



Toxic retinopathy : Etiology, electrophysiology screening

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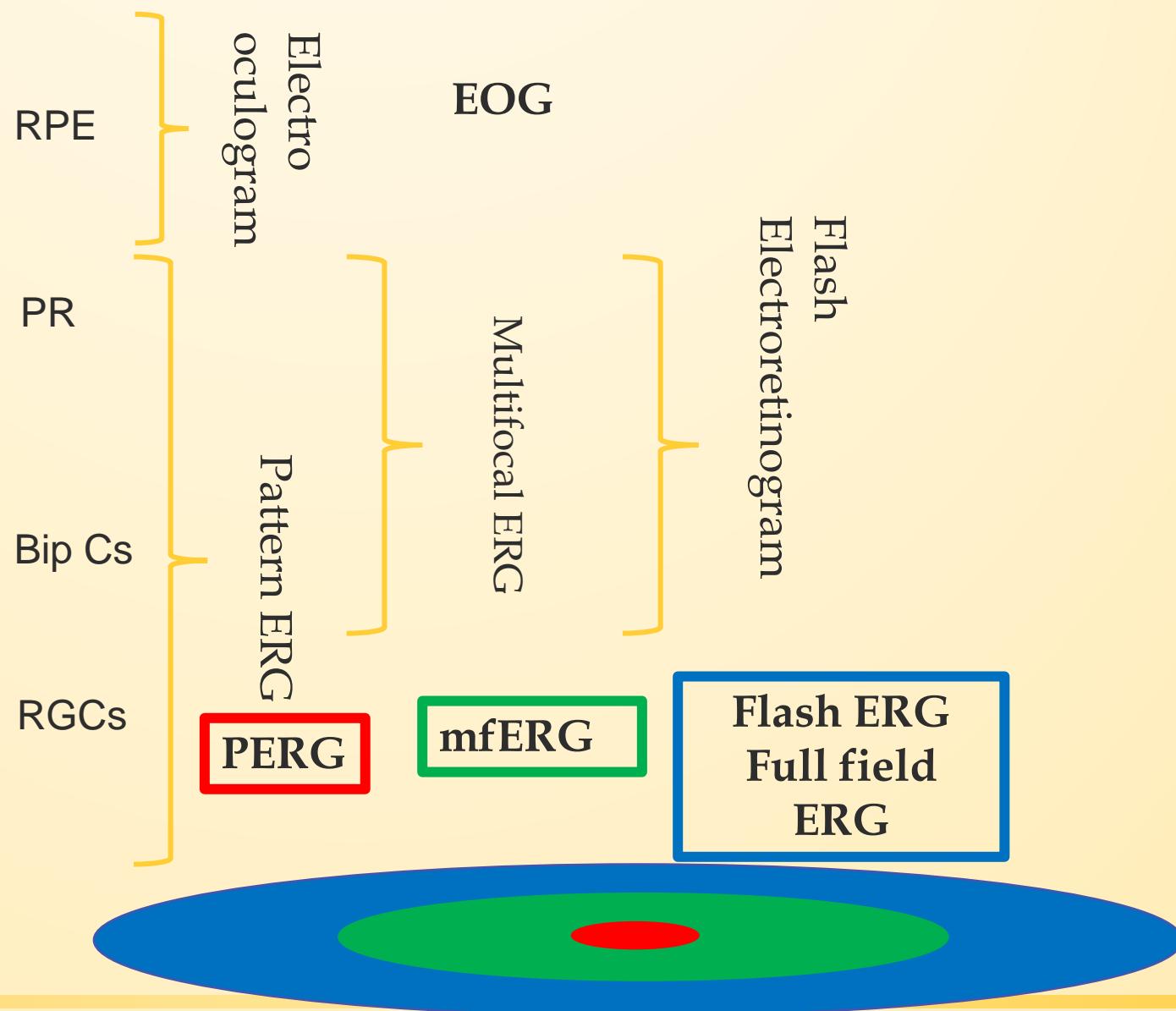
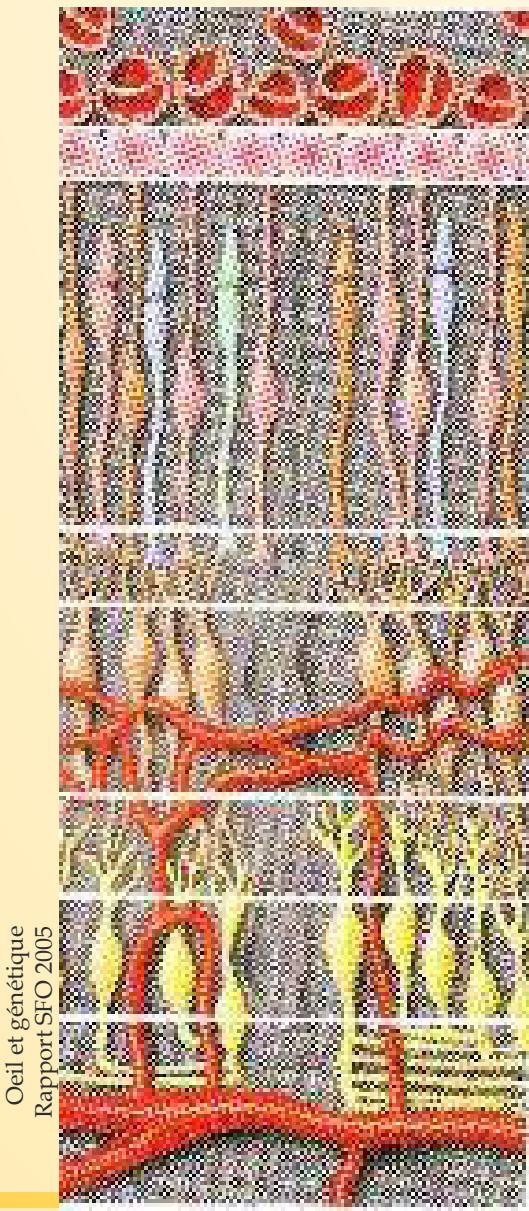
Société libanaise d'ophtalmologie 2018



Toxic retinopathies

- Etiology : medecines, industrial toxics, recreative drugs
- Electrophysiology :
 - Physiopathology
 - Diagnosis
- Screening :
 - Easy to perform and to undergo
 - Widely accessible, *feasible*
 - Cheap for the society
 - *Benefit-risk, cost-benefit*

Electrophysiology : physiopathology, localisation of toxicity



Etiology : Classification on involved elements



VASCULOPATHY

Aminoglycosides
Amiodarone
Cisplatine, carmustine
Interferon
Oral contraceptives
Phenylpropanolamine
Quinine sulfate
Rye Ergot derivatives
Talc

Excluded

RETINAL PIGMENT EPITHELIUM (RPE)

- Chloroquine,
- Hydroxychloroquine
- Deferoxamine
- Quinine sulfate
- Vigabatrin

Chlorpromazine
Cimetidine, carbamazepine

Ecstasy
Fluorodiazepam

MEK inhibitors

Ergotamine

Excluded

PHOTORECEPTORS (PR)

