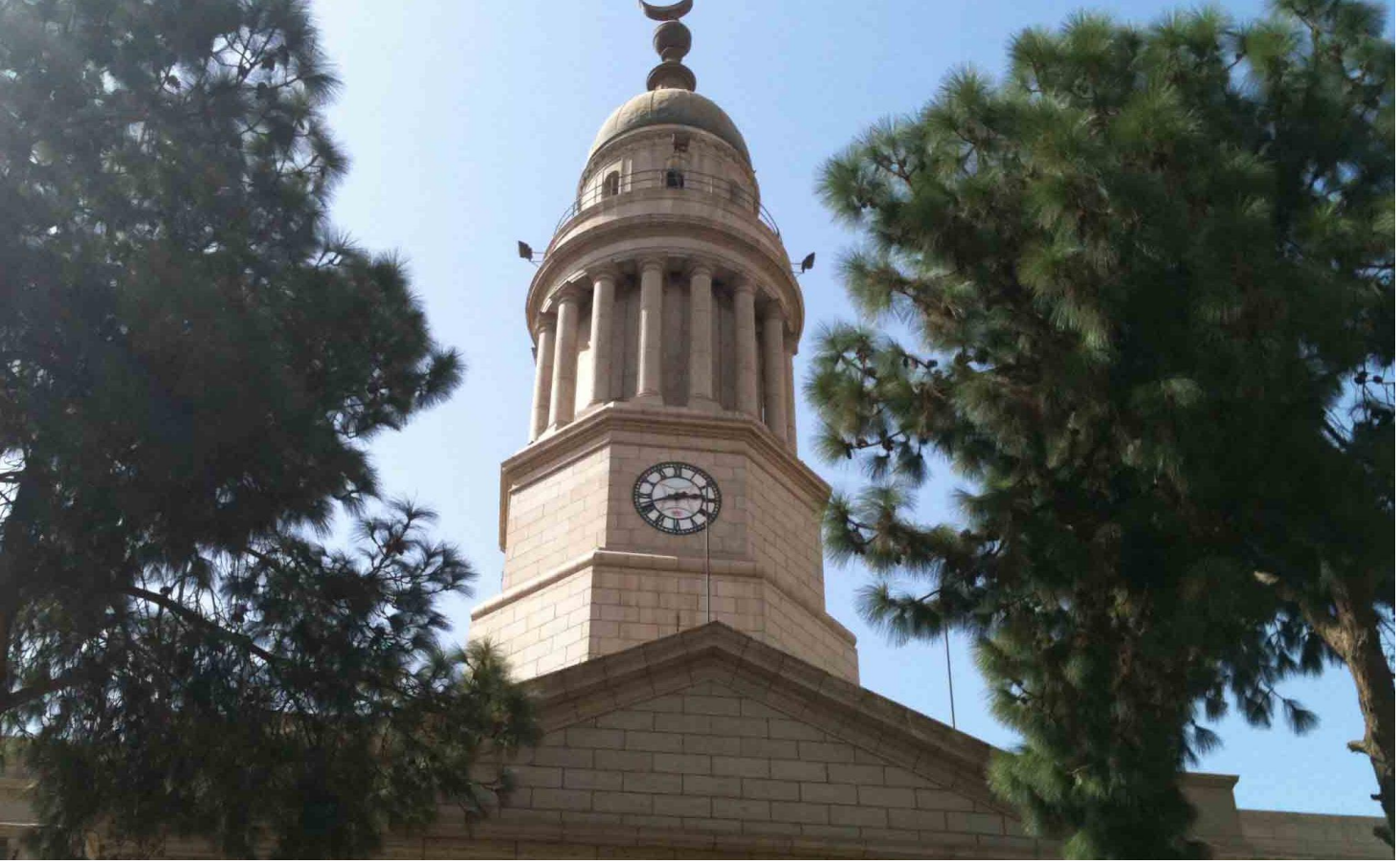

Metabolic Optic Neuropathies

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Metabolic Optic Neuropathies

The three subcategories of metabolic optic neuropathies are

- Heredodegenerative (such as leber's hereditary optic neuropathy).
- Nutritional deficiencies (such as vitamins B12 or folic acid).
- Toxicities (such as ethambutol or cyanide).

Metabolic Optic Neuropathies

TABLE 5-1 Expected Clinical Characteristics of Most Toxic, Nutritional, and Hereditary Optic Neuropathies

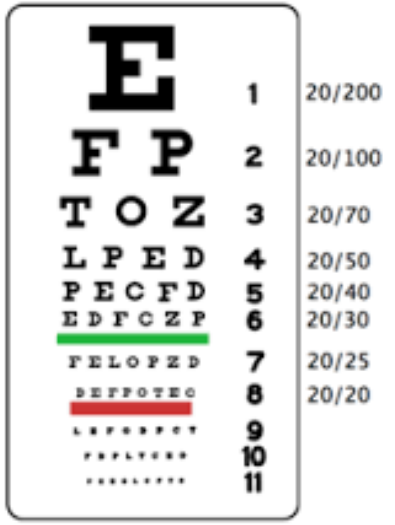
- Gradual, symmetric progression
- Painless onset
- Dyschromatopsia (loss of color perception)
- Central/cecocentral visual field loss
- Visual acuity greater than hand motion
- No optic disc swelling
- No macular symptoms (eg, metamorphopsia, light sensitivity, micropsia)
- Improvement after removing the offending agent or nutritional repletion

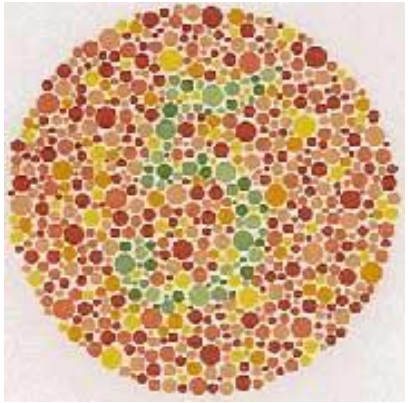
Toxic Optic Neuropathies

Symptoms
Diminution of vision: bilaterally symmetrical, painless, gradually progressive
Dyschromatopsia
Signs
Pupils: sluggish, no RAPD
Optic disc: normal, swollen, or hyperemic in early stages: temporal optic disc pallor later
Visual field defect: centrocaecal scotoma

Toxic Optic Neuropathies

- Visual acuity may vary from minimal reduction to no light perception (NLP) in rare cases.
- Most patients have 20/200 vision or better.
- Color vision should be assessed because dyschromatopsia is a constant feature in these conditions.



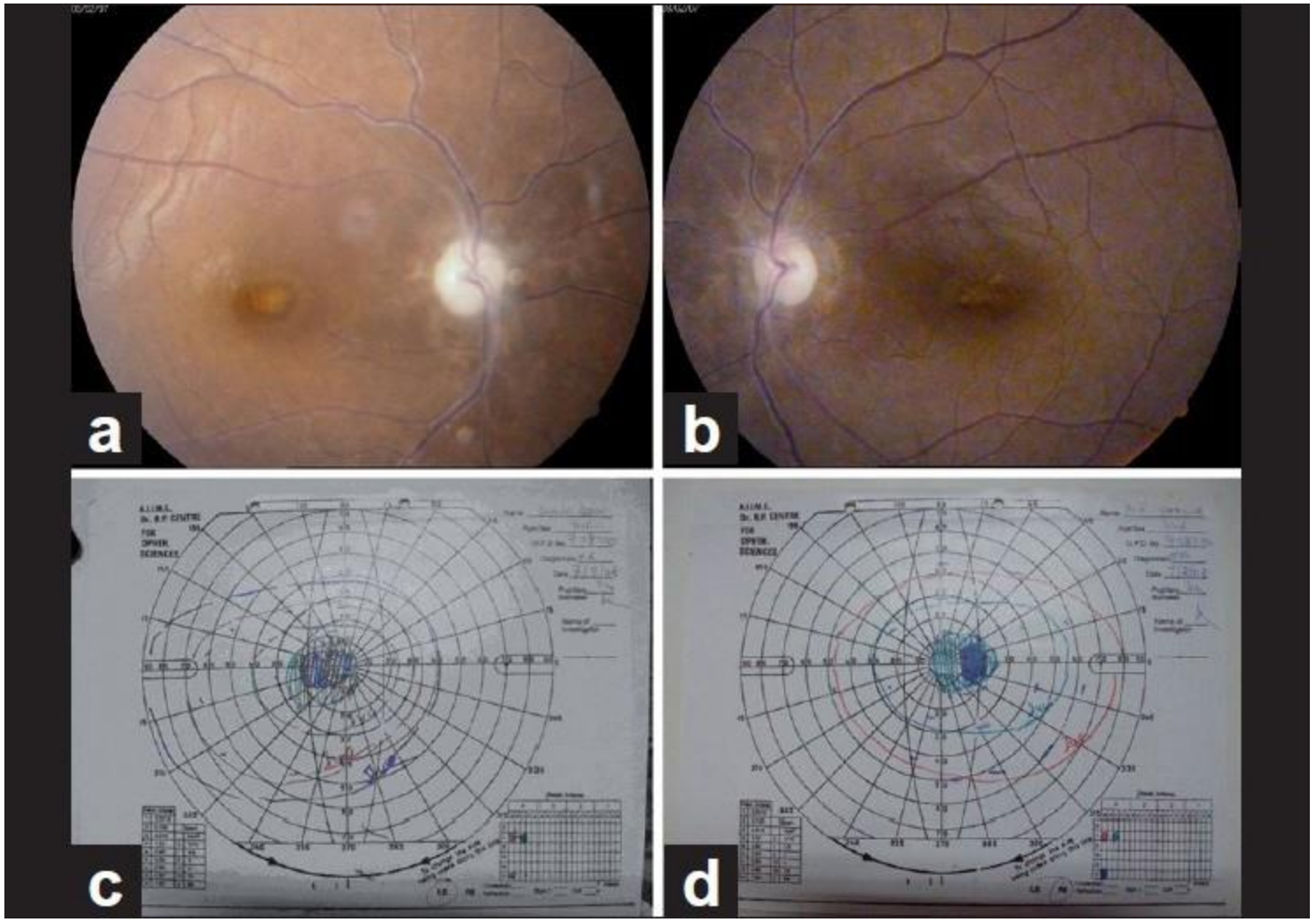


Toxic Optic Neuropathies

- In the early stages of toxic optic neuropathies, most patients also have normal-appearing optic nerves, but disc edema and hyperemia may be seen in some intoxications, especially in acute poisonings.

