

ROP
Retinopatija nedonošenčka

Seminar

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Mentor: doc. dr. Manca Tekavčič Pompe, dr. med.

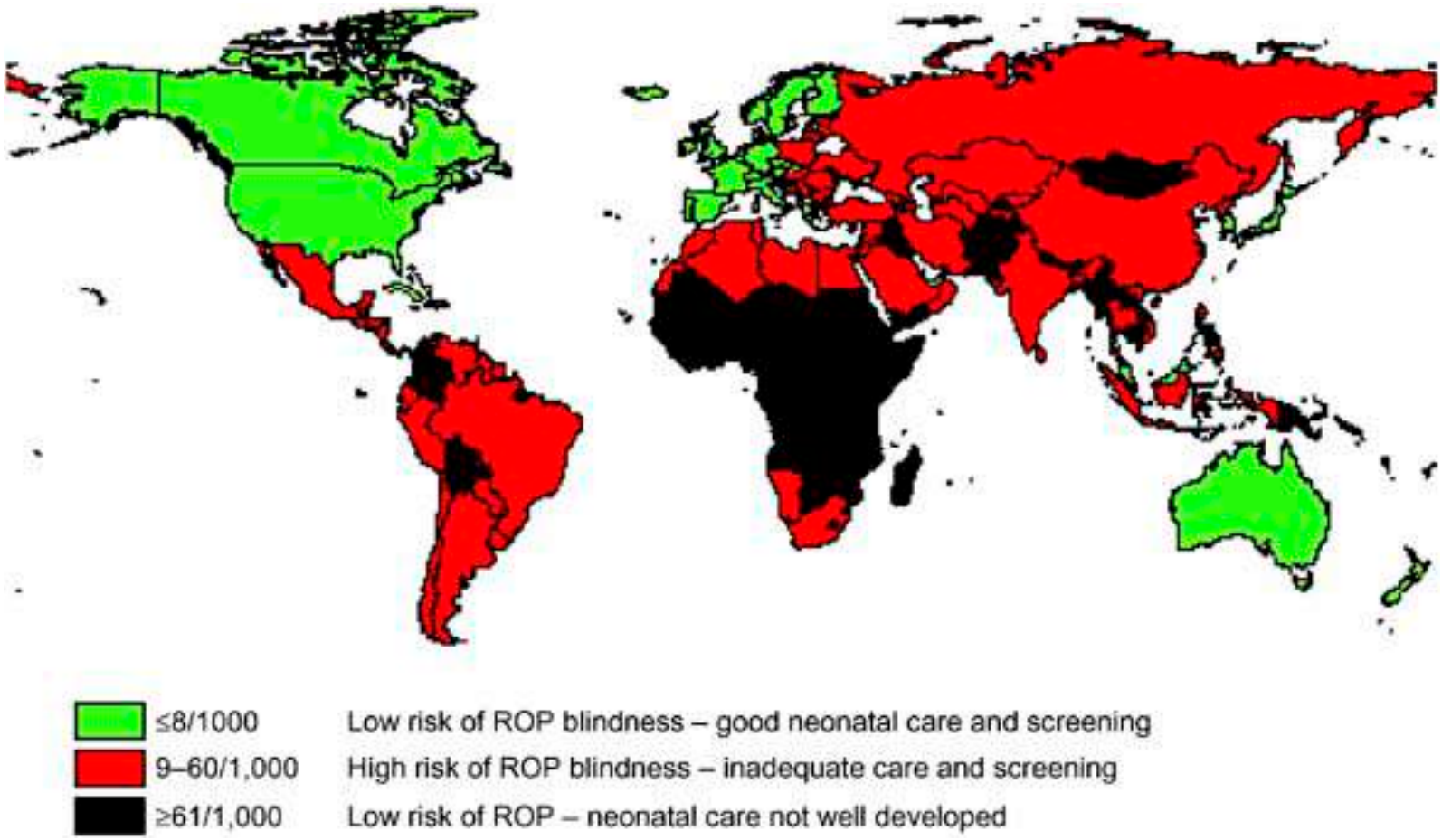
Kaj je ROP?