- Chloroquine,
- Hydroxychloroquine
- IPDE5 : sildenafil
- Ethambutol
- Ocriplasmine
- Poppers

Excluded

Etiology : Classification on involved elements



VASCULOPATHY

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• RETINAL PIGMENT EPITHELIUM (RPE)

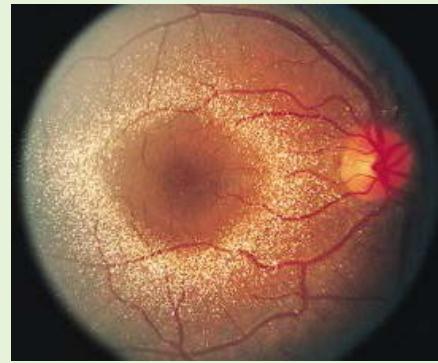
- **Chloroquine,**
- Hydroxychloroquine
- Deferoxamine
- Quinine sulfate
- Vigabatrin
 - Chlorpromazine
 - Cisplatine, Vincristine
 - Clofazimine
 - Phenothiazines
 - Thioridazine
 - MEK inhibitors

• PHOTORECEPTORS (PR)

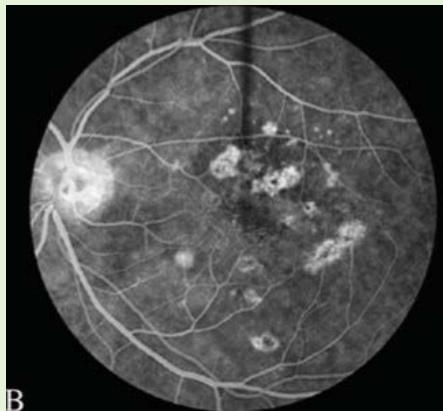
- **Chloroquine,**
- Hydroxychloroquine
- IPDE5 : sildenafil
- Ethambutol
- Ocriplasmine
- **Poppers**

▪ Cristalline Retinopathy

- Tamoxifen
- Canthaxanthin



- Talc
- Nitrofurantoin
- Methoxyflurane*
- Ritonavir (HIV)



ERG

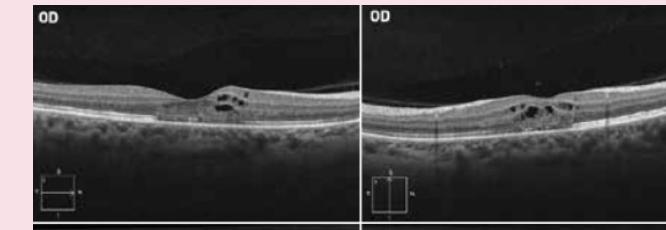
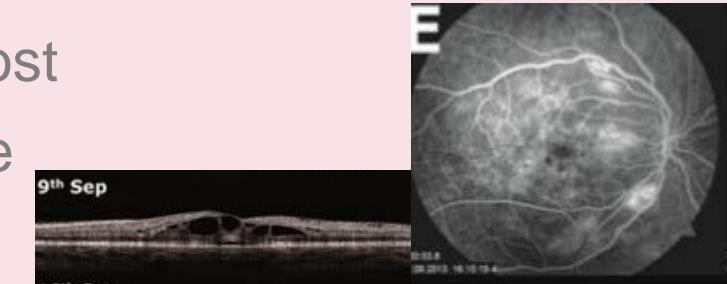
mfERG

PERG

More
Predictive
sensitive

▪ Macular œdema

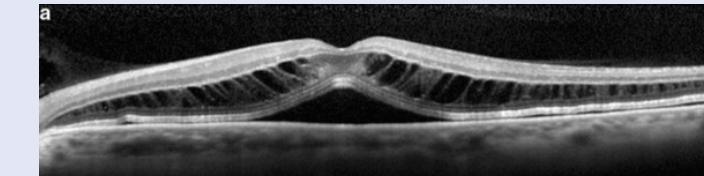
- Glaucoma treatment
 - latanoprost
- Epinephrine
- Fingolimod
- Nicotin acid (Vit B3)
- Taxanes : Doxetaxel, Paclitaxel