- Papillomacular bundle loss and optic atrophy develop after a variable interval depending on the responsible toxin.

Toxic Optic Neuropathies



Toxic Optic Neuropathies

Alcohols: Methanol, ethylene glycol (antifreeze)

Antibiotics: Chloramphenicol, sulfonamides, linezolid

Antimalarials: Chloroquine, quinine

Antitubercular drugs: Isoniazid, ethambutol, streptomycin

Antiarrhythmic agents: Digitalis, amiodarone

Anticancer agents: Vincristine, methotrexate

Heavy metals: Lead, mercury, thallium

Others: Carbon monoxide, tobacco

Toxic Optic Neuropathies

- In the workplace, industrial locations, and related to intentional or accidental poisonings, optic nerve toxicity has been reported to result from

✓ Methanol

✓ Ethylene glycol (antifreeze)

✓ Lead

✓ Mercury

✓ Thallium

✓ Carbon monoxide.

Toxic Optic Neuropathies

- Among the many causes of TON, the top 10 toxins include:

Medications

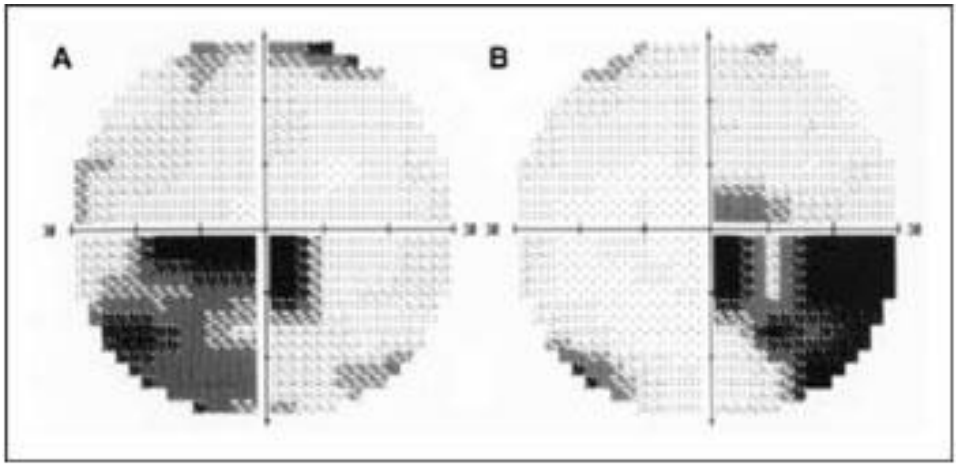
- Ethambutol, rifampin, isoniazid, streptomycin
- Linezolid
- Chloramphenicol
- Isoretinoin
- Cyclosporin

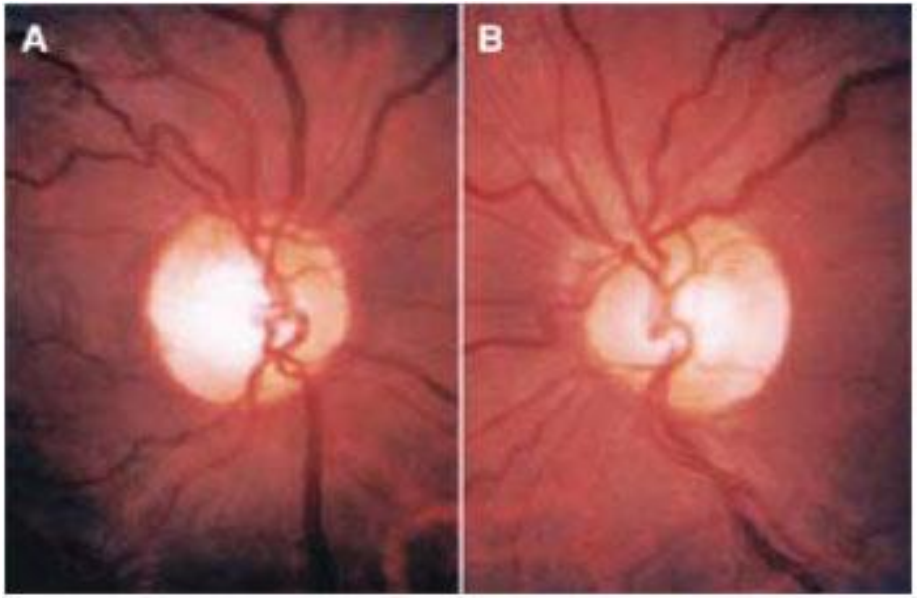
Acute Toxins

- Methanol
- Ethylene glycol

Toxic Optic Neuropathies: Ethambutol

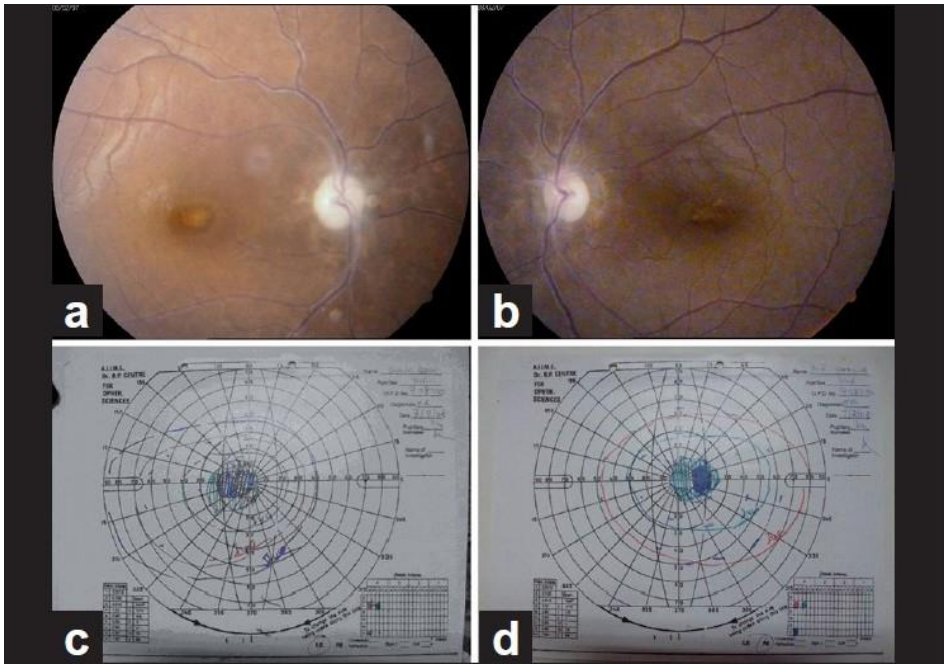
- An anti-TB drug
- Causes a dose-related optic neuropathy
- Usually reversible but occasionally permanent visual damage might occur





Toxic Optic Neuropathies: Ethambutol

- Clinically fundi remain normal initially, thereby rendering early detection challenging.
- Visible atrophy develops later if the drug is not discontinued.

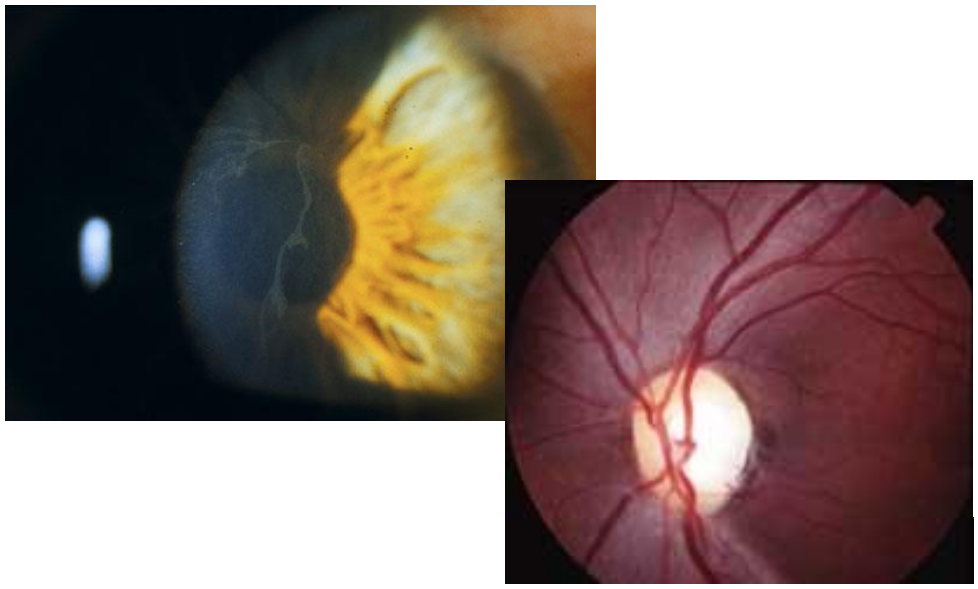


Toxic Optic Neuropathies: Isoniazid

- Vision loss, central or cecocentral scotomas, and acquired dyschromatopsias.
- The color vision deficit tends to be less than that of ethambutol.