- Retinopatija nedonošenčka
- Potencialno vid ogrožujoče stanje, lahko vodi v slepoto (če neodkrito, nezdravljeno)
- *Nižja* kot je *porodna teža* in nižja kot je gestacijska starost, večje je tveganje za razvoj ROP
- 21.8% nedonošenčkov ima prisotno eno od oblik ROP (2010)
- Pomemben vzrok za slabši vid ali slepoto

Screening je preventiva slepote!

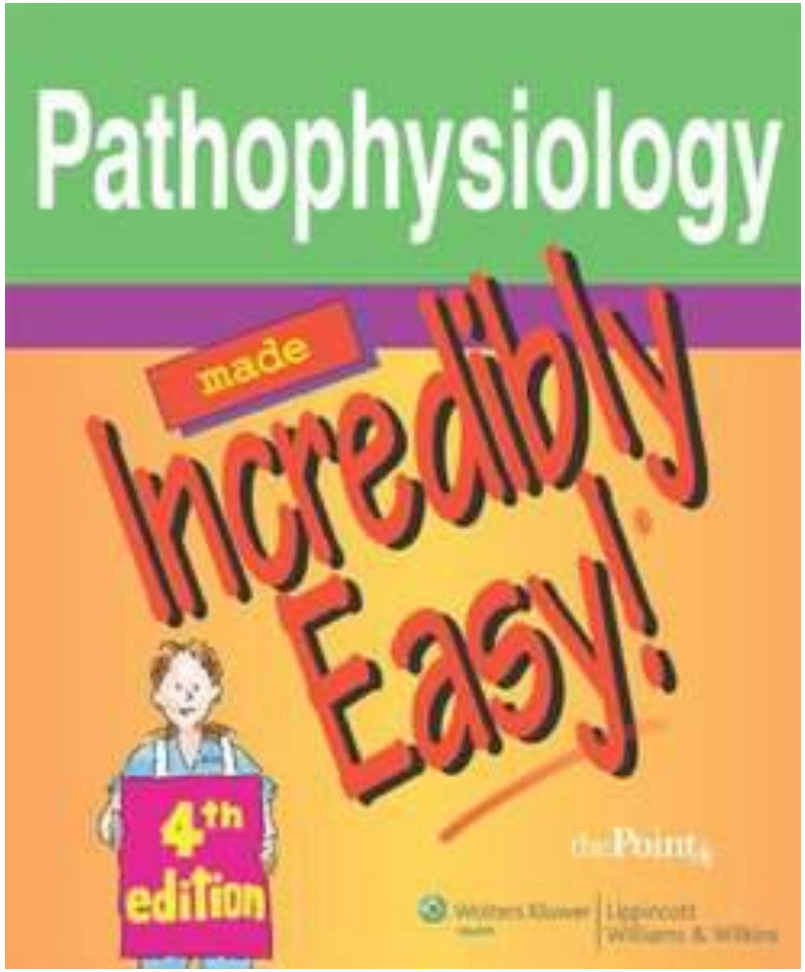
Ključna vprašanja

- Kaj iščemo pri pregledu?
- Kdaj pregledujemo?
- Kdaj zdravimo?



Probable distribution of blindness in children due to retinopathy of prematurity as a public health problem
C. Gilbert, Eye, 2007

Patofiziologija



Patofiziologija

Dejavniki tveganja

znani	**stvar diskusije**	**možno**
	trajanje terapije z O2	transfuzija
Nedonošenost	stopnja hipoksije	železo
Terapija O2	spremembe v PaO2	Epo
pridružene bolezni (sepsa, nekrozantni enterokolitis,…)		
		hiperkapnija
		steroidi
		izpostavljenost svetlobi
		genetski dejavniki

Patofiziologija

- In utero:
  - normalna rast retinalnega žilja (IGF-I, VEGF, epo)
  - Ob rojstvu je mrežnica popolnoma vaskularizirana (nazalno ob 32. tednu, temporalno ob 40.tednu)

NEDONOŠENČEK – razvoj ROP

2 fazi:

1. **Vazo-obliterativna faza**

   hiperoksično novo okolje → ob ↑ O2 → ↓ VEGF, EPO

   smrt retinalnih kapilarnih endotelnih celic ob umiku s hiperoksičnih pogojev

2. **Vazo-proliferativna faza**

   zaradi 'dozorevanja' mrežnice povišana metabolična aktivnost, ki v nepopolno vaskularizirani mrežnici povzroči hipoksijo

   hipoksija stimulus za tvorbo VEGF, EPO, HIF-1 → začetek neovaskularizacije

Klasifikacija

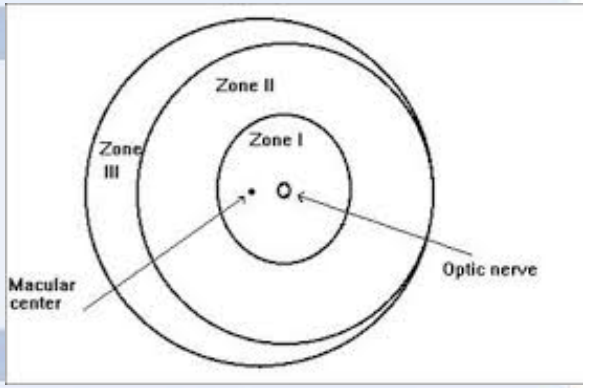
- Mednarodna klasifikacija
- Upošteva glavne 4 kriterije:

1. Anterior – posterior location (zone I-III)
2. Severity (stopnje 1-5)
3. Posterior pole vessel abnormality
4. Extent of disease (clock hours)

Klasifikacija

Table 1. International Classification of ROP

DESCRIPTOR	DEFINITION
Zone	**Location of disease**
I	Area within circle with radius of twice the distance from optic nerve center to fovea
II	Area outside of zone I with radius of optic nerve to nasal ora serrata
III	Residual area outside of zone II
Stage	
1	Thin demarcation line
2	Ridge with height and width
3	Fibrovascular proliferation
4	Subtotal retinal detachment
5	Total retinal detachment
Appearance of posterior pole vessels	
Plus disease	Abnormal dilation and tortuosity that meets or exceeds abnormality of standard photograph
Pre-plus disease	Abnormal dilation and tortuosity insufficient for plus disease
Not plus and not pre-plus	No abnormal dilation and tortuosity