- Tamoxifen

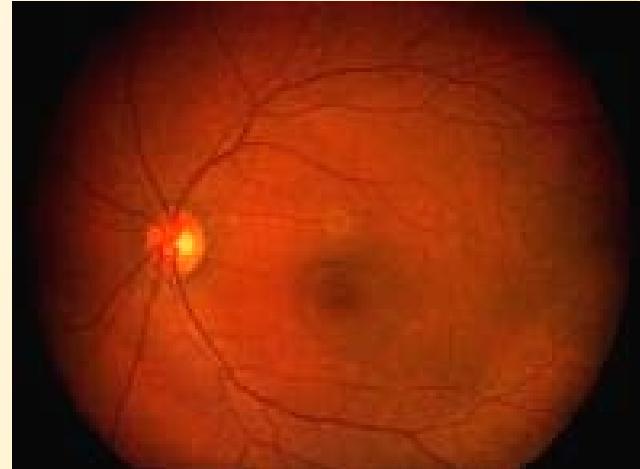
• DSR

- Corticoids
- cefuroxime
- Anti MEK

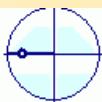
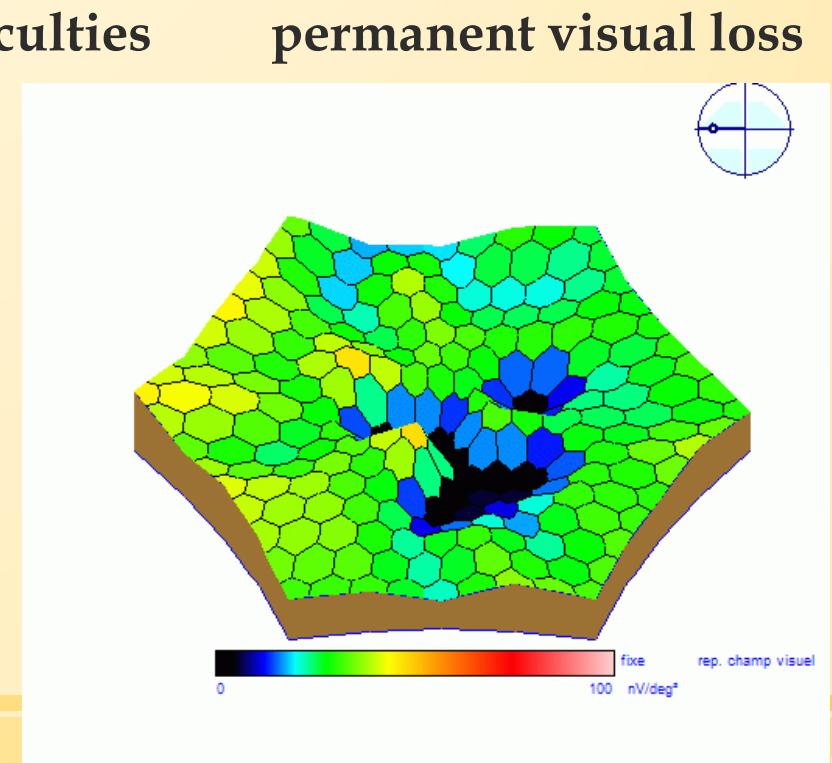
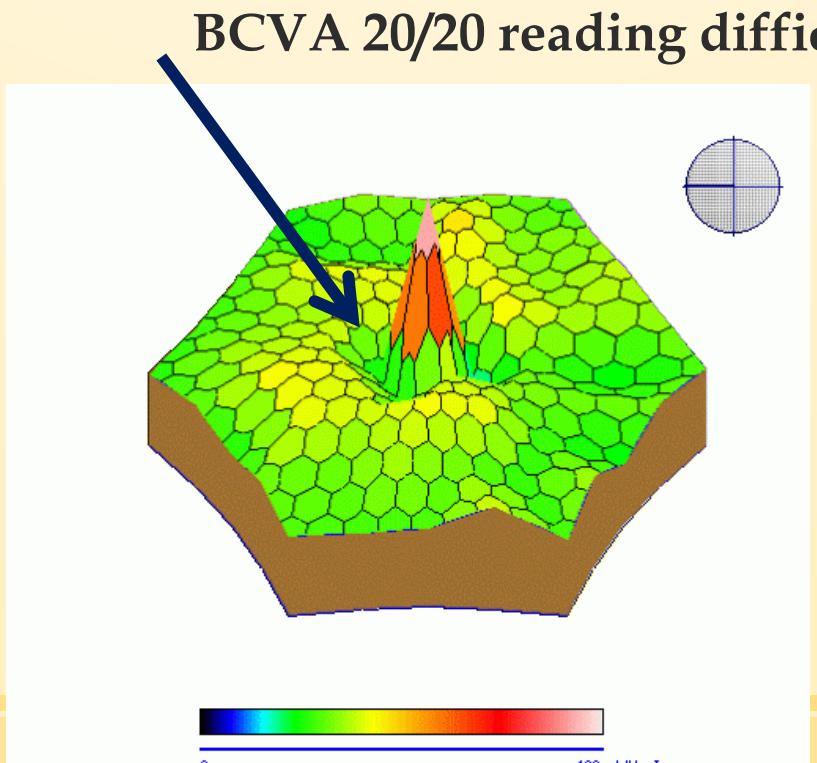
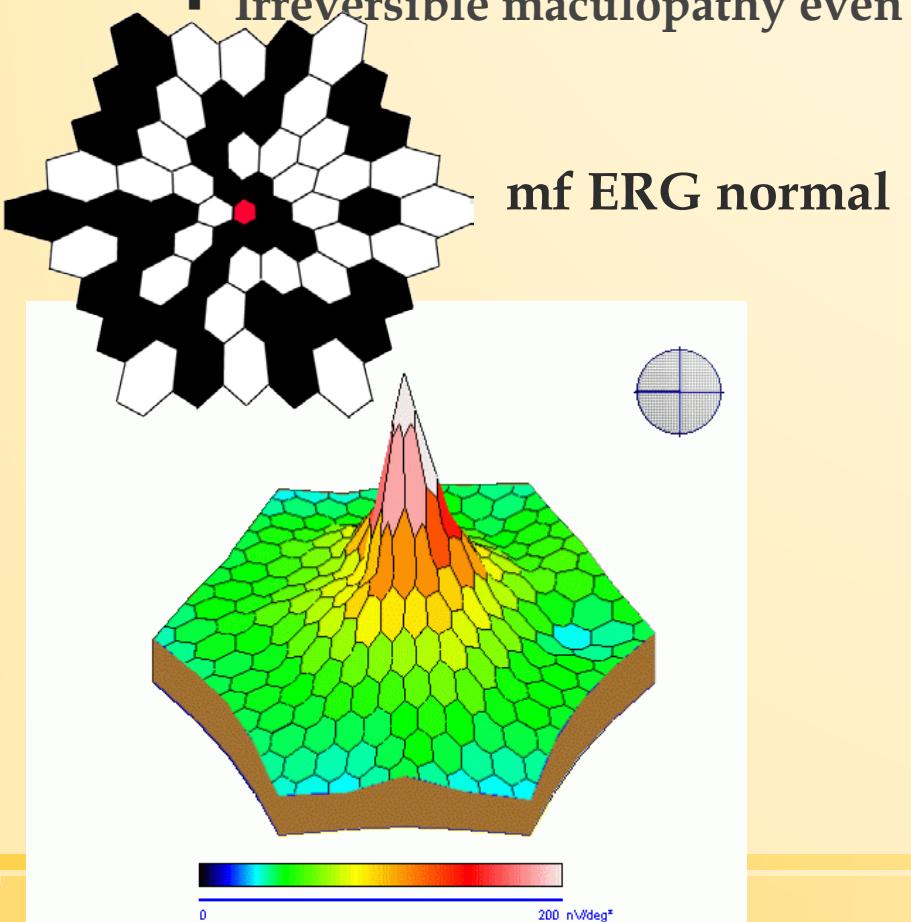


Hydroxychloroquine (HCQ), Chloroquine (CQ)

- Chronic rheumatic diseases (Lupus, RA..) Malaria
- Anatomy : RPE in central 2-10°, Photoreceptors
- Physiopathology : affinity melan cells, interindividual variability 25-100%
 - Irreversible maculopathy even worsening, diagnosis at early stage reversible