Toxic Optic Neuropathies: Amiodarone

- A cardiac arrhythmia drug
- Causes optic neuropathy (mild decreased vision, visual field defects, bilateral optic disc swelling)
- Also causes corneal vortex keratopathy (corneal verticillata) which is whorl-shaped pigmented deposits in the corneal epithelium



Toxic Optic Neuropathies: Digitalis

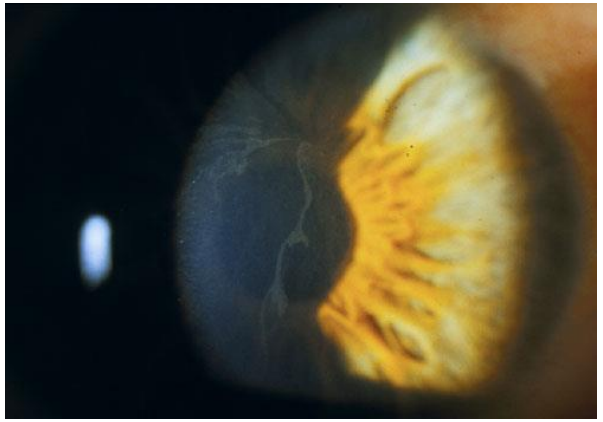
- A cardiac failure drug
- Causes chromatopsia (objects appear yellow) with overdose

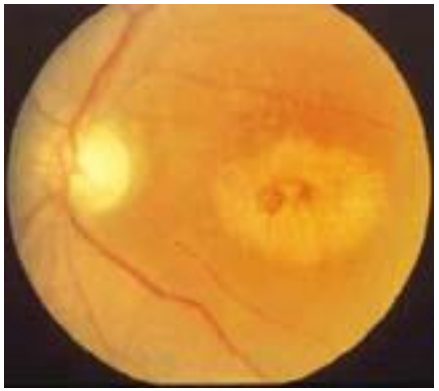
French market scene viewed with no color deficiency

French market scene viewed with xanthopsia

Toxic Optic Neuropathies: Chloroquines

- E.g. chloroquine, hydroxychloroquine
- Used in malaria, rheumatoid arthritis, SLE
- Cause vortex keratopathy (corneal verticillata) which is usually asymptomatic but can present with glare and photophobia
- Also cause retinopathy (bull's eye maculopathy)



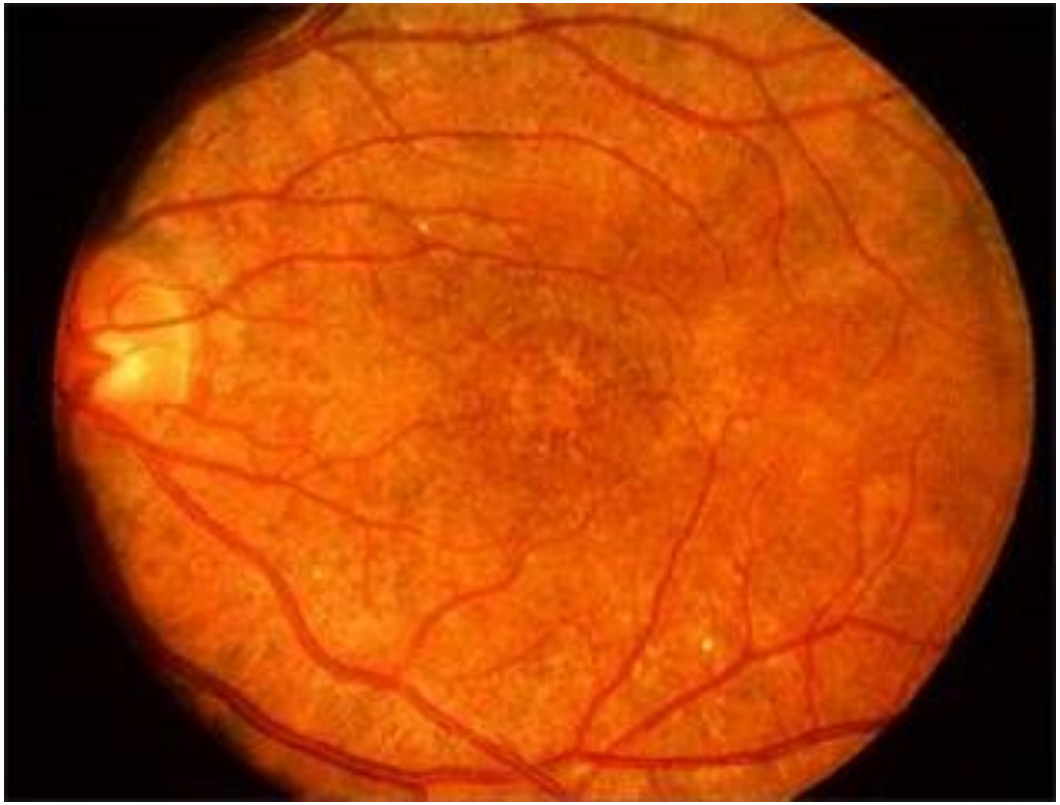


Toxic Optic Neuropathies: Chorpromazine

- A psychiatric drug
- Causes corneal punctate epithelial opacities, lens surface opacities
- Rarely symptomatic
- Reversible with drug discontinuation

Toxic Optic Neuropathies: Thioridazine

- A psychiatric drug
- Causes a pigmentary retinopathy after high dosage



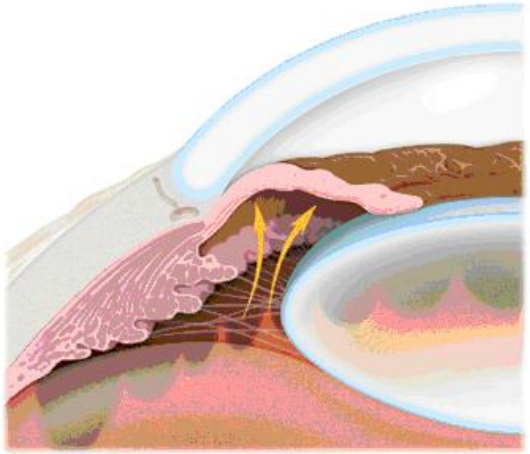
Toxic Optic Neuropathies: Tamoxifen

Used for both prevention and treatment of breast cancer

Toxic optic neuropathy, even at low dosage.

Toxic Optic Neuropathies: Topiramate

- A drug for epilepsy
- Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes).
- Treatment of this type of acute angle-closure glaucoma is by cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug

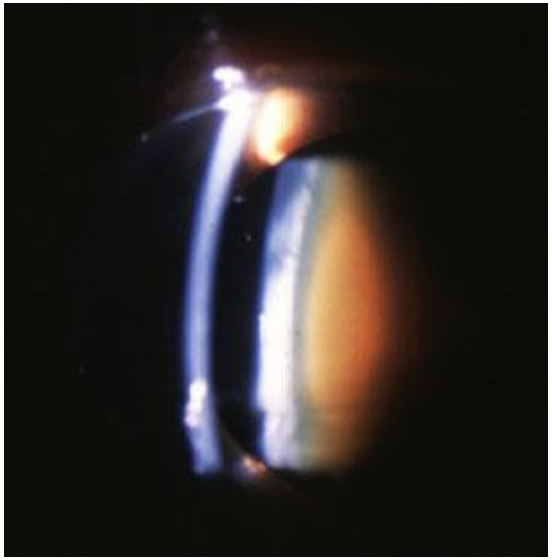


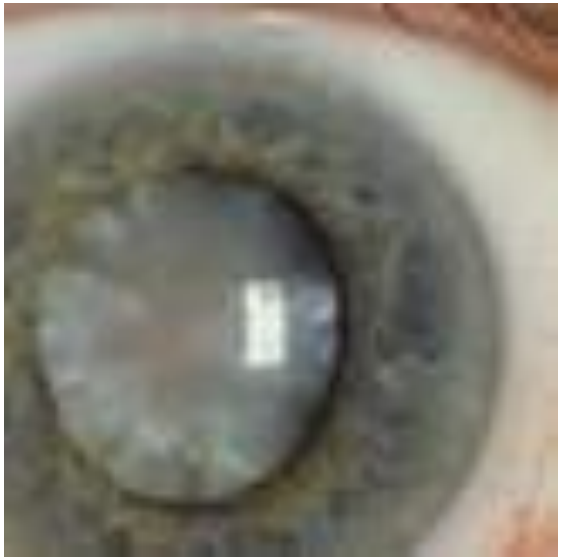
Toxic Optic Neuropathies: Diphenylhydantoin

- AED
- Causes dosage-related cerebellar-vestibular effects:
- Horizontal nystagmus in lateral gaze
- Diplopia, ophthalmoplegia
- Vertigo, ataxia
- Reversible with the discontinuation of the drug

Toxic Optic Neuropathies: Statins

- Cholesterol lowering agents
- E.g. pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin
- Can cause cataract in high dosages specially if used with erythromycin