Stages

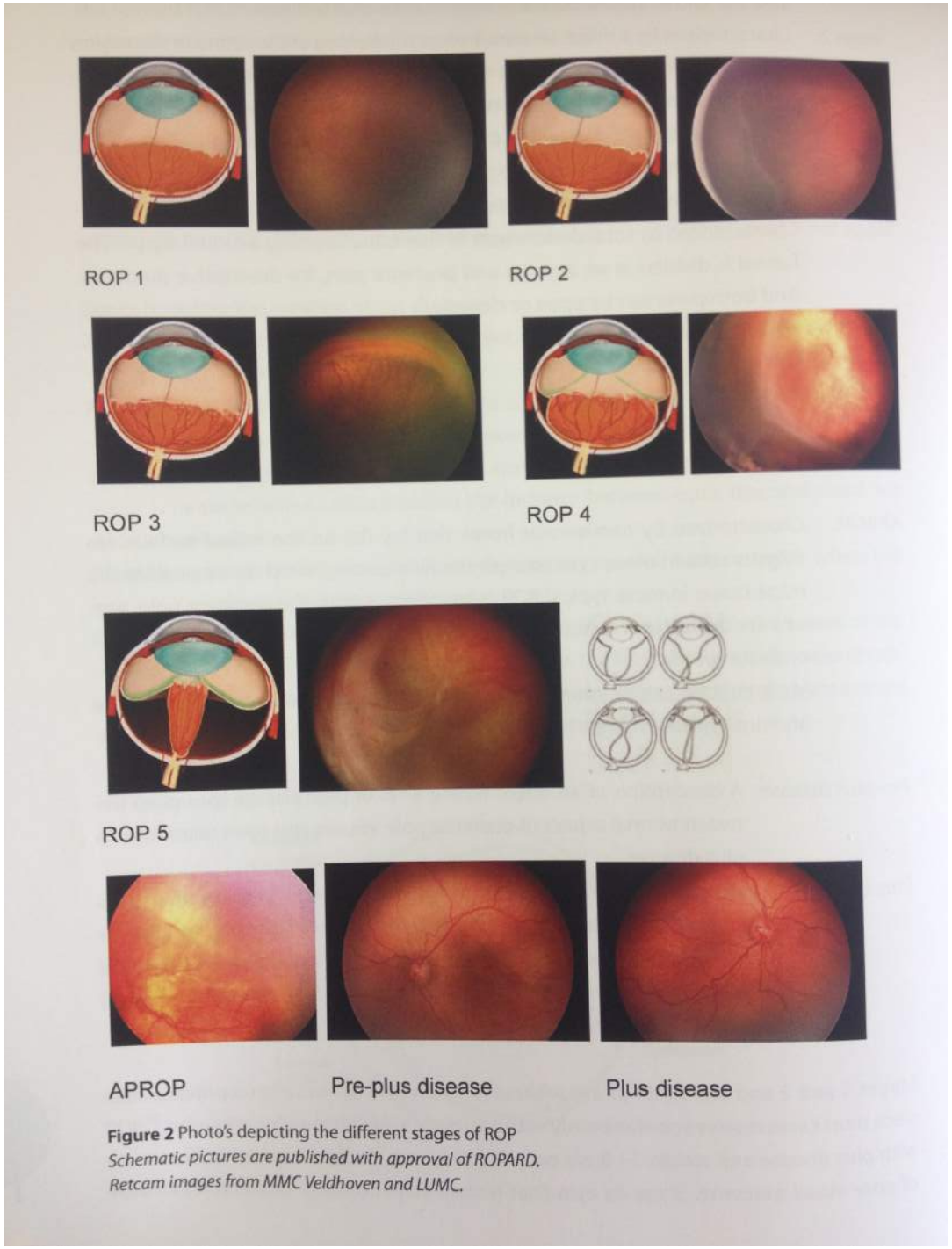


Figure 2 Photo's depicting the different stages of ROP
Schematic pictures are published with approval of ROPARD.
Retcam images from MMC Veldhoven and LUMC.

Plus disease

- Lahko se pojavi v katerikoli ROP fazi
- Tortuozne retinalne arteriole, bolj polne vene v bližni PNO
- Žilje irisa dilatirano, zenica se ne širi, tunica vasculosa lentis
- Prisoten vsaj v 2 kvadrantih in periferne spremembe ROP
- Indikator za severe ROP → potrebna th.

Pre-plus disease: žilne spremembe, ki niso normalne, vseeno pa ne zadostujejo pogojem za izpolnjevanje plus disease

Treshold ROP: 50% možnosti za napredovanje v odstop mrežnice (potrebno je skrbno spremljanje)

Pre-treshold ROP: stage 2 + plus disease

PRESEJANJE (screening)

- UK: porodna teža < 1500g, GA < 31 tednov
- USA: vsi s porodno težo < 1500g, GA < 30 tednov; izbrani s porodno težo 1500-2000g; izbrani GA >30 tednov, klinično manj stabilni, z visokim tveganjem po oceni pediatra oz. neonatologa
- Kanada: vsi s porodno težo < 1500g, GA < 30 tednov
- Nemčija: vsi s porodno težo < 1500g, GA < 32 tednov; GA 32-36 tednov in več kot 3-dnevna potreba po dodatnem kisiku
- Švedska: GA < 31 tednov
- Nizozemska


SAME
SAME
BUT
DIFFERENT

PRESEJANJE (screening)

- Indikacije:
- Porodna teža nižja od 1500g, gestacijska starost manj kot 31 tednov

- 1. pregled: po dopolnjenem 30. tednu, nato pa glede na zrelost žilja, prisotnost/odsotnost ROP na 1-2 tedna, dokler ni žilje ni razvito do cone 3
- Če stanje po th. ali ROP v remisiji: tedenske kontrole do 45-47 tedna GS
- Zaključeno, ko je mrežnica popolnoma vaskularizirana