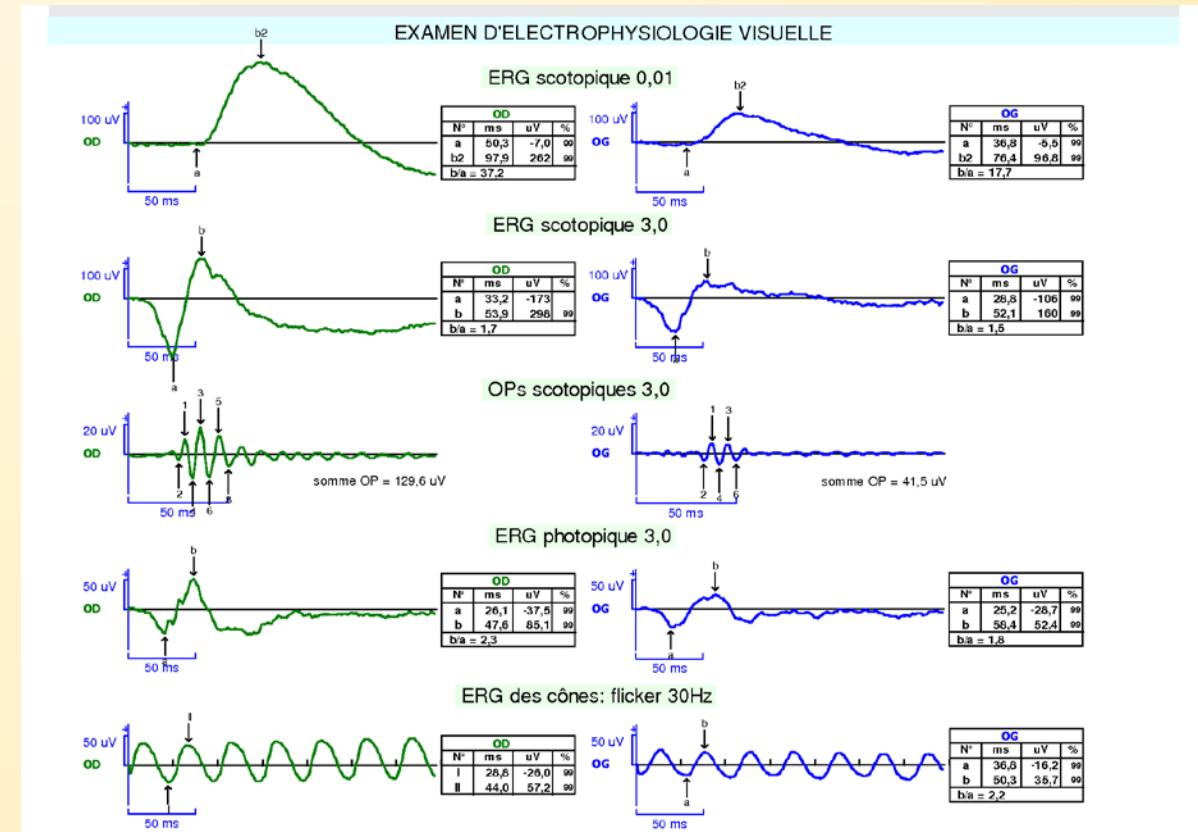
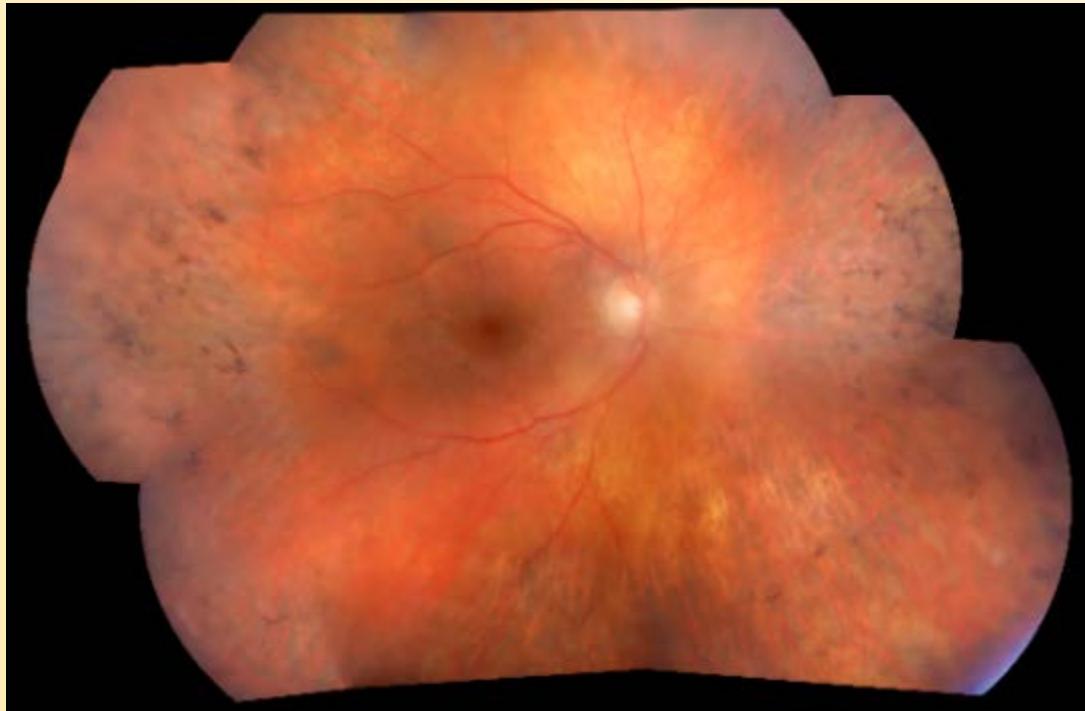


Bull's eye



Hydroxychloroquine (HCQ), Chloroquine (CQ)

- global peripheral retinopathy with optic atrophy \neq bull's eye



Normal

patient

Screening : recommendations

Patients at risks

(SFO 2005, AAO 2011, Marmor AAO 2016)

- Dose : 5 mg/kg/d HCQ ou 2,3 mg/kg/d CQ adapted **to real weight**
- Cumulative dose >1000g(HCQ)-460g (CQ)
- Age > 65 years (at the beginning or in the follow up),
- Treatment duration > 5 years
- Liver or renal diseases .
- Pre -existing lesion, ABCA4 Stargardt
- Association with other drugs, Tamoxifen

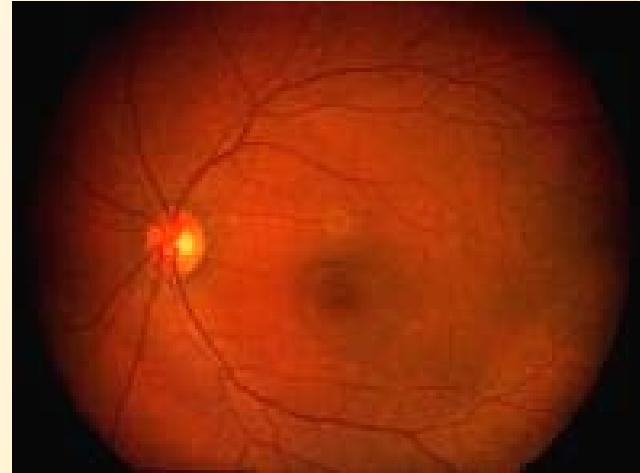
Frequency : examination every 6 -12-18 months

- | Before 5 years | After 5 years |
|---|--|
| ■ Patients « at low risks » : 18 months | ■ Patients without retinopathy : 12 months |
| ■ Patients « at risks without retinopathy » : 12 months | ■ Patients with retinopathy : 6 months |
| ■ Patients « at risks with retinopathy» : 6 months | |

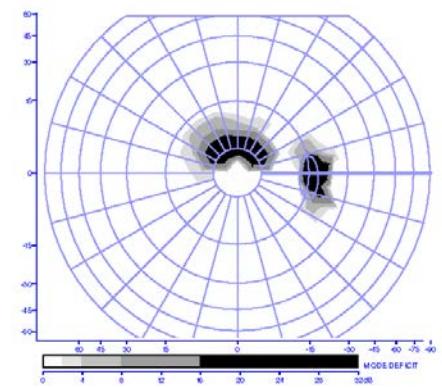
Bull's eye

Hydroxychloroquine (HCQ), Chloroquine (CQ)