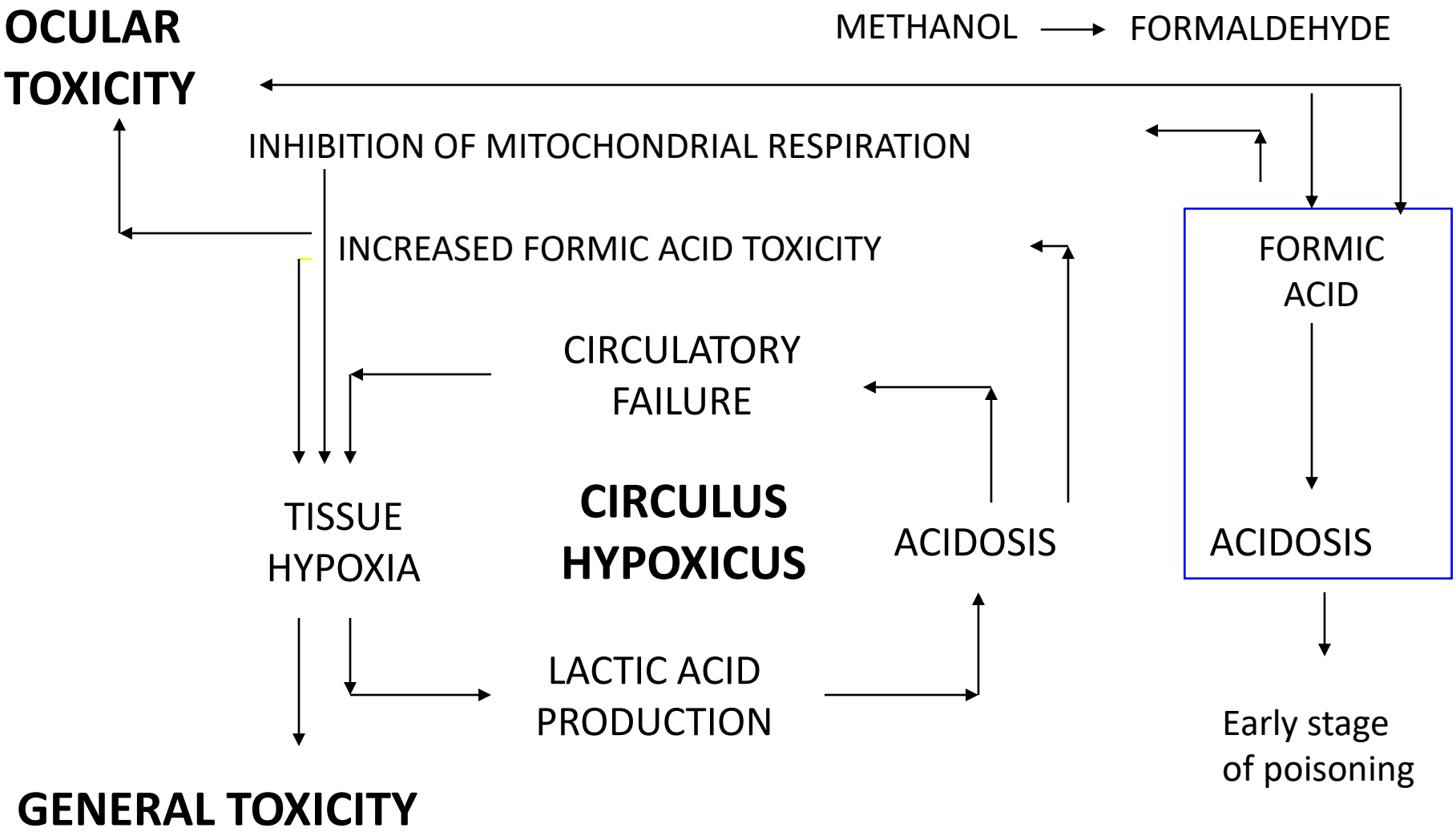


Toxic Optic Neuropathies: Methanol

Alcohol dehydrogenase — ALDEHYDE DEHYDROGENASE

Methanol → Formaldehyde → Formic Acid

Toxic Optic Neuropathies: Methanol



Toxic Optic Neuropathies: Methanol

Methylated spirits is 5% methanol, 95% ethanol.

Acute ingestion presents as ethanol, rather than methanol poisoning.

Methanol intoxication is only a concern if methylated spirits is ingested chronically.

Toxic Optic Neuropathies: Methanol

CNS - Inebriation progressing to coma,Convulsions

Retinal - blurred vision, photophobia, visual Acuity loss, dilated non-reactive pupils, Optic nerve hyperaemic - becoming oedematous

GIT - Nausea, vomiting

Cardiac - tachycardia, hypertension progressing To hypotension and cardiogenic shock

Respiratory - tachypnoea

Toxic Optic Neuropathies: Methanol

Correction of metabolic acidosis

Bicarbonate (aggressive treatment)
Can reverse visual impairment
Reduces movement of formate to the Cns
May require 400 to 600 mmol during first few hours

Rehydration

Folinic acid/folic acid : 50 mg iv every four hours for 24 hours, or while Formic acid may still be accumulating

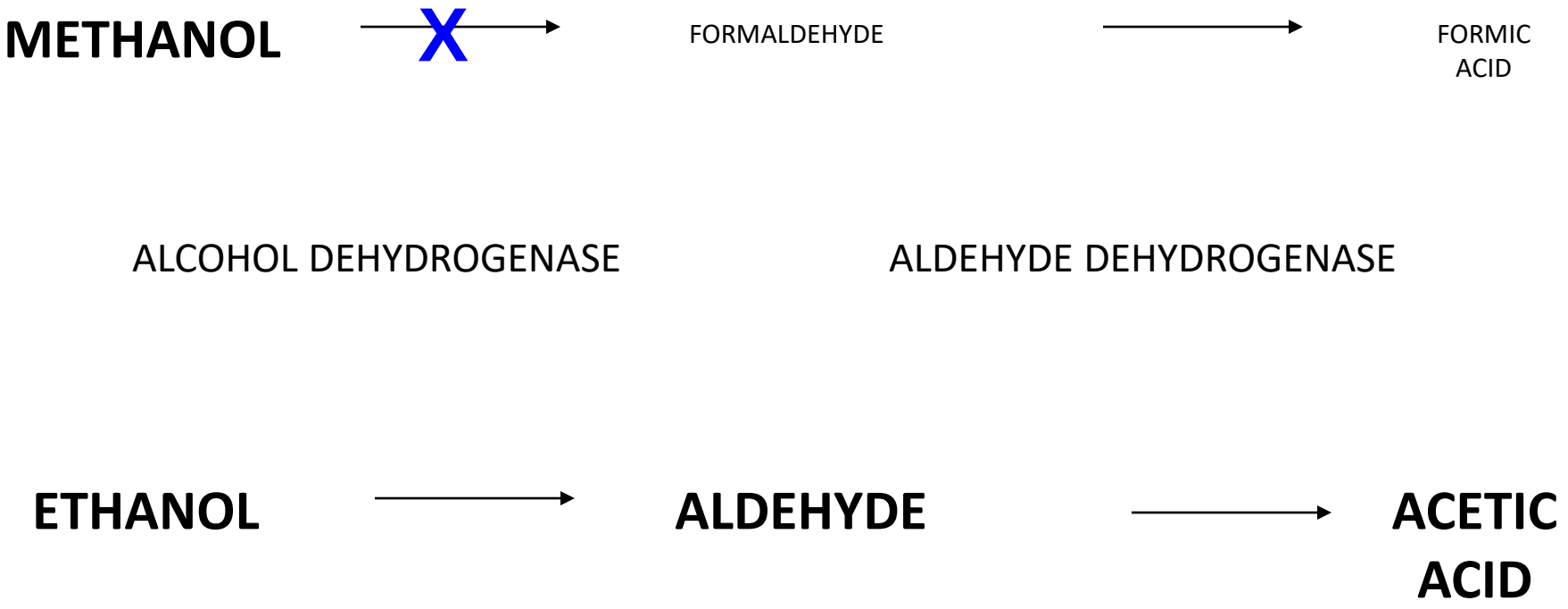
Magnesium
$Mgso_4$ titrated against blood magnesium levels

Toxic Optic Neuropathies: Methanol

ALCOHOL DEHYDROGENASE ALDEHYDE DEHYDROGENASE

METHANOL → FORMALDEHYDE → FORMIC ACID

Toxic Optic Neuropathies: Methanol



Toxic Optic Neuropathies: Methanol

Haemodialysis

Indications

- Any degree of visual impairment
- Severe metabolic acidosis
- Blood methanol level greater than 15 mmol/l (50mg/dl)

Methanol

low molecular weight
Not protein bound
Low volume of distribution

Therefore ideal for haemodialysis

Nutritional Optic Neuropathies

The clinical presentation and basic pathophysiology are similar to TON.

Most often, they present as a non-specific retrobulbar optic neuropathy.

Currently, the treatment is limited to the intensive use of vitamins with variable results in individual cases, and to the implementation of preventive measures, when feasible.

Nutritional Optic Neuropathies

- Optic disc may be normal or slightly hyperemic in the early stages.
- In a small group of patients with hyperemic discs, small splinter hemorrhages on or off the disc.
- Several months to years later , papillomacular bundle dropout and temporal disc pallor, followed by optic atrophy.

Nutritional Optic Neuropathies

Deficiency of

- Thiamine (vitamin B1)
- Cyanocobalamin (vitamin B12)
- Pyridoxine (vitamin B6)
- Niacin (vitamin B3)
- Riboflavin (vitamin B2)
- Folic acid

Nutritional Optic Neuropathies

Tobacco Alcohol Ambylopia (TAA)

- TAA is an old term for a constellation of elements that can lead to a mitochondrial optic neuropathy.
- The classic patient is a man with a history of heavy alcohol and tobacco consumption.