PREGLED

- Stres za nedonošenčka…
- Nežno, previdno; vešče sestre
- Midriaza, topični anestetik
- Glukoza
- Indirektni oftalmoskop, leča 20D ali 28D
- Blefarostat, indentator
- Dober popis stanja ob pregledu

Glukoza

- Nefarmakološki ukrep za vplivanje na zaznavo bolečine
- 12-24% raztopina glukoze ali saharoze v odmerku 0.012 do 0.12g 2 minuti pred posegom (0.05-0.5 ml 24% raztopine)
- Zmanjša ekspresivnost bolečine

Clinics (Sao Paulo). 2013;68(2):199-204.

Oral glucose for pain relief during examination for retinopathy of prematurity: a masked randomized clinical trial.

Costa MC[1], Eckert GU, Fortes BG, Fortes Filho JB, Silveira RC, Procianoy RS.

⊕ Author information

Abstract

OBJECTIVE: Ophthalmologic examination for retinopathy of prematurity is a painful procedure. Pharmacological and non-pharmacological interventions have been proposed to reduce pain during eye examinations. This study aims to evaluate the analgesic effect of 25% glucose using a validated pain scale during the first eye examination for retinopathy of prematurity in preterm infants with birth weight <1,500 g and/or gestational age <32 weeks.

METHODS: A masked, randomized clinical trial for one dose of 1 ml of oral 25% glucose solution 2 minutes before the first ophthalmologic examination for retinopathy of prematurity was conducted between March 2008 and April 2010. The results were compared to those of a control group that did not receive oral glucose solution. Pain was evaluated using a Neonatal Infant Pain Scale immediately before and immediately after the ophthalmologic examination in both groups. Clinicaltrials.gov: NCT00648687

RESULTS: One hundred and twenty-four patients who were examined for the first time for retinopathy of prematurity were included. Seventy were included in the intervention group and 54 in the control group. The number of patients with pain immediately before the procedure was similar in both groups. The number of patients with pain after ophthalmologic examination was 15.7% in the intervention group and 68.5% in the control group ($p<0.001$).

CONCLUSIONS: One ml of oral 25% glucose solution given 2 minutes before an ophthalmologic examination for retinopathy of prematurity was an effective measure for pain relief.

Neonatal Infant Pain Scale

NIPS	0 point	1 point	2 points
Facial expression	Relaxed	Contracted	–
Cry	Absent	Mumbling	Vigorous
Breathing	Relaxed	Different than basal	–
Arms	Relaxed	Flexed/stretched	–
Legs	Relaxed	Flexed/stretched	–
Alertness	Sleeping/calm	Uncomfortable	–

Maximal score of seven points, considering pain ≥ 4.

TERAPIJA

- Jasne profilakse ne poznamo
- Akutna faza: cryoth. in laserska terapija
- Odstop mrežnice: kirurško zdravljenje
- Anti-VEGF

Anti-VEGF in ROP

Early Hum Dev. 2012 Dec;88(12):937-41. doi: 10.1016/j.earlhumdev.2012.09.019. Epub 2012 Oct 15.

Treatment of retinopathy of prematurity with vascular endothelial growth factor inhibitors.

Mintz-Hittner HA[1].

⊕ **Author information**

Abstract

ROP remains a major cause of childhood blindness worldwide. The smallest, sickest infants develop the most severe forms of zone 1 ROP. Such eyes may not be successfully treated by near confluent laser to the avascular retina (current standard of care). With an understanding of ROP pathogenesis, vascular endothelial growth factor inhibitors (anti-VEGF) are being given only when VEGF is elevated in retina and vitreous. Careful screening allows proper timing of administration. Ideal dose (perhaps different for mild and severe cases) and drug (interrupting only pathologic neovascularization and not normal angiogenesis) remain unproven. The author discusses controversial use of anti-VEGF with documented efficacy, observed local complications, and potential systemic toxicities (none observed in six years) to allow retention of vision for severe zone 1 ROP. The benefits have been demonstrated, however, local and systemic risks in these developing premature infants must be carefully studied (both short and long term).