- **Treatment initiation** : in the first 3 months
- complete ophthalmologic examination, **association with Tamoxifen**
- **central visual field (10-2)**
- **imaging retinophotography, OCT**
- **mf ERG** (best sensitivity)if possible **in real life**
- **Follow-up**
 - complete ophthalmologic examination
 - **central visual field(10-2)**
 - **imaging : retinophotography, OCT**
- **mf ERG** (in real life : If VF or OCT is abnormal) to be sure
- **Benefit-risk : useful and harmless drug**



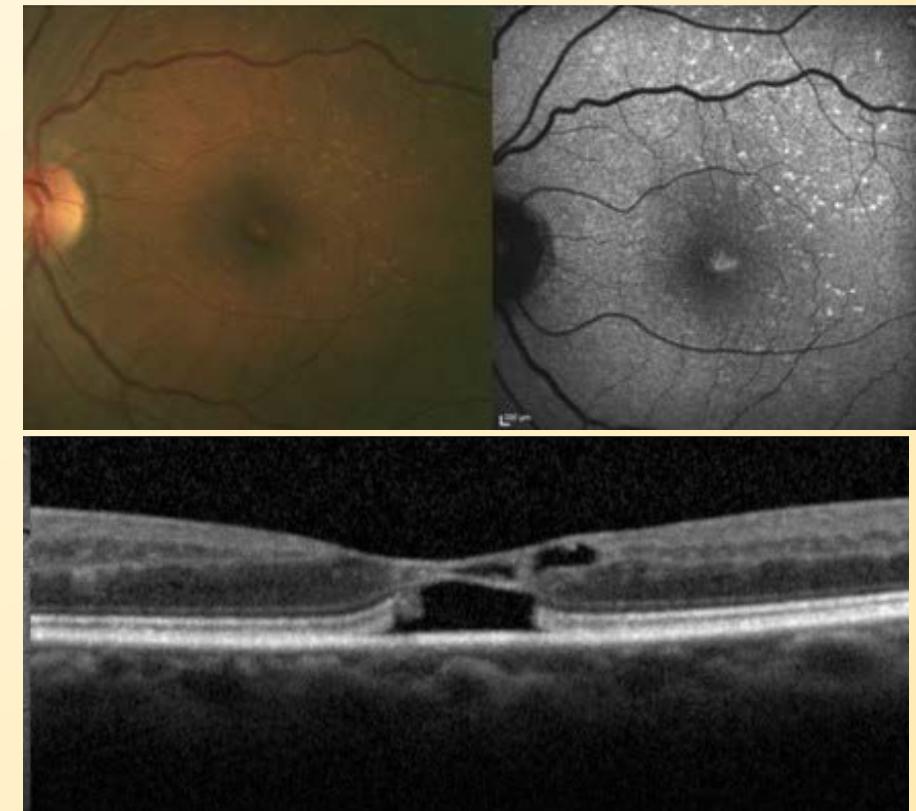
Carte de déficits



Eric Chen 2010
« Flying saucer »

Tamoxifen

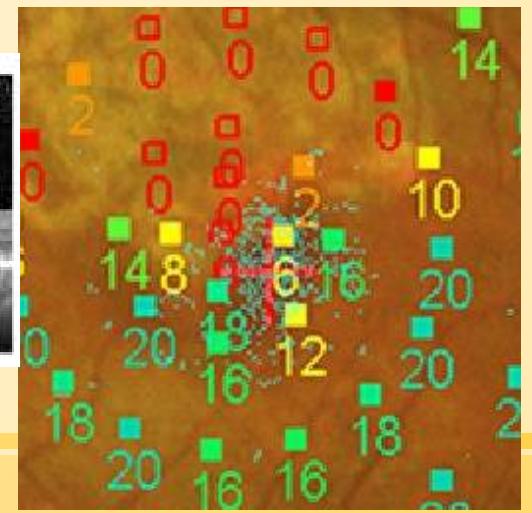
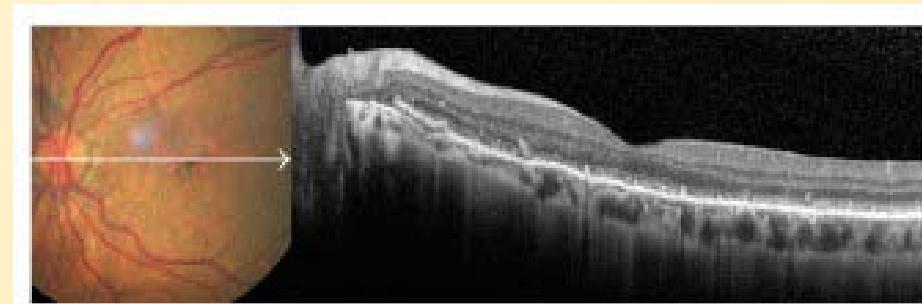
- Anti oestrogen cancer therapy, melanoma, 20-40 mg/d
- Anatomy : RPE, pockets of fluid, SRF along arcades, CRSC (Yanuzzi 2016)
- Physiopathology : glutamate Muller cells
- **occurency maculopathy : 10 %,** (Hui-Bon-How 2011),
- dosage > 120 mg/d >1 year : macular oedema
- Dosage 20 mg/d cavitations Gualin AJO 2005, Doshi AJO 2014



- **Treatment initiation :**
- complete ophthalmologic examination, SD OCT, mf ERG
- **Follow-up**
- Ophthalmologic examination, SD- OCT
- Mf ERG : reduced responses in paracentral and pericentral areas , variability

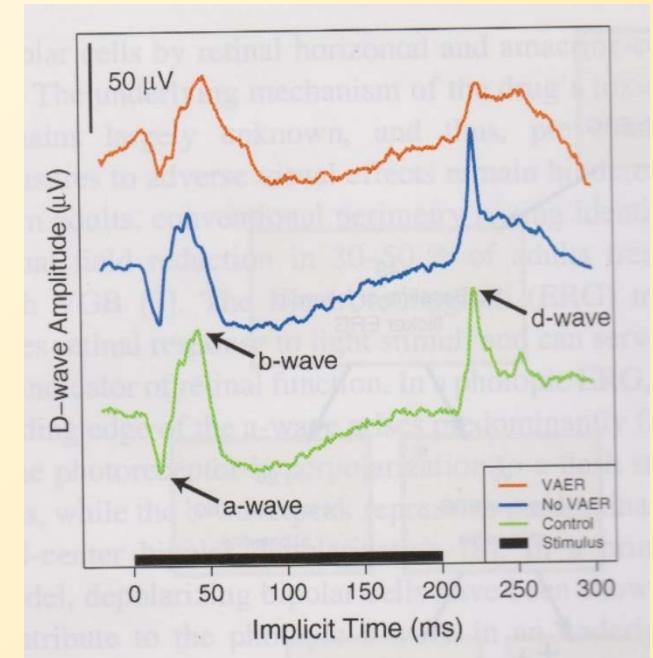
Deferoxamine mesylate (DFO) Desferal®

- iron-chelating drug for treatment of hemosiderosis, thalassemia, sickle cell disease
- Anatomy : optic neuropathy and retinopathy. macular and peripheral pigmentary changes, retinal pigment epithelium degenerations and **bull's eye maculopathy**
- **Follow-up :** all electrophysiology in literature
 - ERG : early **dose-related** suppression of b-wave, sometimes reversible (Arden)
 - EOG slightly lower, P- ERG more pronounced
 - **mf ERG** : reduced amplitudes (half of normal values) in the central retina , **progressive worsening of mfERG traces after cessation of DFO therapy**
- **Screening ?**
 - Visual field , OCT, microperimetry ?
 - mfERG ? **maculopathy**