Nutritional Optic Neuropathies

Tobacco Alcohol Ambylopia (TAA)

- Combined nutritional mitochondrial impairment, from vitamin deficiencies (folate and B-12) classically seen in alcoholics, with tobacco-derived products, such as cyanide and ROS.
- It has been suggested that the additive effect of the cyanide toxicity, ROS, and deficiencies of thiamine, riboflavin, pyridoxine, and b12 result in TAA

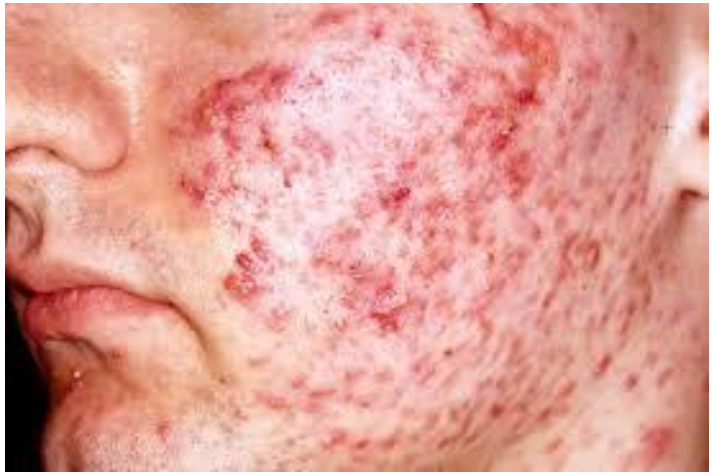
Toxic Optic Neuropathies: Other agents

- Hypovitaminosis A – night blindness (nyctalopia), keratomalacia.

- Hypervitaminosis A – yellow skin and conjunctiva, pseudotumor cerebri (papilledema), retinal hemorrhage.

Toxic Optic Neuropathies: Isotretinoin

- Used in the treatment of severe acne vulgaris,
- Rarely causing toxic optic neuropathy, presenting as decreased night vision and loss of color vision.



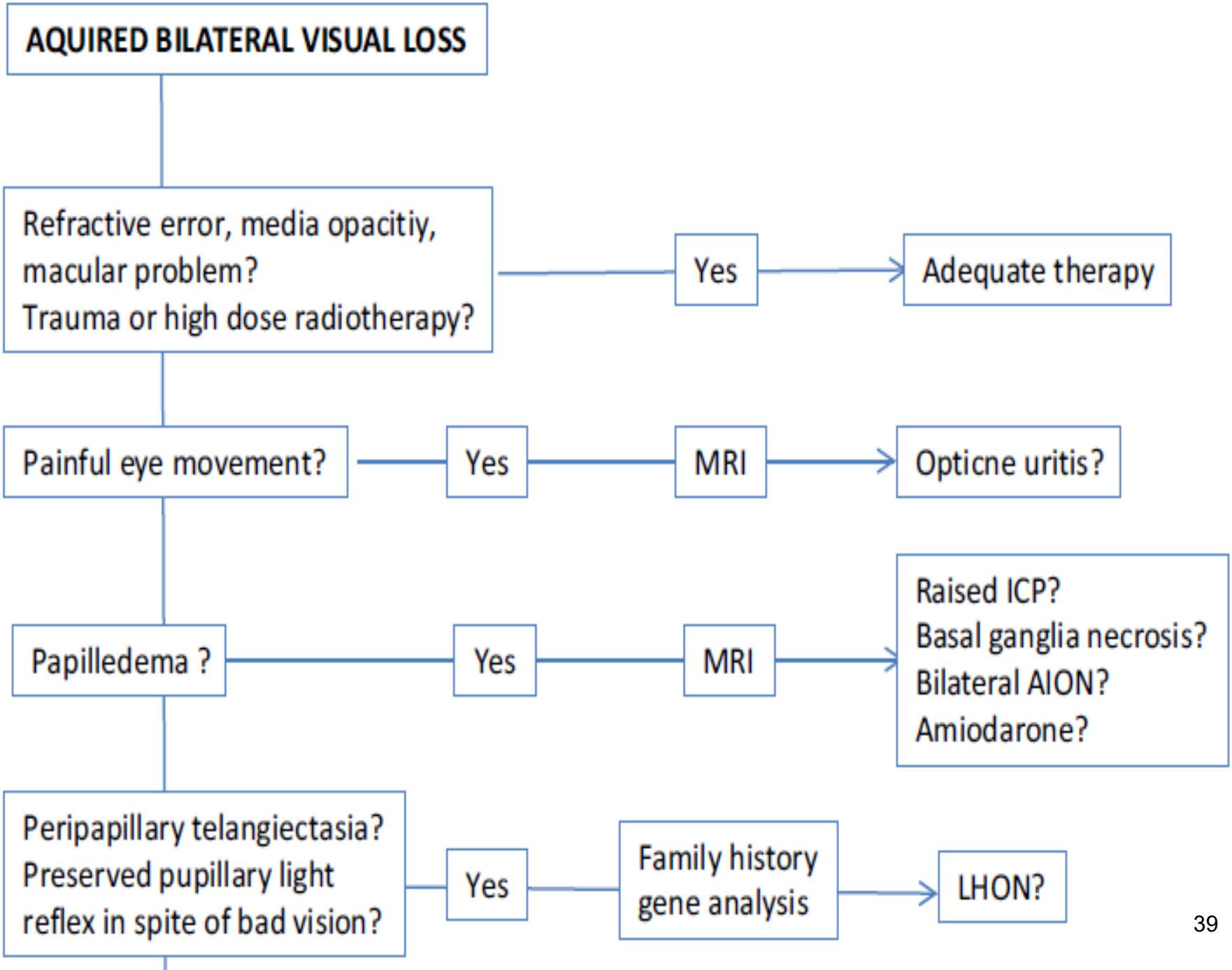
Optic Neuropathies : Causes

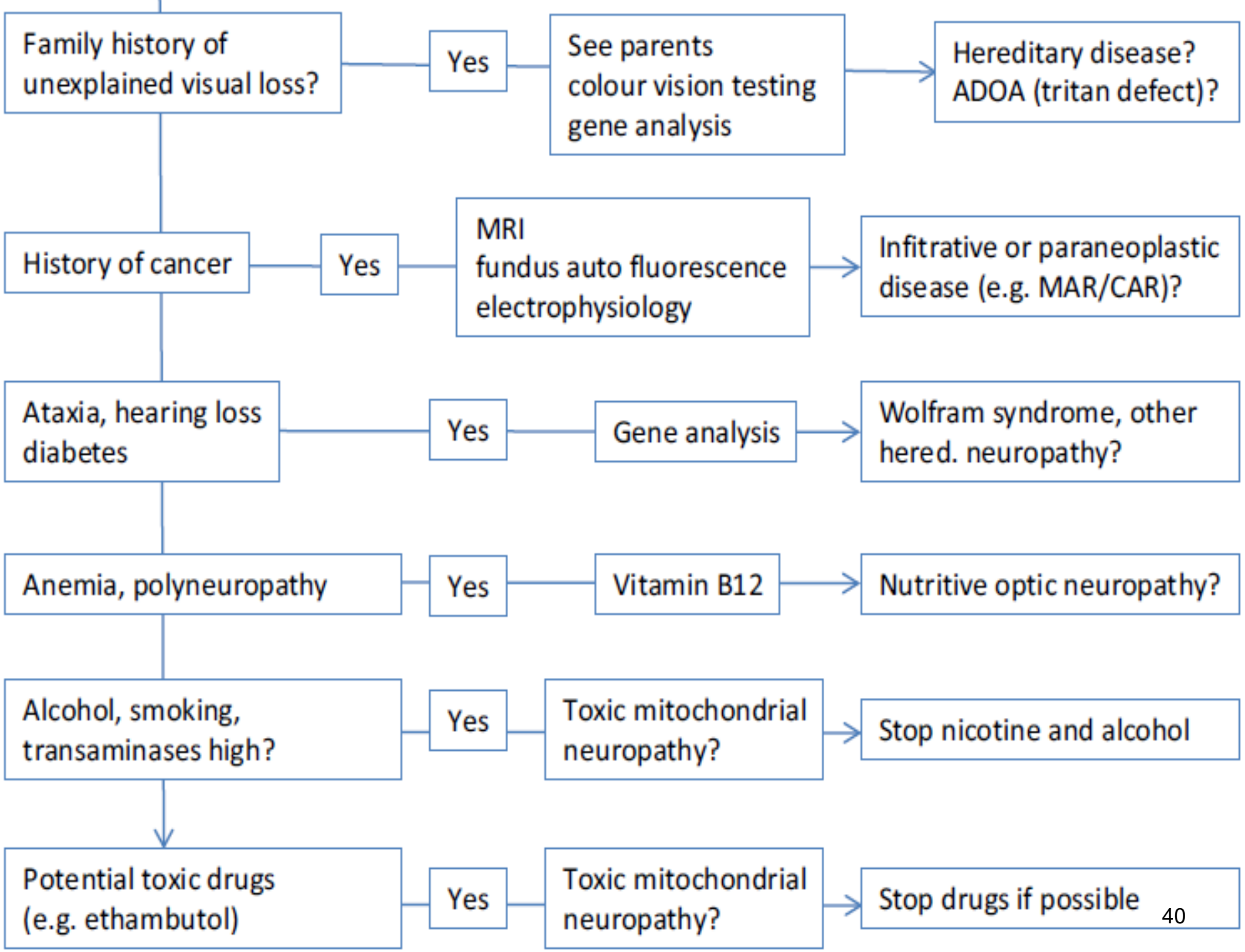
- Demyelinating
- Inflammatory
- Non-arteritic Ischemic
- Arteritic Ischemic
- Traumatic

Rapid onset

- Infiltrative
- Compressive
- Hereditary
- Radiation
- Paraneoplastic
- Toxic/nutritional

Gradual onset


AQUIRED BILATERAL VISUAL LOSS
Refractive error, media opacitiy, macular problem? Trauma or high dose radiotherapy?
Yes
Adequate therapy
Painful eye movement?
Yes
MRI
Opticne uritis?
Papilledema ?
Yes
MRI
Raised ICP? Basal ganglia necrosis? Bilateral AION? Amiodarone?
Peripapillary telangiectasia? Preserved pupillary light reflex in spite of bad vision?
Yes
Family history gene analysis
LHON?