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Eur J Ophthalmol. 2012 Sep-Oct;22(5):685-6. doi: 10.5301/ejo.5000176.

Intravitreal pegaptanib as adjunctive treatment for stage 3+ ROP shown to be effective in a prospective, randomized, controlled multicenter clinical trial.

Mintz-Hittner HA[1].

⊕ **Author information**

Abstract

PURPOSE: Both intravitreal pegaptanib with laser therapy and intravitreal bevacizumab monotherapy have been found to be more efficacious than laser therapy alone in prospective, randomized, controlled clinical trials.

RESULTS: The use of pegaptanib with laser therapy was efficacious in 91.2% compared with 69.0% in controls. The use of bevacizumab monotherapy was efficacious in 95.7% compared with 78.1% in controls.

CONCLUSIONS: The use of anti-vascular endothelial growth factor therapy for retinopathy of prematurity has been shown to be efficacious, without toxicity reported to date; however, the best drug and dose which allows greatest efficacy with fewest recurrences and without toxicity must be determined.

POSLEDICE ROP

- Začetne in lažje oblike brez posledic
- Slabša vidna ostrina in kontrastna senzitivnost
- Vidno polje..
- Strabizem: prevalenca s 6% poraste tudi čez 30%
- Sprednji segment: microcornea-microftalmos
- myopia

ŠTUDIJE

- CRYO ROP
- ETROP
- BEAT ROP

CRYO ROP

- Multicentrična študija, leto 1988
- 9751 nedonošenčkov v 23 centrih v ZDA, 23 mesecev
- Porodna teža nižja od 1251 g
- Prvi pregled 4-6. teden, nato vsaka 2 tedna do zaključene vaskularizacije
- Krioterapija = signifikantno pomembna za razvoj očesa in vidne ostrine
- Signifikantno zmanjšano napredovanje treshold ROP, ki nezdravljen pomeni 50% možnosti za slepoto

- 10 letni follow up:
- 44,4% zdravljenih vs. 62.1% nezdravljenih VA 20/200 ali manj
- Po 15 letih: število neugodnih razpletov 30% pri zdravljenih in 51.9.% (p<0.001) pri očeh, kjer ni bila opravljena krioterapija

Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years.

Cryotherapy for Retinopathy of Prematurity **Cooperative Group**.

Arch Ophthalmol. 2001 Aug;119(8):1110-8.

ETROP

- Early Treatment for Retinopathy of Prematurity
- Multicentrična, 26 centrov v ZDA, podatki iz študije CRYO ROP, 6 letna študija, leto 2003
- študija potrdi učinkovitost th. pri hudih oblikah ROP in redefinira indikacije za zdravljenje
- Razdelitev na ure, definira izraz treshold in pre-treshold ROP, nova kategorizacija ROP, ki je razdeljen v 2 skupini

Final results of the Early Treatment for Retinopathy of Prematurity (**ETROP**) randomized trial.

Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group.

Trans Am Ophthalmol Soc. 2004;102:233-48; discussion 248-50.

BEAT ROP

- Bevacizumab eliminates the angiogenic threat of ROP
- Prospektivna, kontrolirana, randomizirana, multicentrična študija
- Primerjava ROP 3+ v coni I ali II, th. ali laser ali bevacizumab intravitr.

N Engl J Med. 2011 Feb 17;364(7):603-15. doi: 10.1056/NEJMoa1007374.

Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity.

Mintz-Hittner HA[1], Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group.

⊕ Collaborators (83)

⊕ Author information

Abstract

BACKGROUND: Retinopathy of prematurity is a leading cause of childhood blindness worldwide. Peripheral retinal ablation with conventional (confluent) laser therapy is destructive, causes complications, and does not prevent all vision loss, especially in cases of retinopathy of prematurity affecting zone I of the eye. Case series in which patients were treated with vascular endothelial growth factor inhibitors suggest that these agents may be useful in treating retinopathy of prematurity.

METHODS: We conducted a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity. Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age.

RESULTS: We enrolled 150 infants (total sample of 300 eyes); 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary-outcome analyses. Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], P=0.002). A significant treatment effect was found for zone I retinopathy of prematurity (P=0.003) but not for zone II disease (P=0.27).