Vigabatrin

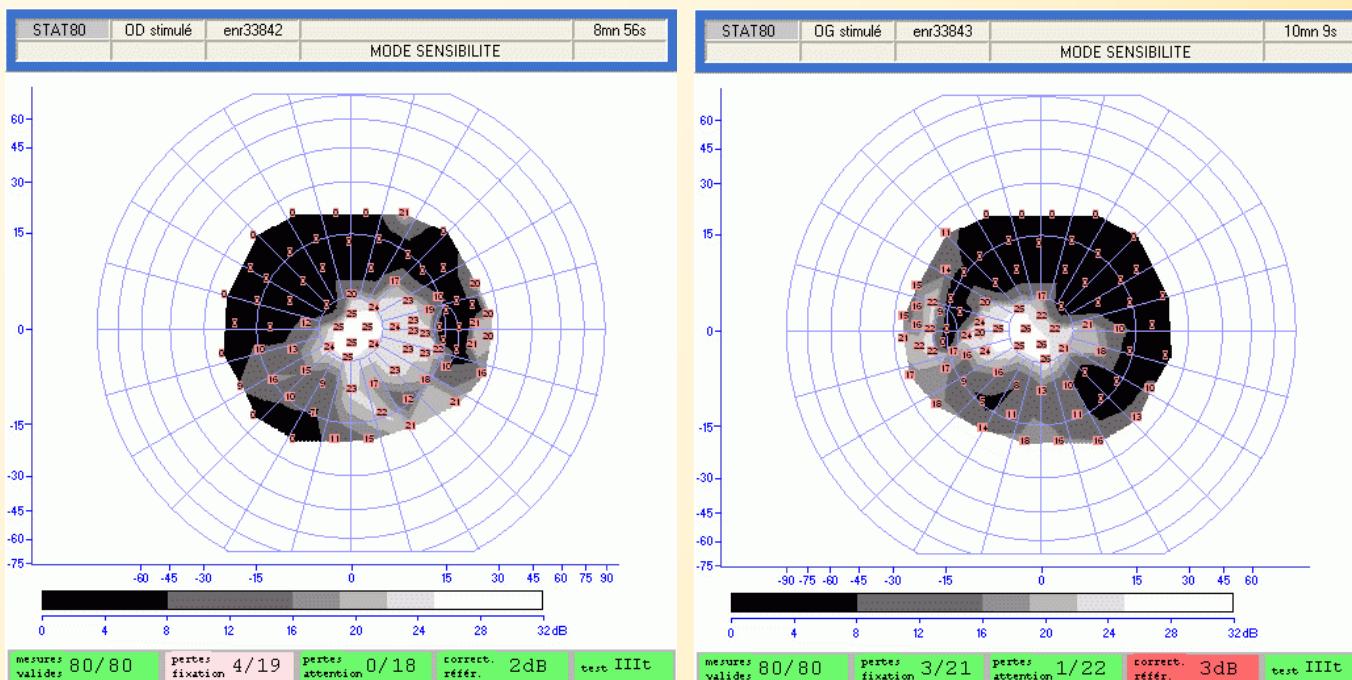
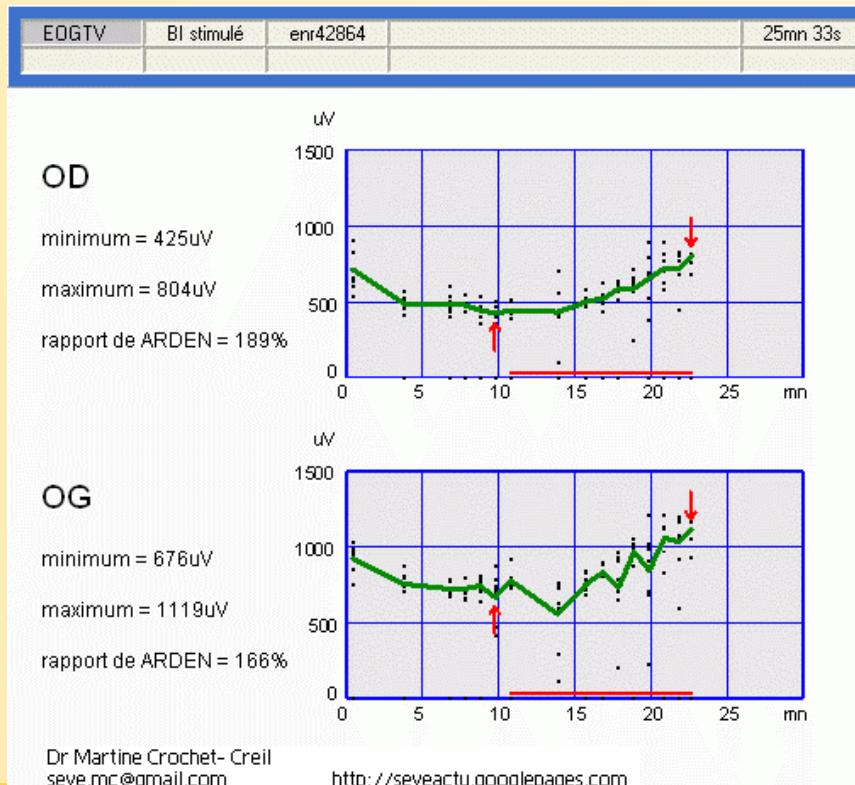
- irreversible inhibitor of the enzyme γ - aminobutyric acid transaminase used in the treatment of epilepsy.
- Anatomy : RGCs, OFF Bipolar cells , cones or main in inner retina
- Physiopathology : Deficiency in Taurine ?, individual susceptibility
- **Screening :** (Sergott 2011)
 - VGB toxicity is bilateral VF constrictions
- **Treatment initiation:**
 - ophthalmologic examination , visual field if not feasible: ERGs
 - ERG abnormalities may be more diffuse than VF findings and persist after the drug is withdrawn.
 - **b-wave** : amplitude reduced, implicit time increased, **d-wave** (long duration flash) stimulation (Dragas-Westal 2014)
- **Follow-up** every 3 months on therapy, 6 months after discontinuation
- EOG in the past