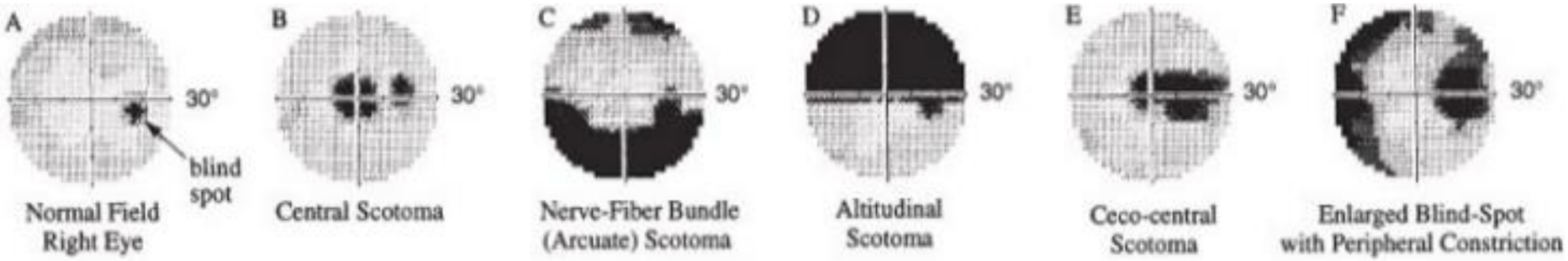

Family history of unexplained visual loss?
Yes
See parents
colour vision testing
gene analysis
Hereditary disease?
ADOA (tritan defect)?
History of cancer
Yes
MRI
fundus auto fluorescence
electrophysiology
Infitrative or paraneoplastic disease (e.g. MAR/CAR)?
Ataxia, hearing loss diabetes
Yes
Gene analysis
Wolfram syndrome, other hered. neuropathy?
Anemia, polyneuropathy
Yes
Vitamin B12
Nutritive optic neuropathy?
Alcohol, smoking, transaminases high?
Yes
Toxic mitochondrial neuropathy?
Stop nicotine and alcohol
Potential toxic drugs (e.g. ethambutol)
Yes
Toxic mitochondrial neuropathy?
Stop drugs if possible

Type of optic neuropathy	Onset	Pattern of visual field loss	Ophthalmoscopic findings	Additional features
Demyelinating	Acute	Central, cecocentral, arcuate	75% normal disc (retrobulbar)	Neurological signs of brain stem (diplopia, ataxia, weakness) or spinal cord involvement (leg weakness, bladder symptoms, paresthesias, abnormal MRI)
Non-arteritic Ischemic	Acute	Arcuate, altitudinal	Swollen disc (usually sectoral) with disc hemorrhages	Crowded (anamalous) disk, systemic vascular risk factors (diabetes, hypertension, hyerlipedemia)
Arteritic Ischemic	Acute	Arcuate	Pallid swelling of the disc	Headache, jaw claudications, transient visual loss or diplopia, myalgias, fever, weight loss, High ESR and CRP
Inflammatory	Acute, sub-acute	Arcuate, central, cecocentral	Swollen disc	Features of auto-immune diseases (skin rash, arthritis, Raynaud's phenomenon), exquisite responsiveness to systemic steroids

Type of optic neuropathy	Onset	Pattern of visual field loss	Ophthalmoscopic findings	Additional features
Hereditary	Chronic (dominant and recessive), acute or subacute (Leber's)	Central, cecocentral	Pale (dominant and recessive) or mildly swollen with peripapillary telengiectatic vessels (Leber's)	Onset in childhood with positive family history, Mitochondrial DNA testing may reveal Leber's mutataion
Traumatic	Acute	Arcaute, central or hemianopic	Normal	Head or facial trauma
Radiation	Acute	Arcuate, hemianopic	Normal	History of radiation to the brain or orbit, MRI may show enhancement of the optic nerve with Gadolinium
Paraneoplastic	Subacute, chronic	Central	Swollen disc	Associated small-cell lung carcinoma, CRMP-5 marker may be positive, paraneoplastic cerebellar syndrome

Type of optic neuropathy	Onset	Pattern of visual field loss	Ophthalmoscopic findings	Additional features
Infiltrative	Acute, subacute	Arcuate, hemianopic	Normal or swollen disc	Systemic malignancy may be present, MRI may show optic nerve or meningeal infiltration
Compressive	Chronic	Arcuate, hemianopic	Normal or pale disc	MRI will show a compressive mass
Toxic/nutritional	Acute, subacute or chronic	Central, cecocentral	Normal or mildly swollen disc	History of drug use (ethambutol, alcohol)

Optic Neuropathy: VF defect



Macula damage

Glaucoma
Optic neuritis

(destroy axon of optic disc)

Turkish scimitar

Ischemic optic neuropathy

Horizontal meridian

Optic neuritis
Toxic metabolic nutrition

macula

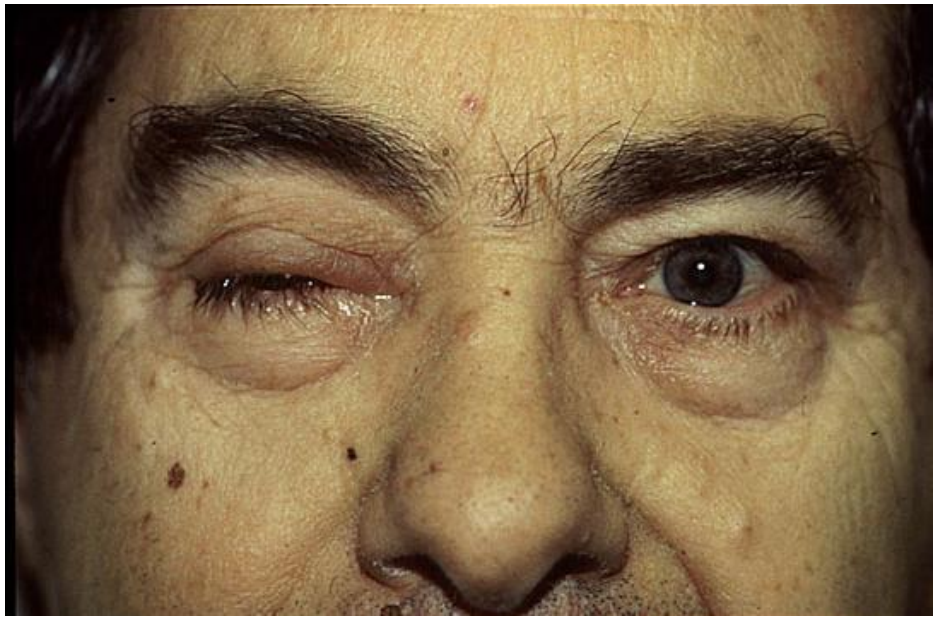
Metabolic ophthalmoplegia

Clinical diagnosis

Metabolic ophthalmoplegia: DM

- Isolated ex ophthalmolpegia
- Combined ex ophthalmolpegia

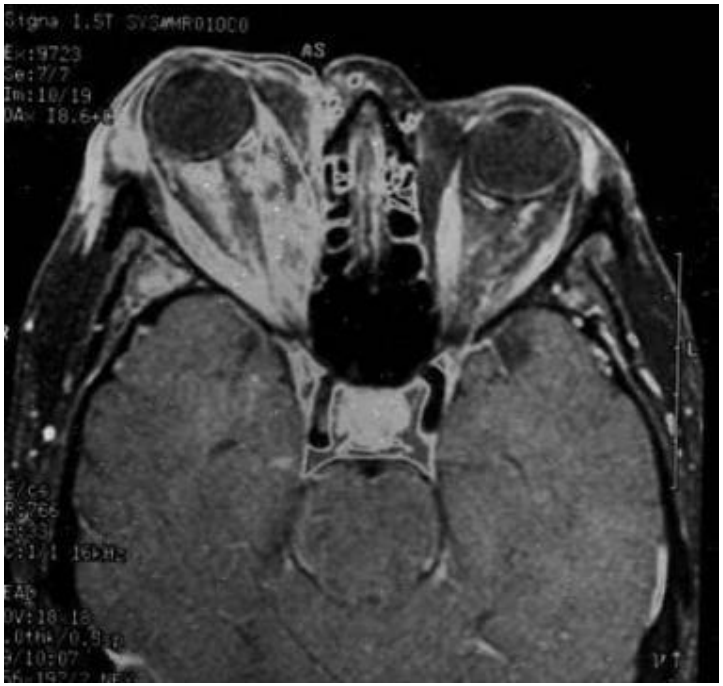
- Retinopathy
- Cataract



Metabolic ophthalmoplegia: Thyroid ophthalmopathy

- Thyroid eye disease and can present as asymmetric progressive visual loss.

- This will require prompt therapy (orbital radiation, orbital decompression, high-dose systemic steroids).



