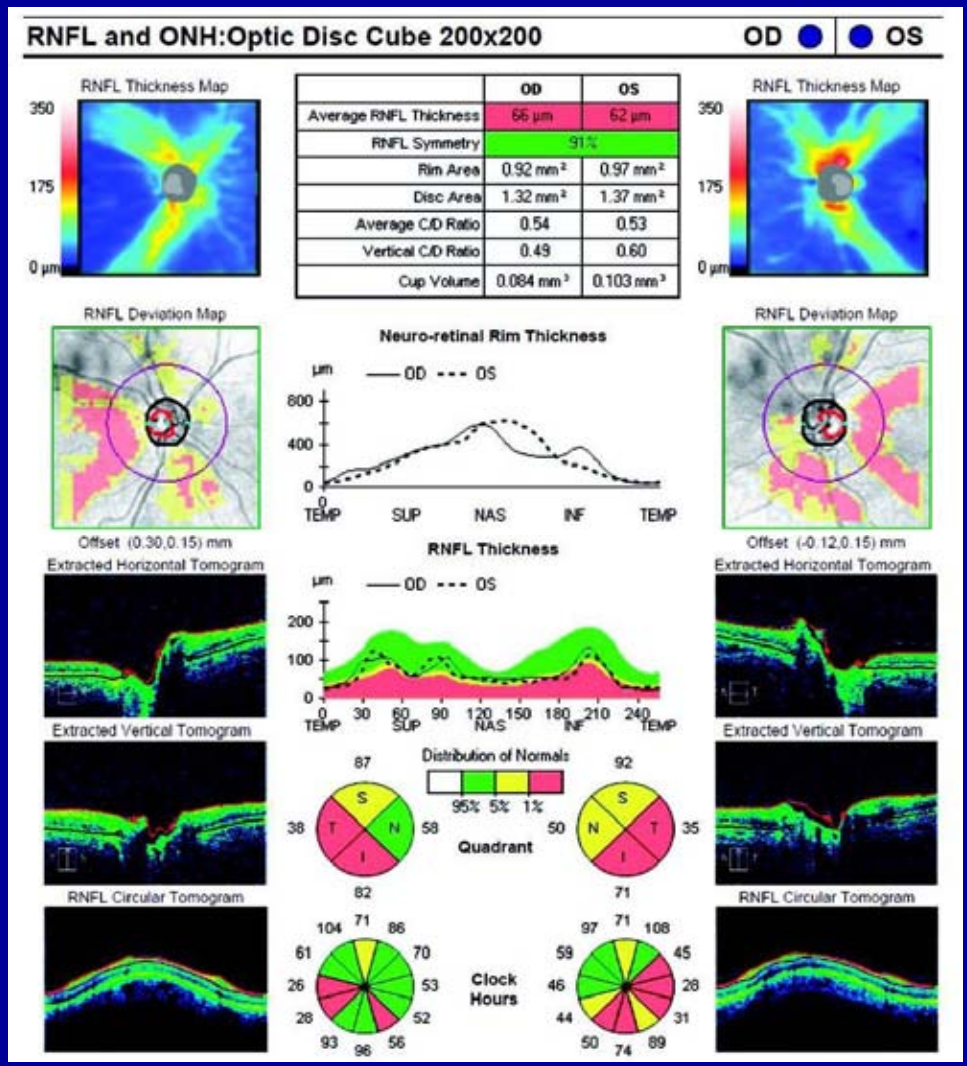


ABSTRACT

Objective: 1) To evaluate the management of acute isolated optic neuritis (ON) by ophthalmologists and neurologists; 2) to evaluate the impact of clinical trials; 3) to compare these practices among 7 countries.
Methods: A survey on diagnosis and treatment of acute isolated ON was sent to 5443 neurologists and 6099 ophthalmologists in the southeast-USA, Canada, Australia/New Zealand, Denmark, France, and Thailand. USA data were compared to those of other countries.
Results: We collected 3142 surveys (1449 neurologists/1693 ophthalmologists) (29.8% response rate). In all countries, ON patients more frequently presented to ophthalmologists, and were subsequently referred to neurologists or subspecialists. Evaluation and management of ON varied among countries, mostly because of variations in healthcare systems, imaging access, and local guidelines. A brain MRI was obtained for 70–80% of ON patients; lumbar punctures were obtained mostly in Europe and Thailand. Although most patients received acute treatment with intravenous steroids, between 14% and 65% of neurologists and ophthalmologists still recommended oral prednisone (1 mg/kg/day) for the treatment of acute isolated ON. In all countries, steroids were often prescribed to improve visual outcome or to decrease the long-term risk of multiple sclerosis.
Interpretation: Although recent clinical trials have changed the management of acute ON around the world, many neurologists and ophthalmologists do not evaluate and treat acute ON patients according to the best evidence from clinical research. This confirms that evaluation of the impact of major clinical trials ("translational T2 clinical research") is essential when assessing the effects of interventions designed to improve quality of care.

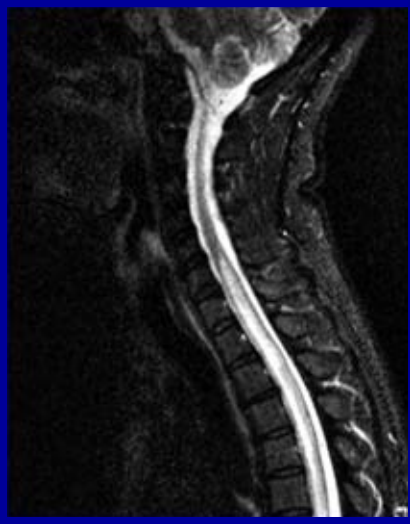
OCT: Retinal Nerve Fiber Layer (RNFL) Thickness

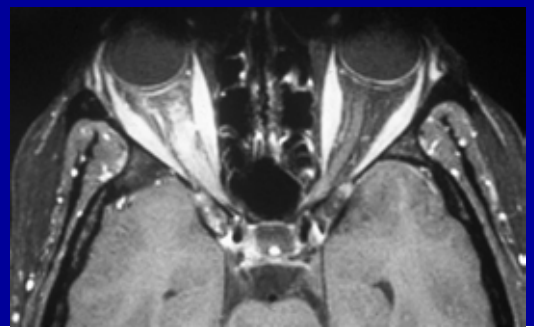
- Correlates with axonal loss
- Predicts visual recovery after optic neuritis
- Correlates with brain atrophy in MS

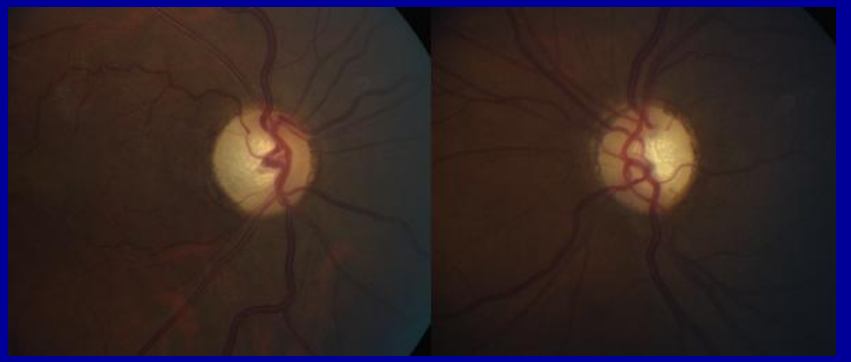


Neuromyelitis Optica (Devic)