CONCLUSIONS: Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina. This trial was too small to assess safety. (Funded by Research to Prevent Blindness and others; ClinicalTrials.gov number, NCT00622726.).

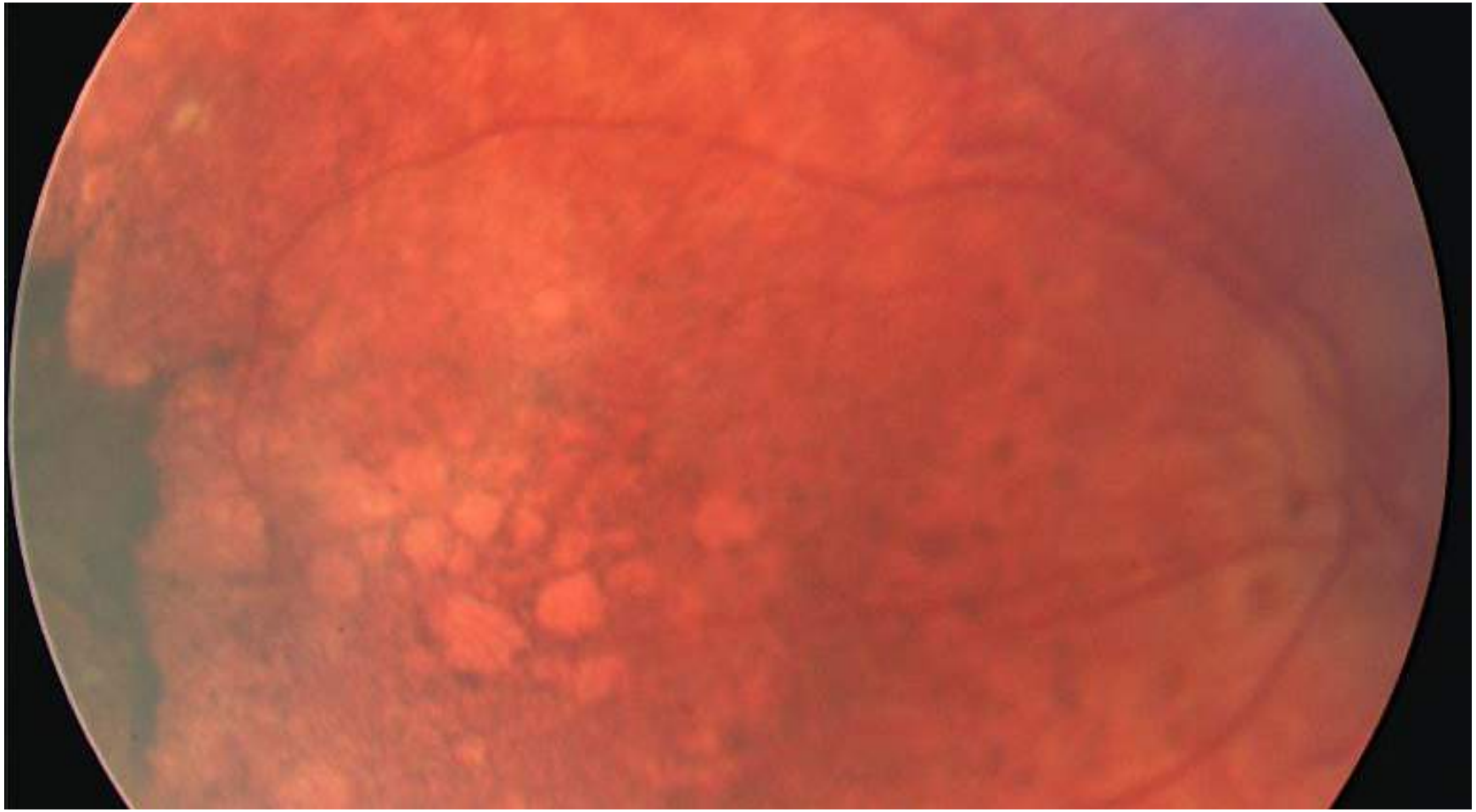