Metabolic ophthalmoplegia: WE

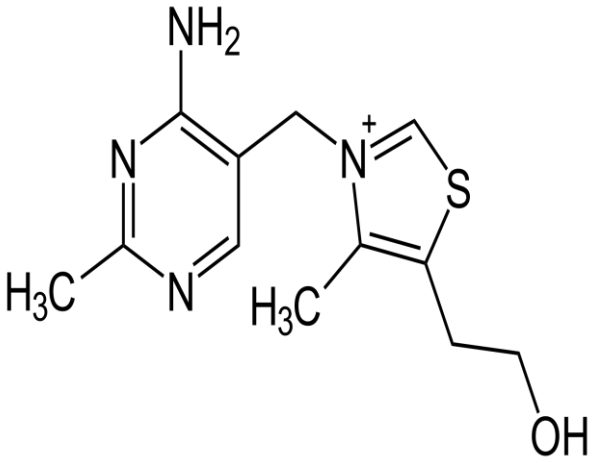
Symptoms of WE & KP

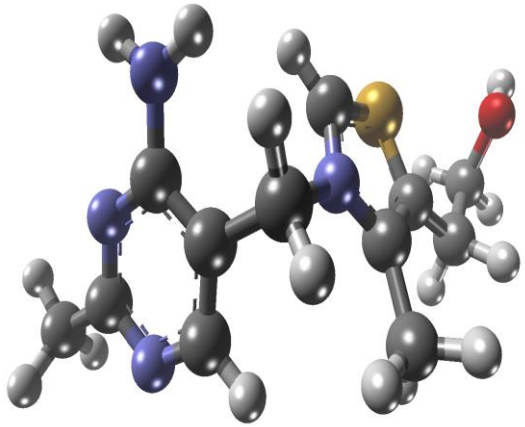
WERNICKE	KORSAKOFF
Confusion	Anterograde amnesia
Ataxia	Retrograde amnesia
Ophthalmoplegia/Nystagmus	Confabulation

Metabolic ophthalmoplegia: WE

Recommended Dietary Thiamine

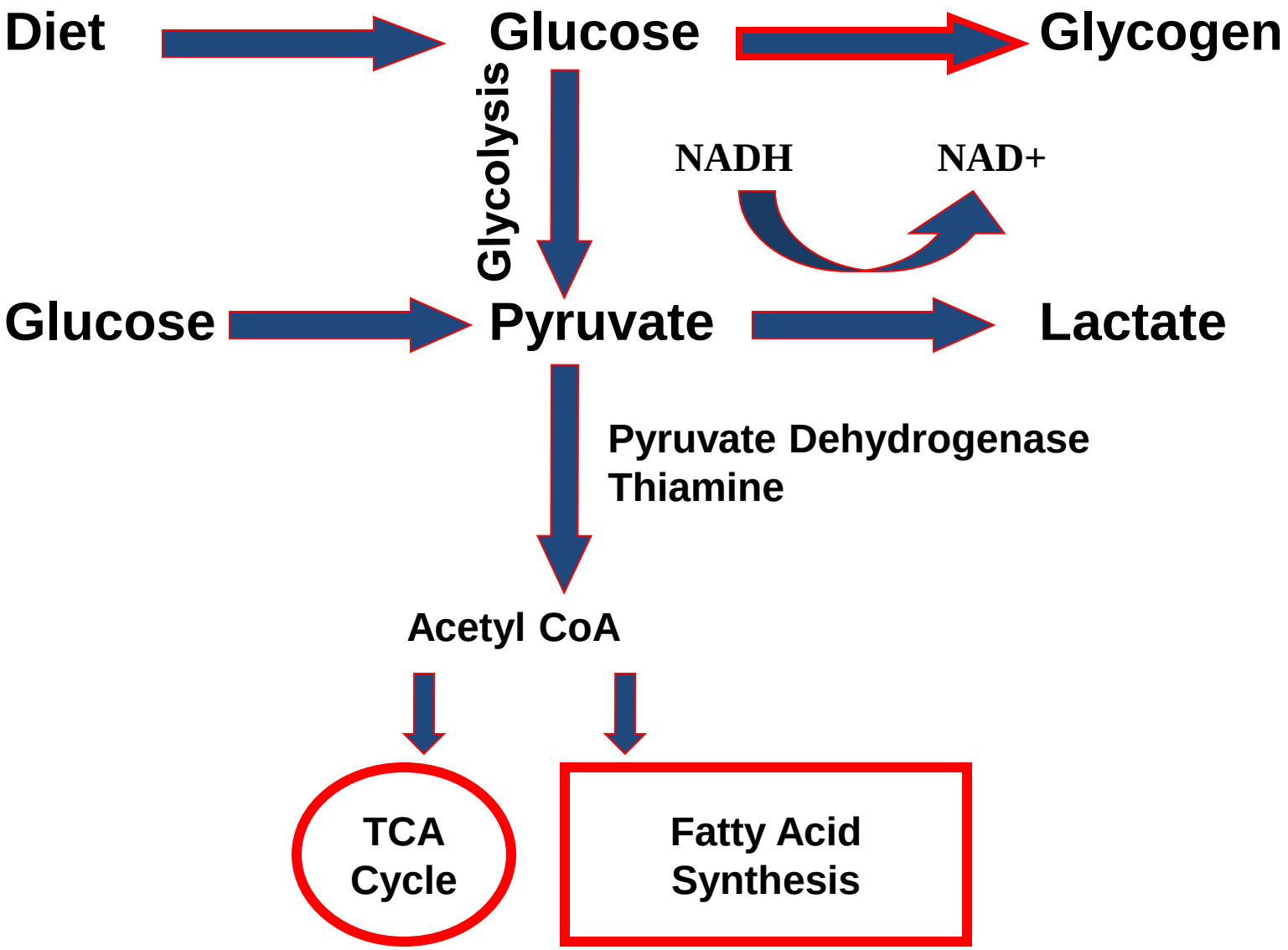
- 1 mg/day
- 0.5 mg/1000kcal
- Thiamine depletion develops within 18 days in thiamine free diet.
- Normally: organ meats, yeast, eggs, green leafy vegetables.
- Poorly absorbed in the presence of ethanol.