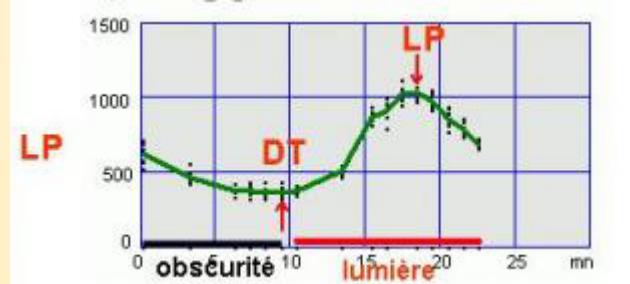
Vigabatrin

EOG : electrooculogram

drug efficacy rather than toxicity



Normal EOG

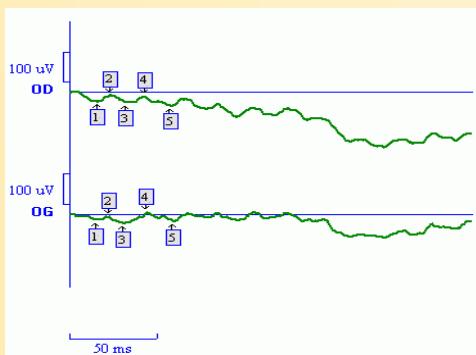


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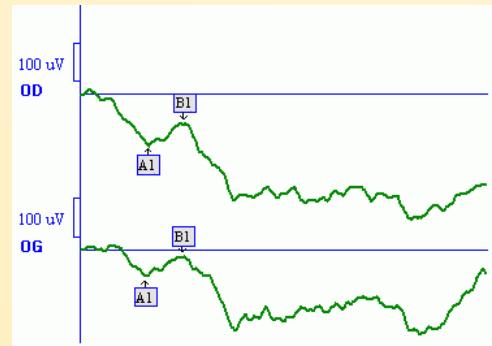
Quinine sulfate

- Cinchona alkaloid treatment of malaria, nocturnal muscular cramps. Acute toxicity abortion suicide, overdose error of dosage. Not a screening, **an enquiry**
- Anatomy : outer layer, vasculopathy, arterial vasoconstriction ?
- Visual loss with ERG normal at the beginning,
- after 10 hours ERG : severe retinal desorder, remains abnormal but without complaint

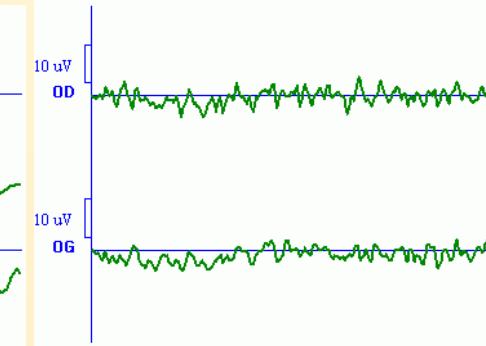
ERG : ISCEV rod



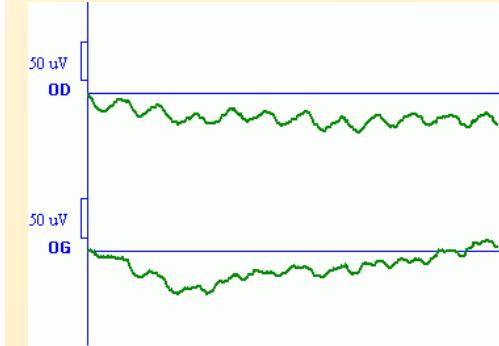
ERG : ISCEV SF



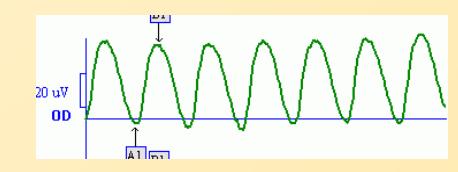
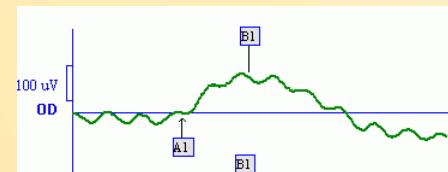
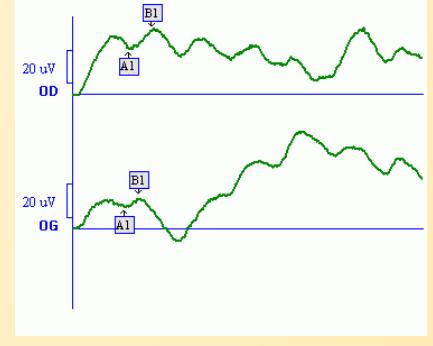
ERG : OPs



ERG : ISCEV Cone

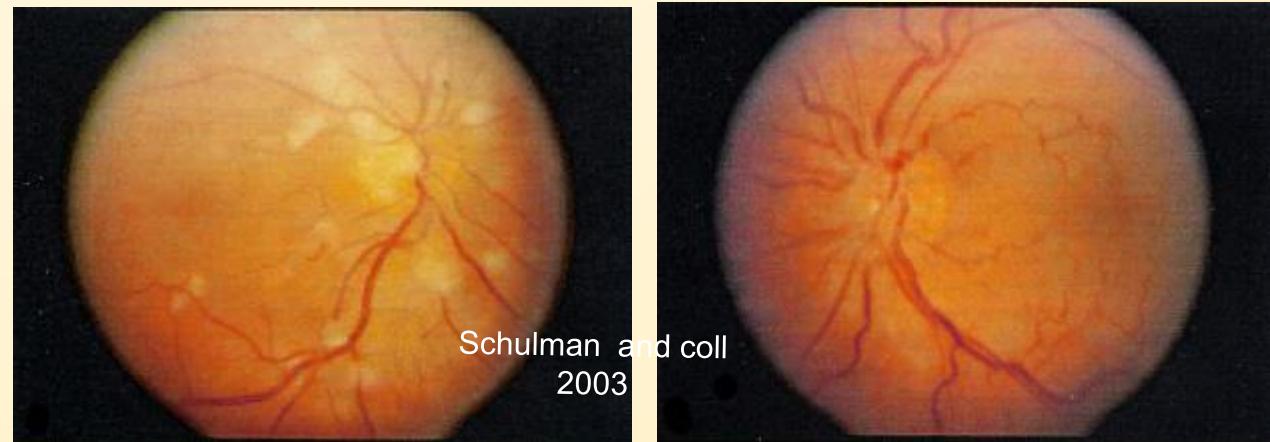


ERG : flicker



Interferon - α

- combination of antiviral drugs interferon- α and ribavirin in treatment of chronic hepatitis B - C.
 - Leukemia, lymphoma
- Anatomy : **optic neuropathy and retinopathy** : photoreceptors and bipolar cells
 - immun complex