- Severe uni- or bilateral optic neuritis
- Transverse myelopathy
- Abnormal cervical spine MRI (long T2-hypersignal over more than 3 segments)
- Brain MRI normal or with atypical T2-hypersignals
- Positive NMO IgG antibodies (blood test)
- Prognosis poor







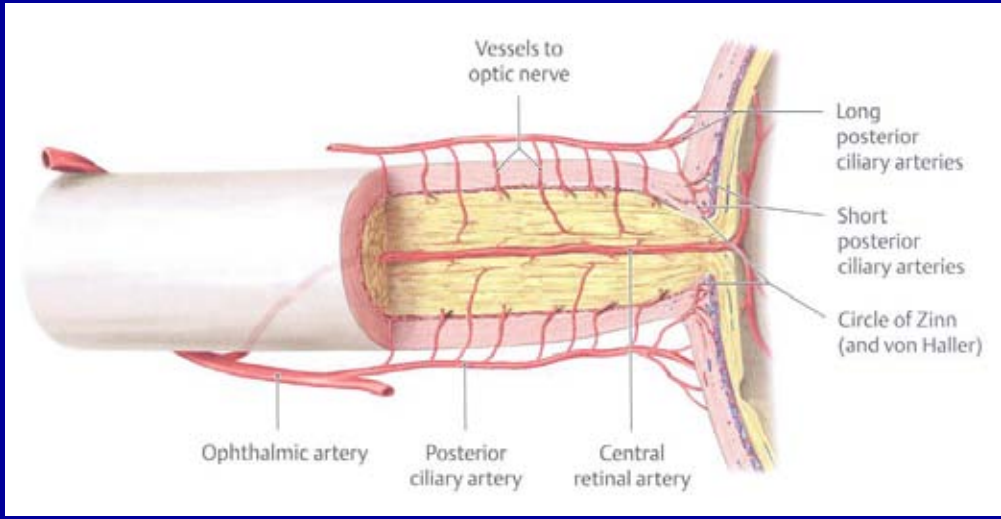
When to test NMO-IgG in isolated optic neuritis

- Visual acuity at nadir of LP or NLP
- Visual acuity after recovery of 20/50 or worse
- Symptomatic bilateral visual loss
- Recurrent optic neuritis
- Mild symptoms or findings of myelopathy
- Systemic autoimmune disease
- Brain MRI not consistent with MS
- Mean OCT-RNFL thickness of <70 mm

Morrow and Wingerchuk: J Neuro-Ophthalmol 2012; 32: 154-166

Ischemic Optic Neuropathy

- **Anterior ischemic optic neuropathy (AION):** disc edema
- **Posterior ischemic optic neuropathy (PION):** optic nerve normal acutely
- AION >> PION



- Local small vessel disease (not embolic!)

Arteritic vs Non-Arteritic

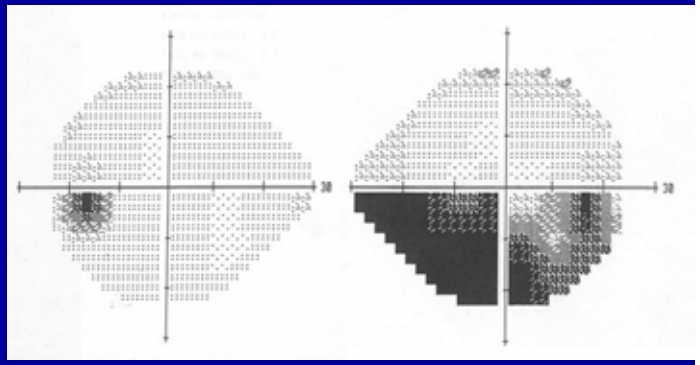
- Rule-out giant cell arteritis (ESR, CRP, platelets) in all > 50 yo patients with ischemic optic neuropathy

- Arteritic ION:
  - AION or PION
  - Systemic symptoms of GCA absent in 25%
  - Often with transient visual loss or diplopia
  - Bilateral if no treatment
  - Steroids emergently, then temporal artery biopsy
  - Poor visual prognosis

Optic Neuropathy

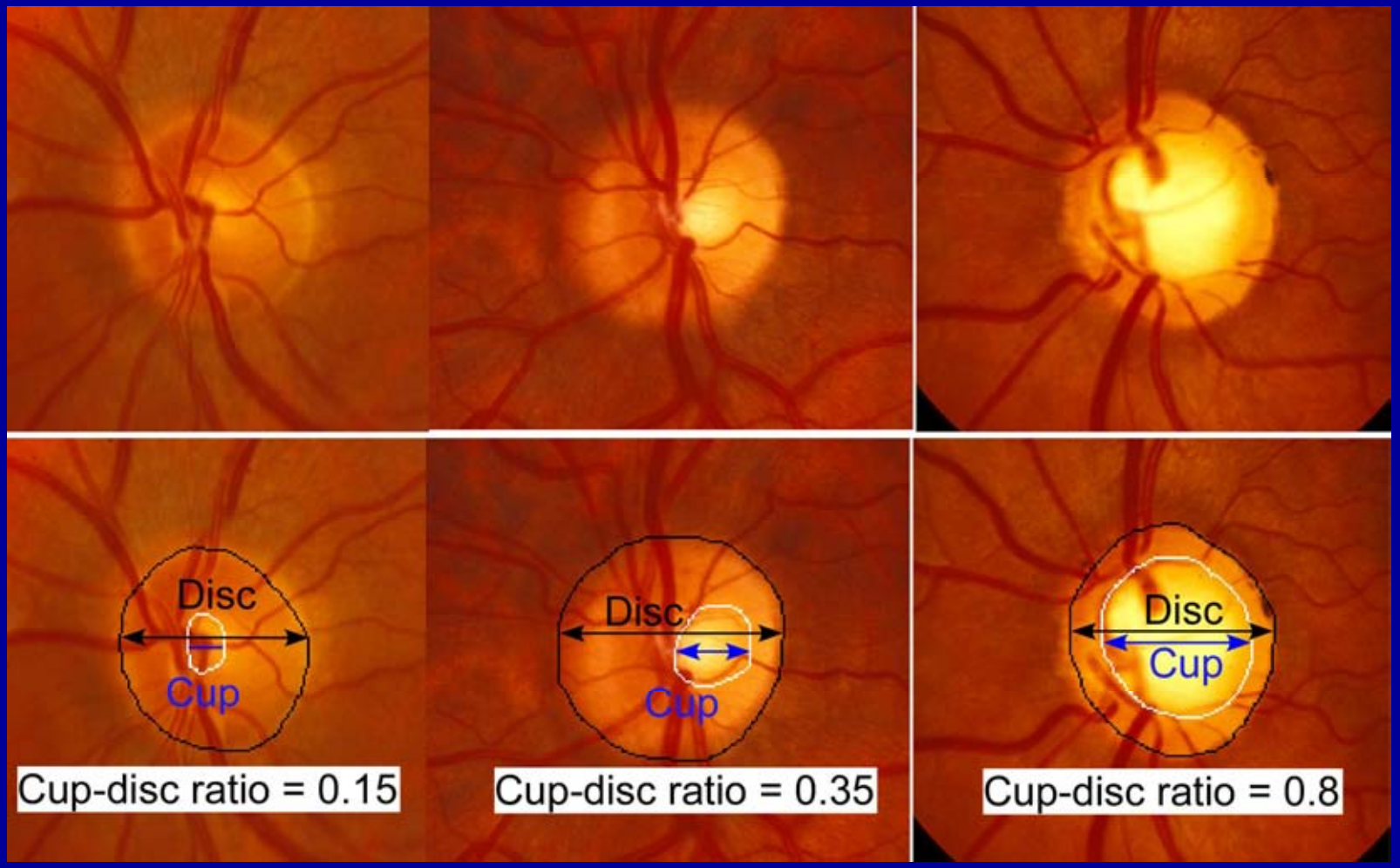
Nonarteritic Anterior Ischemic Optic Neuropathy