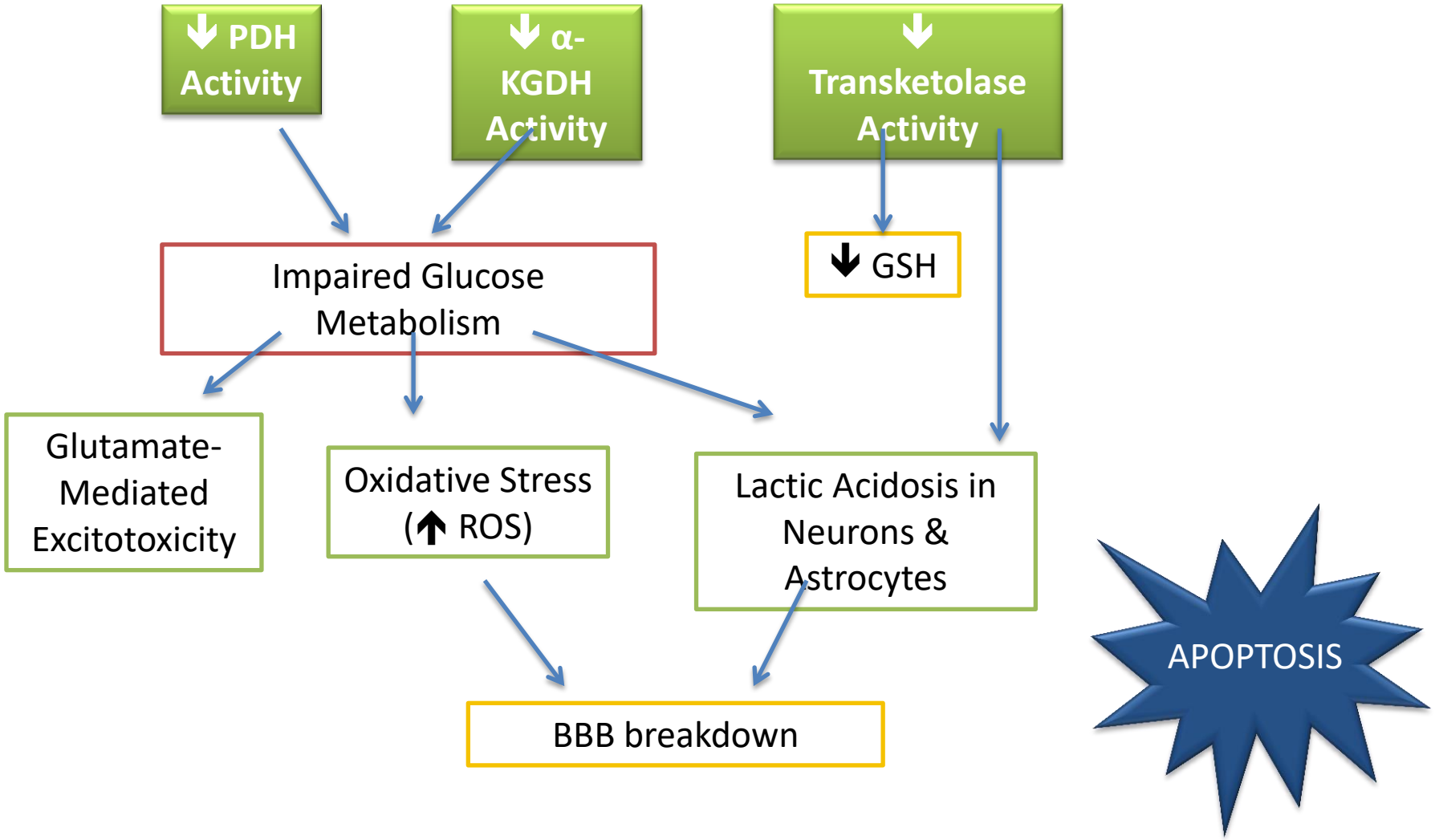


http://www.pharmacopeia.cn/v29240/images/v29240/g-812.gif

The Role of Pyruvate in Intermediary Metabolism



Metabolic ophthalmoplegia: WE



Metabolic ophthalmoplegia: WE

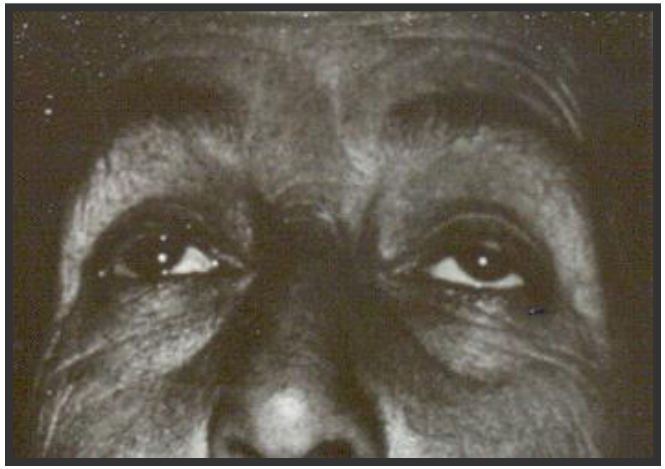
Ophthalmologic Findings

Horizontal nystagmus (85%)

Bilateral VI nerve palsy (54%)

Conjugate gaze palsy (45%)

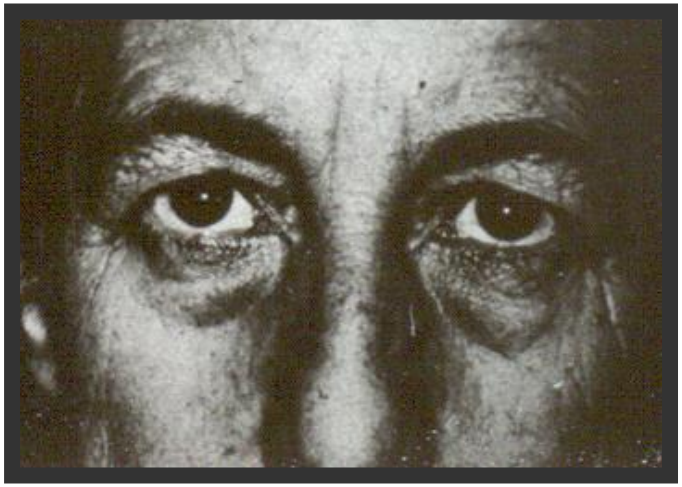
Metabolic ophthalmoplegia: WE



Ophthalmoplegia

Bilateral ptosis (L > R)

Palsy of upward conjugate gaze.



Day 3

Ptosis has disappeared.

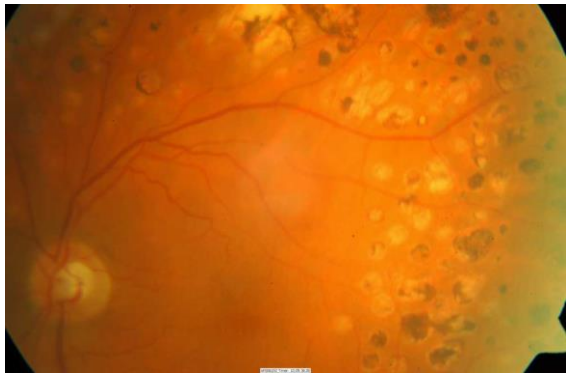
Gaze palsy has improved.

When Should Thiamine Be Given?

- Before glucose?
- After glucose?
- With glucose?

Metabolic ophthalmoplegia: KSS

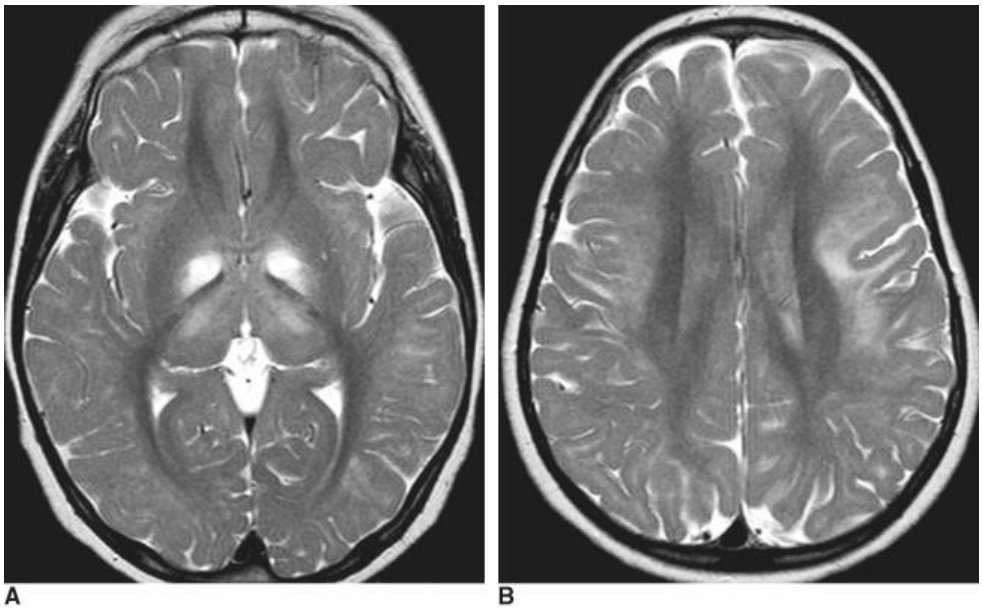
- Insidiously progressive disease with CPEO before the age of 20.



- **Symptoms/Clinical Features:**
  - Mitochondrial Myopathy (proximal weakness
  - CPEO
  - retinal degeneration (pigmentary retinopathy)
  - cardiac conduction defects (heart block)
  - Ataxia/cerebellar syndrome
  - Other symptoms include small stature, deafness, dementia, delayed puberty, and endocrine dysfunction

Metabolic ophthalmoplegia: KSS

- Laboratory: Increased CSF protein and lactate
- MRI- bilateral subcortical white matter T2 hyperintensities involving basal ganglia, thalamus, and brainstem
- Pathology: ragged red fibers



Metabolic ophthalmoplegia: CPEO

Ptosis

Symmetric ophthalmoplegia with relative sparing of downgaze

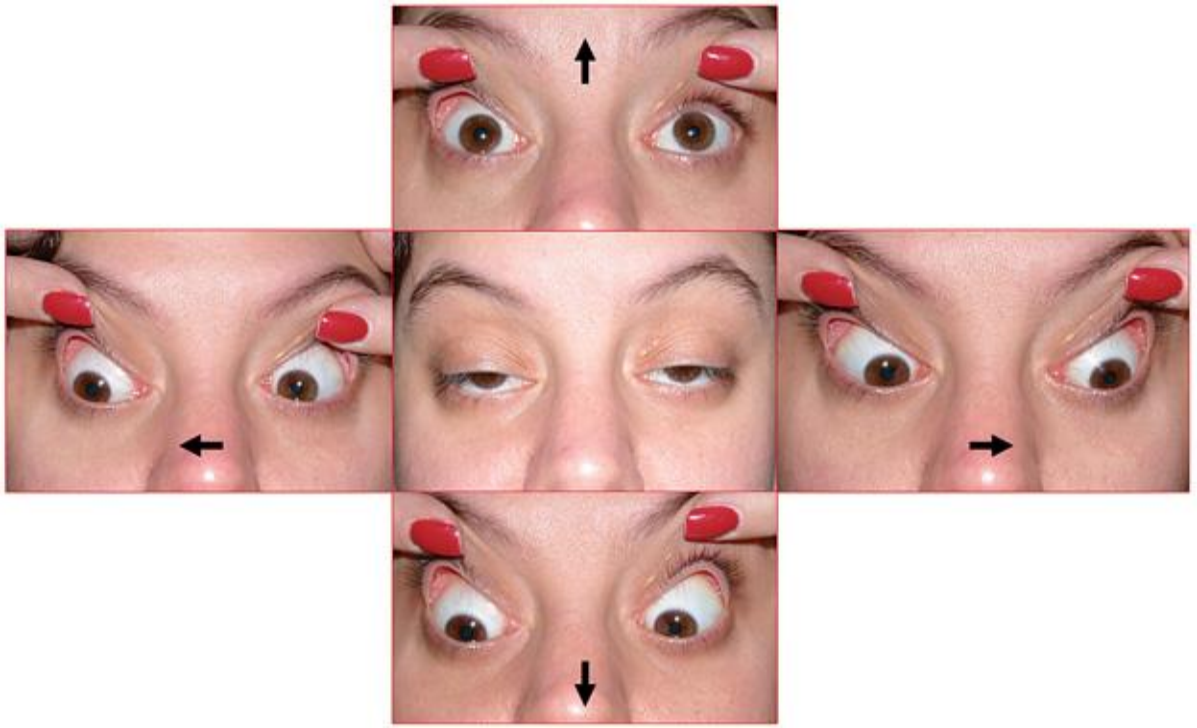
Facial weakness, frontalis

Dysarthria

Sparing of ciliary and iris muscles

Common presentation of any mitochondrial myopathy

Can be isolated or part of KSS

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THANK YOU