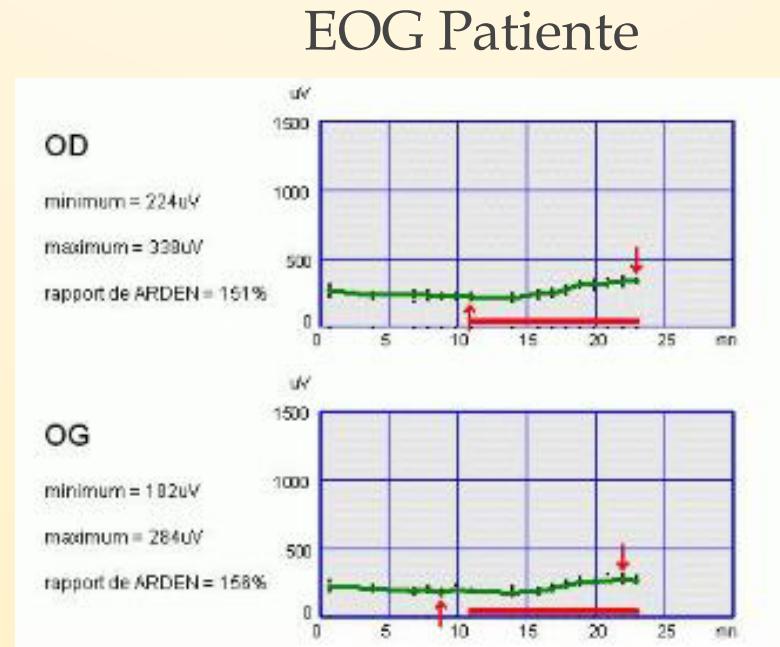
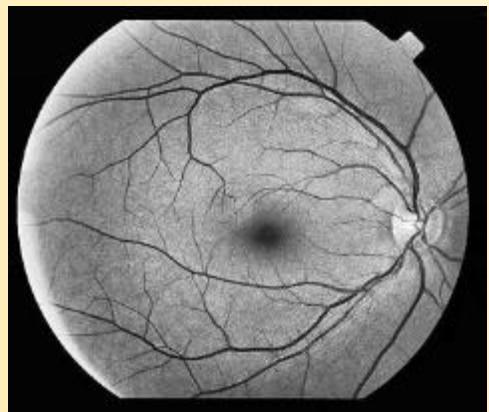
Follow-up

- **mf ERG** abnormal responses in **asymptomatic patients** with normal fundus appearance,
- Visual loss : sometimes **irreversible**
- **pegylated interferon- α** (injection every week, now every 3 weeks, **extended efficacy => increased toxicity?**)

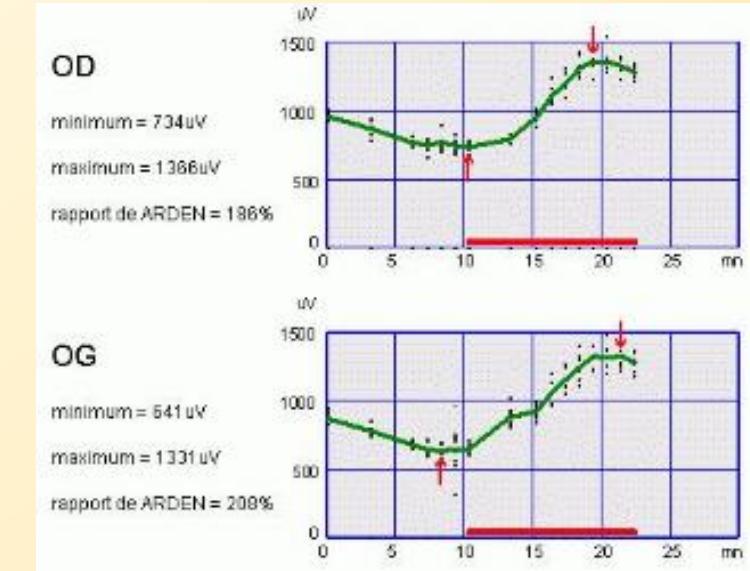
Interferon -α :

about a clinical case and screening

Patient complained « to be dazzled » => ophthalmologic examination : normal VA, FO, VF, VEP, ERG : normal, electrooculogram ?



EOG Normal



Cessation : Electro oculogram => normal / glare disappeared

Screening recommendations ? Electrooculogram ?

Interferon - α :

about a clinical case and screening

Screening recommendations ?

Collaboration with amiens university hospital hepatology dpt,
2003

- **Treatment initiation :**

ophthalmologic examination, guidance for any trouble occurring

- **Follow-up**

Ophthalmologic examination :

electrophysiology as soon as complain

don't let any question or fear without response : irreversibility and suicide in
Interferon therapy



Amiens

MEK inhibitors

- cancer therapy, melanoma
- Anatomy : RPE, pockets of fluid, SRF along arcades, CRSC (Yanuzzi 2016)
- Physiopathology : **auto Antibodies anti RPE anti-retina**
- occurrency 100 %, (Urner Bloch 2014) Visual acuity 30-70 %, EOG PLAT
- **Treatment initiation :**
- complete ophthalmologic examination
- **Follow-up**
- Ophthalmologic examination, OCT, EOG

Etiology, physiopathology



VASCULOPATHY

- RETINAL -
PIGM
EPITHELIUM

- PHOTORECEPTORS

- Chloroquine,

- Hydroxychloroquine

- Ethambutol

- IPDE5 : sildenafil

- Poppers

- Ocriplasmine

Ethambutol

- treatment of tuberculosis and *Mycobacterium avium* complex infections.
- Anatomy : optic neuropathy and retinopathy : photoreceptors and bipolar cells
- **Follow-up**
 - Pattern VEP for neuropathy but sometimes the visual loss is due to the retina
 - **mf ERG** P1 reduced amplitude and increased implicit time indicating ethambutol-induced retinal dysfunction
 - => **Photoreceptors and bipolars cells, not restricted to optic nerve as so far considered**
 - Reversible after cessation

PDE inhibitors (PDE5) sildenafil tadalafil

- Erectile dysfunction HTAP
- Anatomy : RGs, Bipolar cells , cones ?
- Physiopathology : inhibition PDE6
- Dyschromatopsia , cyanopsia:
- **Follow-up**
- **acute high dose (100mg) :**
 - **ERG** : transiently increased photopic but not scotopic implicit times,
 - **mf ERG** : delayed and attenuated waveforms in posterior pole
- **chronic, daily, high dose (100 mg) : mf ERG** small increase in cone implicit time

poppers

- Recreative drug : isopropyl nitrite, alkyl nitrite (nitric oxide doner)
- Anatomy : **maculopathy**, photoreceptors
- Physiopathology : dose-dependent
- Electrophysiology : ERG : reduced amplitudes
- Evolution : **inconstant improvement** with cessation
- **Association with Sildenafil increases maculopathy**
- genuine public health risk. ?

Toxic retinopathies

Drug-induced toxicity :

- Electrophysiology is more predictive and more sensitive
- No specific test for retinal toxicity
- Prescribing physician and Ophthalmologist
 - we are answerable to patients
 - Screening in early stage

=> Considering benefit-risk

Toxic retinopathies

Collaboration : more efficient than any screening based on test non specifically dedicated to each toxicity

- Prescribing physician
- Ophthalmologist
- Pharmacologist
- Patient

=> Considering benefit-risk

Thank you for your attention

- Department of university hospital of Lille Dr Sabine Defoort-Dhellemmes
- The electrophysiologists, and the libanese society of ophthalmology

May, Saturday 5 and Monday 7 :
electrophysiology at the French Society of Ophthalmology

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- ISCEV 2018 France- Reims 18 - 24 june www.Iscev2018.fr

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