- Ischemia to the optic nerve head
- M:F 1:1
- Age: older than 50
- Diabetes, hypertension
- Painless
- Altitudinal defect
- Swollen disc
- Permanent visual loss



AION

Disc At Risk



Non-Arteritic AION

- Age range 11-91 (mean 60s)
- Discomfort (up to 12%)
- Progression over days-weeks (up to 46%)
- Spontaneous improvement (up to 27%)
- Recurrences in same eye rare
- Bilateral within 5 years in 15%
- Vascular risk factors in 60%

Anterior Ischemic Optic Neuropathy in Patients Younger than 50 Years

PISIT PREECHAWAT, BEAU B. BRUCE, NANCY J. NEWMAN, AND VALÉRIE BIOUSSE

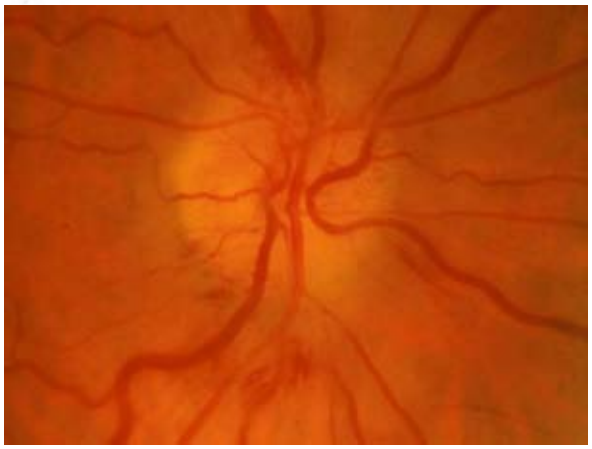
• PURPOSE: To characterize anterior ischemic optic neuropathy (AION) in patients younger than 50 years.

• DESIGN: Retrospective study.

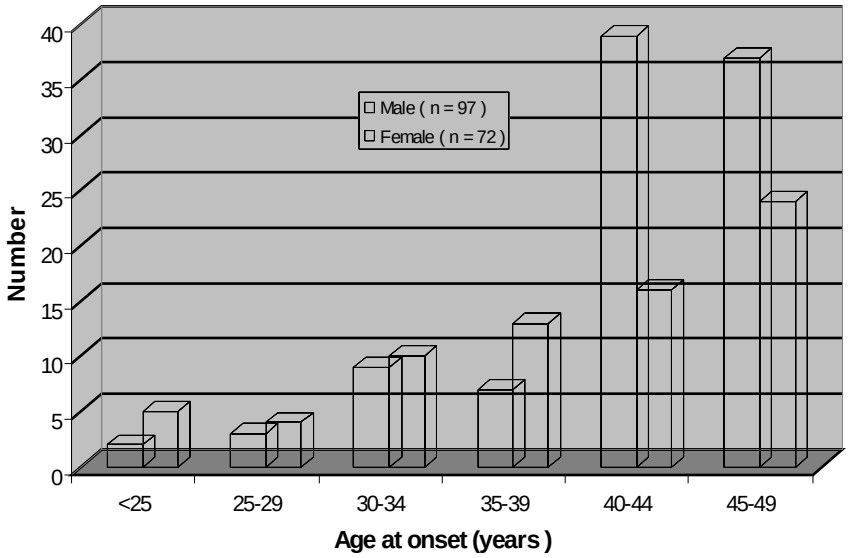
• METHODS: Records of all AION patients seen between 1989 and 2006 were reviewed. Patients younger than 50 years when initial visual loss occurred were included.

• RESULTS: Of 727 consecutive patients with AION, 169 (23%) were younger than 50 years (median, 43 years; range, 13 to 49 years; 58% men; 93% White). Involvement was unilateral in 59% of patients and bilateral in 41%. At least one cardiovascular risk factor was found in 74% of patients. Hypercoagulable states and vasculitis were found in 8%. An underlying small or anomalous optic disk was found in 92% of eyes (210/230). Isolated disk anomalies (without systemic risk factors) were present in 26% of eyes. Final visual acuities were 20/40 or better in 64% of eyes and 20/200 or worse in 22%. Among patients with bilateral involvement, final visual acuity was similar in the two eyes in 70% of patients. Anemia and type I diabetes were associated significantly with fellow eye involvement. Recurrent AION in the same eye occurred in 6% of patients.

• CONCLUSIONS: AION in younger patients is not uncommon and represents 23% of AION patients in a tertiary neuro-ophthalmic service. Except for giant cell arteritis, ocular and systemic risk factors and associated disorders are similar to those described in older AION patients. Younger AION patients have better visual acuity outcomes but a higher risk of fellow eye involvement than older AION patients. (Am J Ophthalmol 2007;xx:xxx.

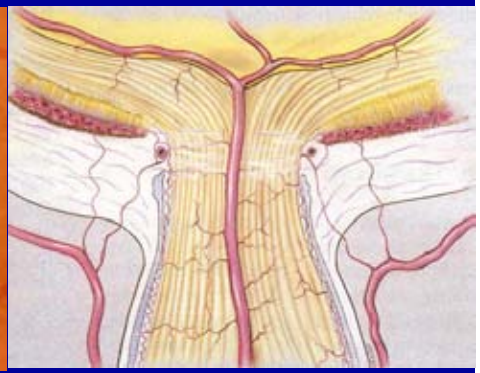


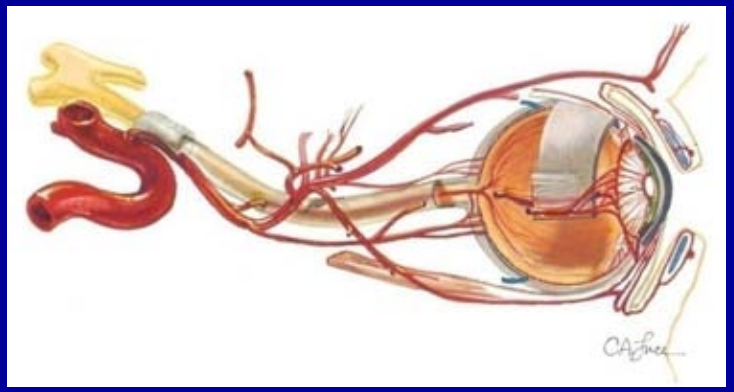
Distribution of age and sex in 169 young patients with AION



Perioperative Ischemic Optic Neuropathy

- Anterior optic nerve
  - Acute: swelling of disc
  - > 6 wks: pallor of disc
- Posterior optic nerve
  - Acute: normal fundus
  - > 6 wks: pallor of disc





Anesthesiology 2006; 105:652–9

The American Society of Anesthesiologists Postoperative Visual Loss Registry

Analysis of 93 Spine Surgery Cases with Postoperative Visual Loss

Lorri A. Lee, M.D., Steven Roth, M.D.,† Karen L. Posner, Ph.D.,‡ Frederick W. Cheney, M.D.,§ Robert A. Caplan, M.D.,‖ Nancy J. Newman, M.D.,# Karen B. Domino, M.D., M.P.H.***

CME This article and its accompanying editorial have been selected for the *Anesthesiology* CME Program. After reading both articles, go to http://www.asahq.org/journal-cme to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

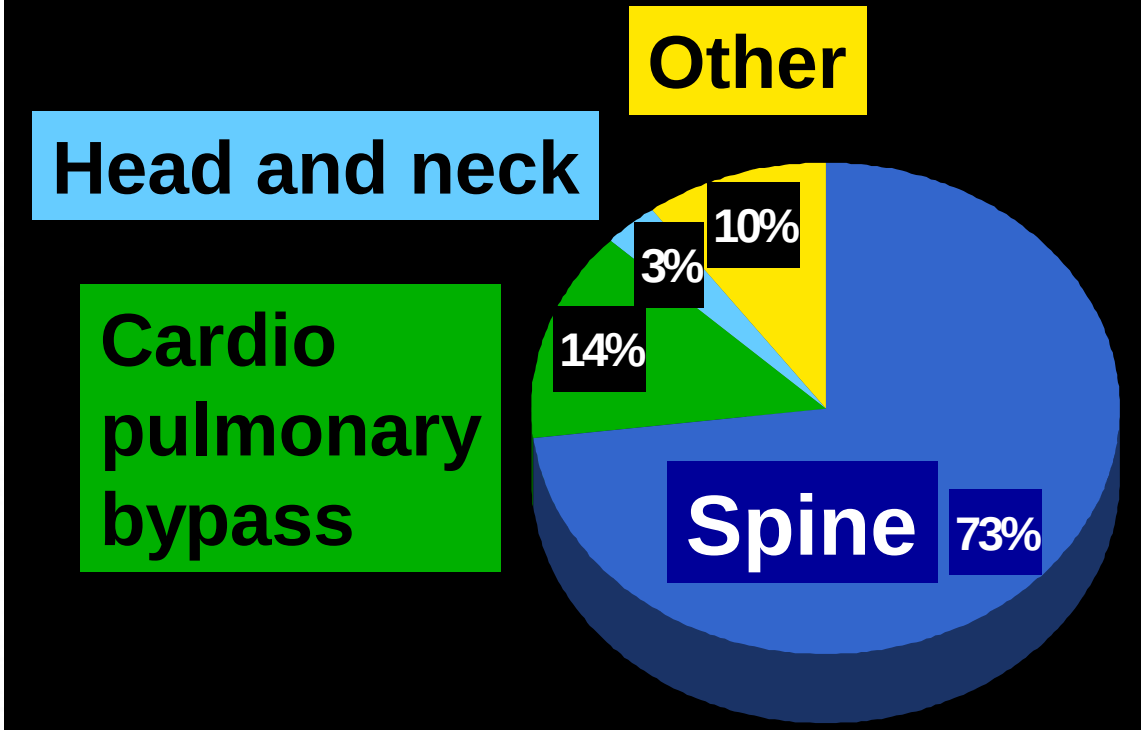
Background: Postoperative visual loss after prone spine surgery is increasingly reported in association with ischemic optic neuropathy, but its etiology is unknown.

Methods: To describe the clinical characteristics of these patients, the authors analyzed a retrospectively collected series of 93 spine surgery cases voluntarily submitted to the American Society of Anesthesiologists Postoperative Visual Loss Registry on standardized data forms.

Results: Ischemic optic neuropathy was associated with 83 of 93 spine surgery cases. The mean age of the patients was 50 ± 14 yr, and most patients were relatively healthy. Mayfield pins supported the head in 16 of 83 cases. The mean anesthetic duration was 9.8 ± 3.1 h, and the median estimated blood loss was 2.0 l (range, 0.1–25 l). Bilateral disease was present in 55 patients, with complete visual loss in the affected eye(s) in 47. Ischemic optic neuropathy cases had significantly higher anesthetic duration, blood loss, percentage of patients in Mayfield pins, and percentage of patients with bilateral disease compared with the remaining 10 cases of visual loss diagnosed with central retinal artery occlusion ($P < 0.05$), suggesting they are of different etiology.

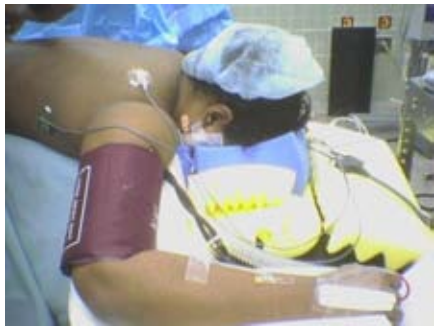
Conclusions: Ischemic optic neuropathy was the most common cause of visual loss after spine surgery in the Registry, and most patients were relatively healthy. Blood loss of 1,000 ml or greater or anesthetic duration of 6 h or longer was present in 96% of these cases. For patients undergoing lengthy spine surgery in the prone position, the risk of visual loss should be considered in the preoperative discussion with patients.

ASA Registry- n=131



Risk Factors Associated with Ischemic Optic Neuropathy after Spinal Fusion Surgery

The Postoperative Visual Loss Study Group*



ABSTRACT

Background: Perioperative visual loss, a rare but dreaded complication of spinal fusion surgery, is most commonly caused by ischemic optic neuropathy (ION). The authors sought to determine risk factors for ION in this setting.

Methods: Using a multicenter case-control design, the authors compared 80 adult patients with ION from the American Society of Anesthesiologists Postoperative Visual Loss Registry with 315 adult control subjects without ION after spinal fusion surgery, randomly selected from 17 institutions, and matched by year of surgery. Preexisting medical conditions and perioperative factors were compared between

What We Already Know about This Topic

- Visual loss after spinal fusion surgery is a devastating complication most commonly caused by ischemic optic neuropathy (ION)
- The risk factors for ION after spinal fusion surgery have not been systematically evaluated with detailed perioperative data

What This Article Tells Us That Is New

- In a case-control examination of 80 patients with ION compared with 315 matched control subjects, independent risk factors were male sex, obesity, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and lower percent colloid administration

Anesthesiology 2012; 116: 15-24

Optic Neuropathy

Causes

- Inflammatory
- Vascular
- Compressive/Infiltrative
- Toxic/Nutritional
- Hereditary
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure

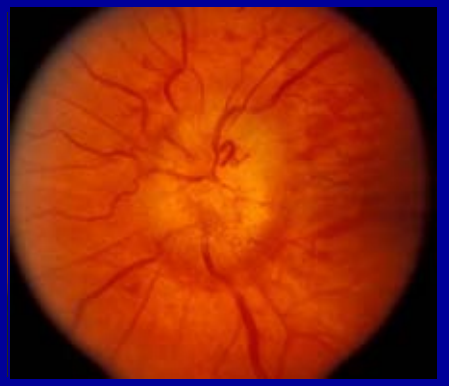
Compressive Optic Neuropathy

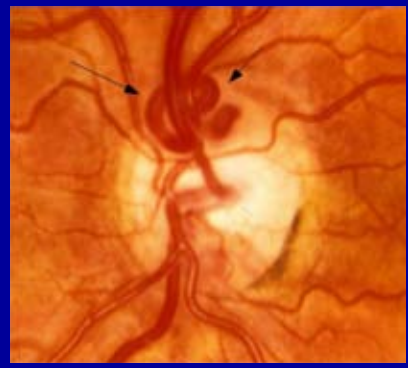
- Progressive, painless, visual loss
- RAPD if unilateral or asymmetric
- Pale nerve (or swollen if orbital mass)

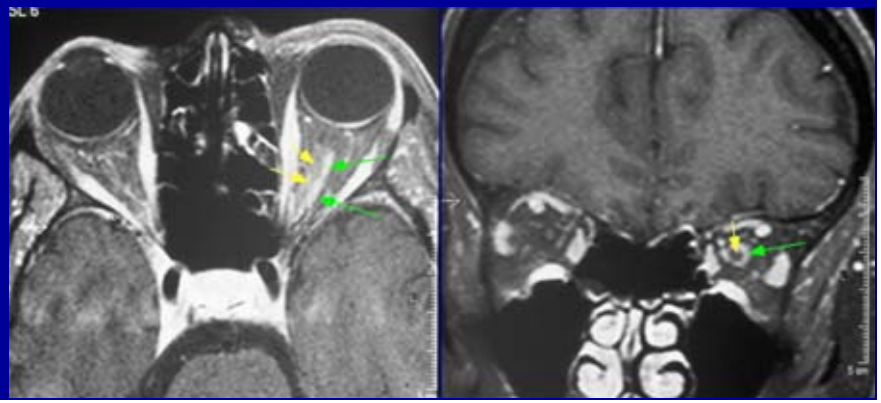
  – Any orbital mass (thyroid) or infiltrative process
  – Any orbital apex lesion
  – Any intracranial mass or infiltrative process compressing the anterior visual pathways

Optic Nerve Sheath Meningioma

- Middle aged women
- Slowly progressive, painless, visual loss
- Often disc swelling (optociliary shunt vessels)
- Tram-track enhancement of sheath on CT or MRI
- Radiation if visual loss

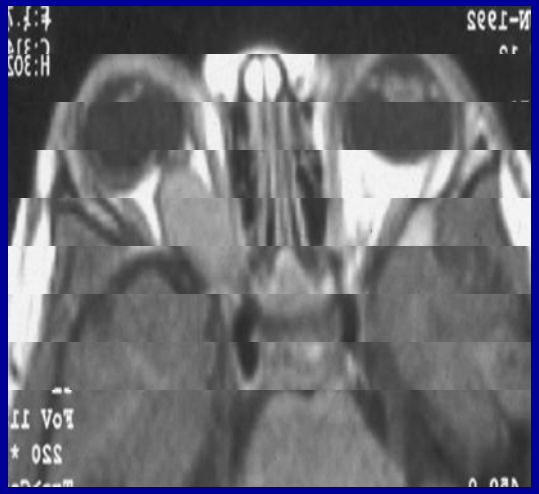




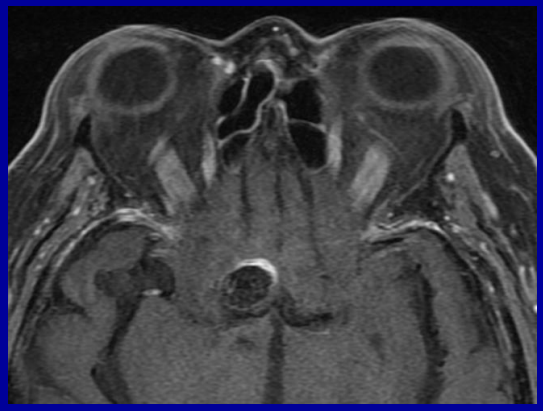


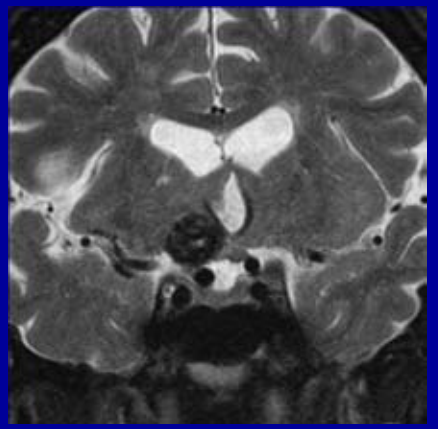
Optic Nerve Glioma

- Common and benign in neurofibromatosis type 1
- Malignant in adults

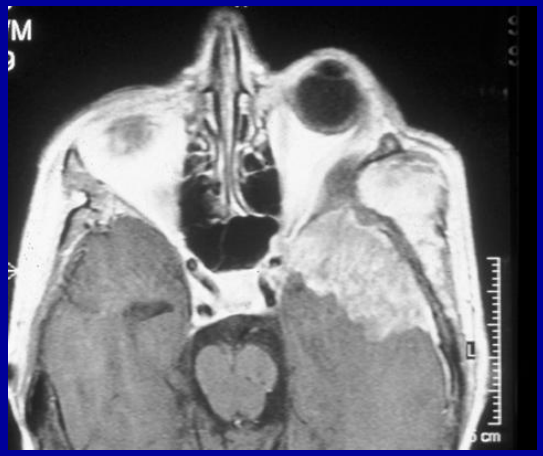


Ophthalmic Artery Aneurysm



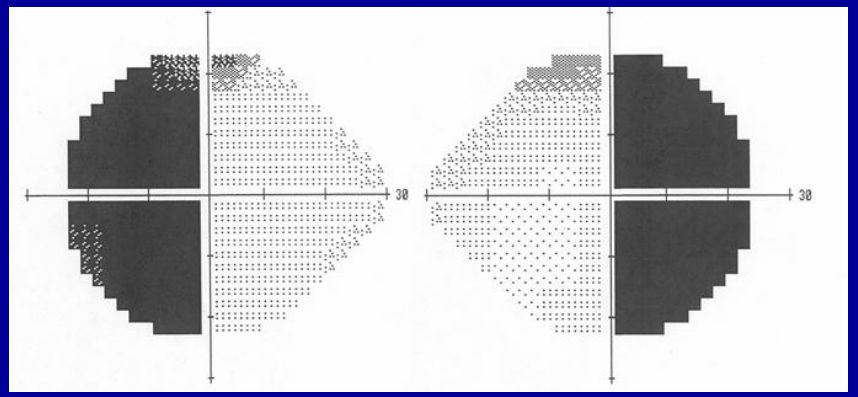


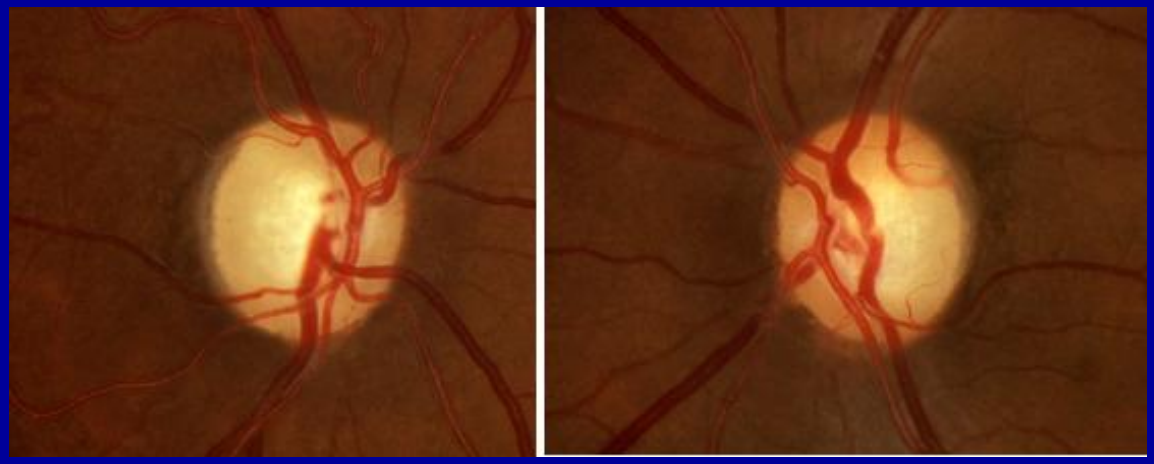
Sphenoid Wing Meningioma

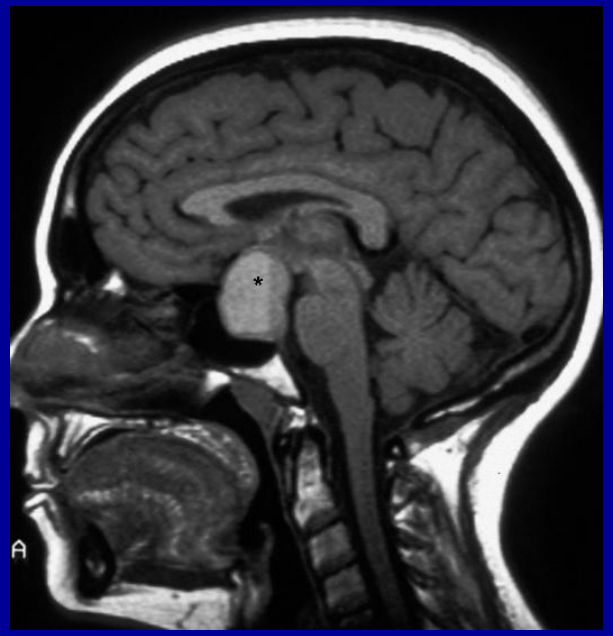


Pituitary Tumors

- Uni- or bilateral progressive visual loss
- Bitemporal VF defect
- Optic atrophy





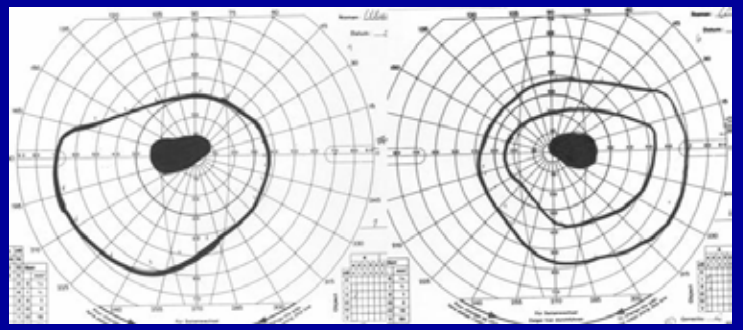


Optic Neuropathy

Causes

- Inflammatory
- Vascular
- Compressive/Infiltrative
- Toxic/Nutritional
- Hereditary
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure

Toxic/Nutritional

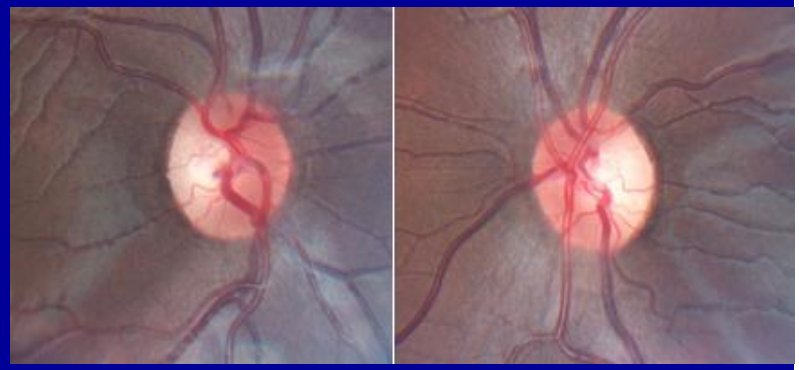


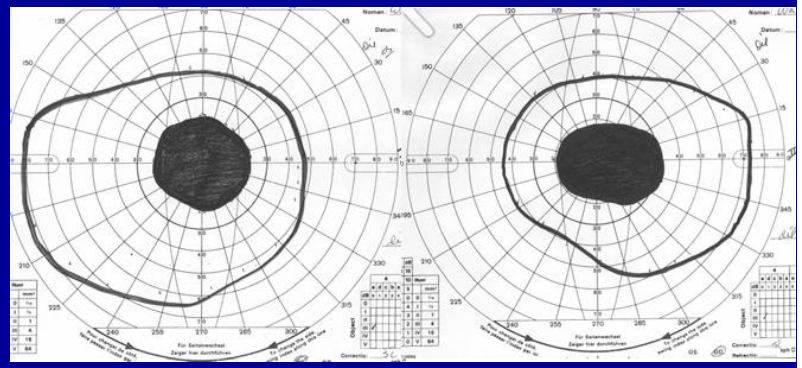
- **Vitamin B12 deficiency**
- **Tobacco (cigars > cigarettes)**

- Progressive, bilateral, symmetric central visual loss
- Dyschromatopsia
- Cecocentral scotomas
- Acutely optic nerve normal or appears swollen
- Temporal optic disc pallor may be delayed

Toxic Optic Neuropathies

- **Ethambutol**
  - Dose-related
  - Early dyschromatopsia
- **Linezolide**
  - Dose-related
  - Mild disc edema
  - Peripheral neuropathy
- **Amiodarone**
  - Disc edema (mimics AION)
- **Methanol and ethylene glycol**





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Hereditary Optic Neuropathies

- **Isolated optic neuropathies:**
  - Leber hereditary optic neuropathy
  - Dominant optic atrophy
- **Optic neuropathies associated with other neurologic and systemic abnormalities:**
  - DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness)
  - Friedreich ataxia
  - Spinocerebellar ataxia
  - Charcot-Marie Tooth (HMSN type VI)

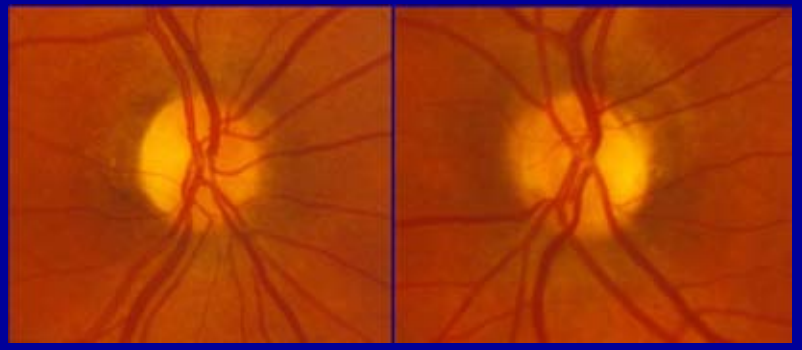
Leber Hereditary Optic Neuropathy

- Bilateral sequential painless central visual loss
- Male >> female, age 15-35
- Hyperemic optic nerve acutely
- Cecocentral scotomas
- Pale optic nerve late
- Poor visual prognosis
- EKG (cardiac conduction abnormalities)

- 3 primary mutations in mitochondrial DNA (11778, 14484, 3460)
- Inherited maternally

Dominant Optic Atrophy (Kjer)

- Bilateral slowly progressive painless visual loss
- Pale optic nerves temporally
- Cecocentral scotomas
- Vision loss relatively moderate
- May have hearing loss



- Autosomal dominant
- Genetic testing (OPA1 gene, chromosome 3)
- Gene codes for mitochondrial protein

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NEUROLOGY 2005;64:940–941

Editorial

HIGH LIGHT

Optic mitochondriopathies

Patrick F. Chinnery, PhD, MRCP; and Philip G. Griffiths, FRCOphth

Hereditary Optic Neuropathies: From the Mitochondria to the Optic Nerve

NANCY J. NEWMAN, MD

• PURPOSE: To review our current knowledge of inhe
ited optic neuropathies.
• DESIGN: Perspective.
• METHODS: Literature review.
• RESULTS: The hereditary optic neuropathies consist
a group of disorders in which optic nerve dysfunctic
figures solely or prominently and direct inheritance
clinically or genetically proven. The most common
these disorders are autosomal dominant optic atroph
(Kjers' disease) and maternally-inherited Leber's here
itary optic neuropathy. Other inherited neurologic an
systemic syndromic diseases will frequently manife
optic neuropathy. A selective vulnerability of the opt
nerve to perturbations in mitochondrial function ma
underlie a final common pathway among these disorder
• CONCLUSIONS: The ophthalmologist should be famili
with the clinical characteristics and diagnosis of the here
itary optic neuropathies. Recent advances in our unde
standing of the underlying pathophysiology of the inherite
optic neuropathies may provide insight into their treatmer
and the treatment of acquired optic nerve disorders. (A
J Ophthalmol 2005;140:517–523. © 2005 by Elsevier In
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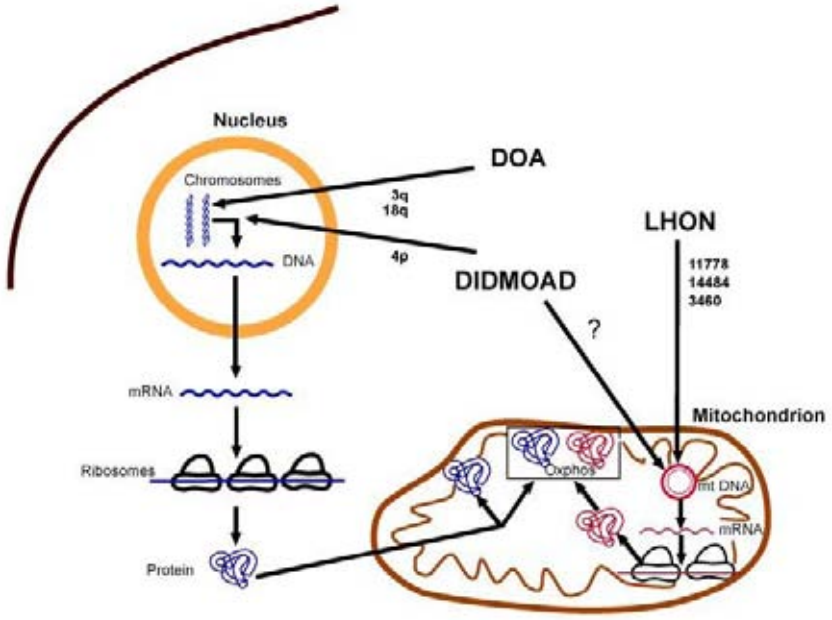


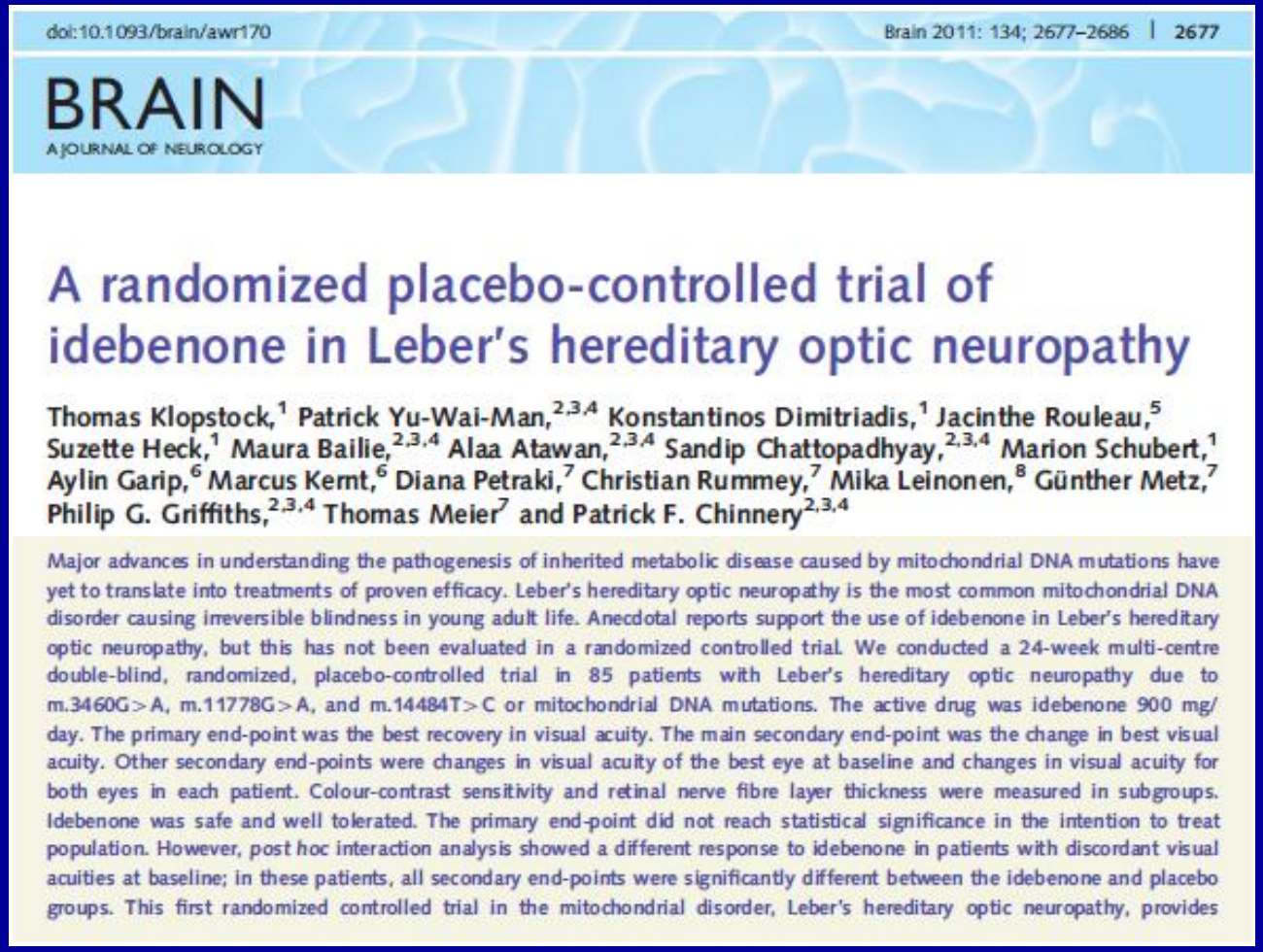
Hereditary Optic Neuropathies

Treatment

- Symptomatic
- Disease-modifying
  - Mitochondrial diseases
  - Hereditary optic neuropathies
- Gene therapy
- Genetic counseling

Leber Hereditary Optic Neuropathy

Treatment – Idebenone?



doi:10.1093/brain/awr170 Brain 2011: 134; 2677–2686 | 2677

BRAIN
A JOURNAL OF NEUROLOGY

A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy

Thomas Klopstock,[1] Patrick Yu-Wai-Man,[2,3,4] Konstantinos Dimitriadis,[1] Jacinthe Rouleau,[5] Suzette Heck,[1] Maura Bailie,[2,3,4] Alaa Atawan,[2,3,4] Sandip Chattopadhyay,[2,3,4] Marion Schubert,[1] Aylin Garip,[6] Marcus Kernt,[6] Diana Petraki,[7] Christian Rummey,[7] Mika Leinonen,[8] Günther Metz,[7] Philip G. Griffiths,[2,3,4] Thomas Meier[7] and Patrick F. Chinnery[2,3,4]

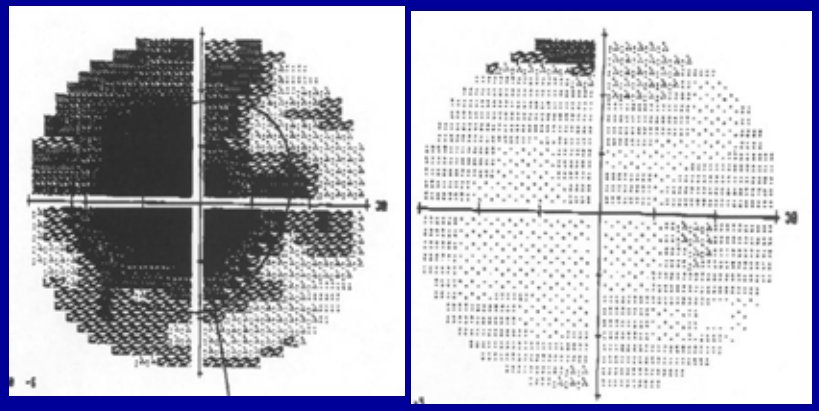
Major advances in understanding the pathogenesis of inherited metabolic disease caused by mitochondrial DNA mutations have yet to translate into treatments of proven efficacy. Leber's hereditary optic neuropathy is the most common mitochondrial DNA disorder causing irreversible blindness in young adult life. Anecdotal reports support the use of idebenone in Leber's hereditary optic neuropathy, but this has not been evaluated in a randomized controlled trial. We conducted a 24-week multi-centre double-blind, randomized, placebo-controlled trial in 85 patients with Leber's hereditary optic neuropathy due to m.3460G>A, m.11778G>A, and m.14484T>C or mitochondrial DNA mutations. The active drug was idebenone 900 mg/day. The primary end-point was the best recovery in visual acuity. The main secondary end-point was the change in best visual acuity. Other secondary end-points were changes in visual acuity of the best eye at baseline and changes in visual acuity for both eyes in each patient. Colour-contrast sensitivity and retinal nerve fibre layer thickness were measured in subgroups. Idebenone was safe and well tolerated. The primary end-point did not reach statistical significance in the intention to treat population. However, *post hoc* interaction analysis showed a different response to idebenone in patients with discordant visual acuities at baseline; in these patients, all secondary end-points were significantly different between the idebenone and placebo groups. This first randomized controlled trial in the mitochondrial disorder, Leber's hereditary optic neuropathy, provides

-Carelli V, La Morgia C, Valentino ML, et al. Idebenone treatment in Leber's hereditary optic neuropathy. Brain 2011;134:1-5/e188

Leber Hereditary Optic Neuropathy

Treatment

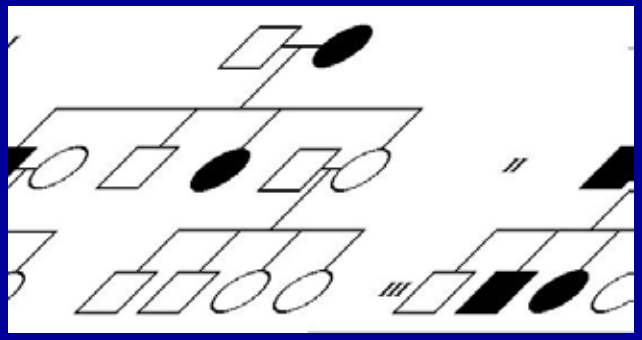
- Ideal “laboratory” for testing treatment efficacy
  - Sequential visual loss: therapeutic window
  - Accessibility via topical or intravitreal route
  - Implications for other optic neuropathies

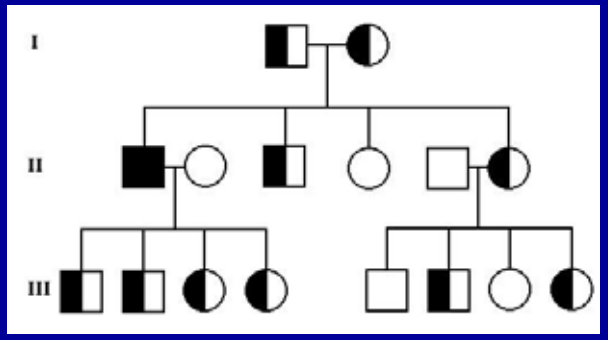


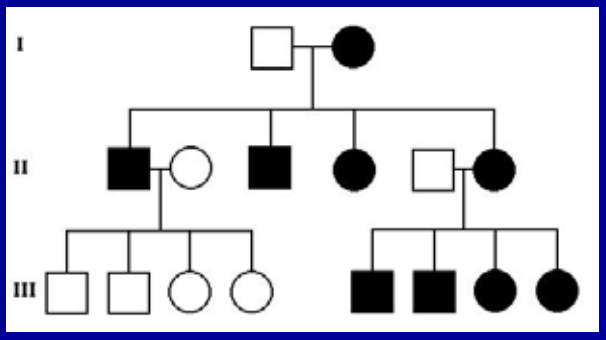
Hereditary Optic Neuropathies

Genetic Counseling

- Autosomal Dominant
- Autosomal Recessive
- Maternal (Mitochondrial)







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