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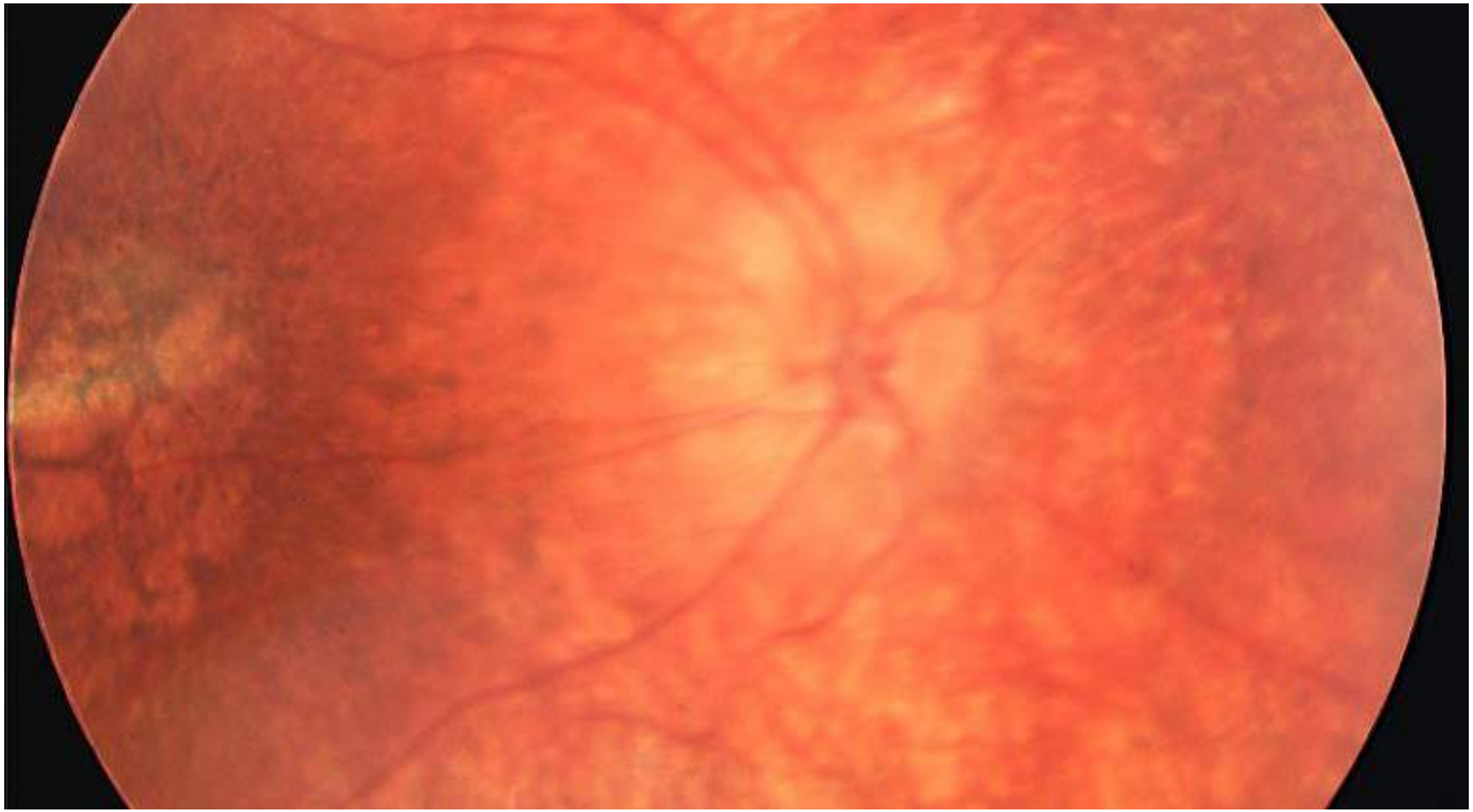
- FEVR (familial exudative vitreoretinopathy)
- Norries disease
- Incontinentia pigmenti
- PPV (persistent fetal vasculature)
- CRMCC (cerebroretinal microangiopathy with calcifications and cysts)

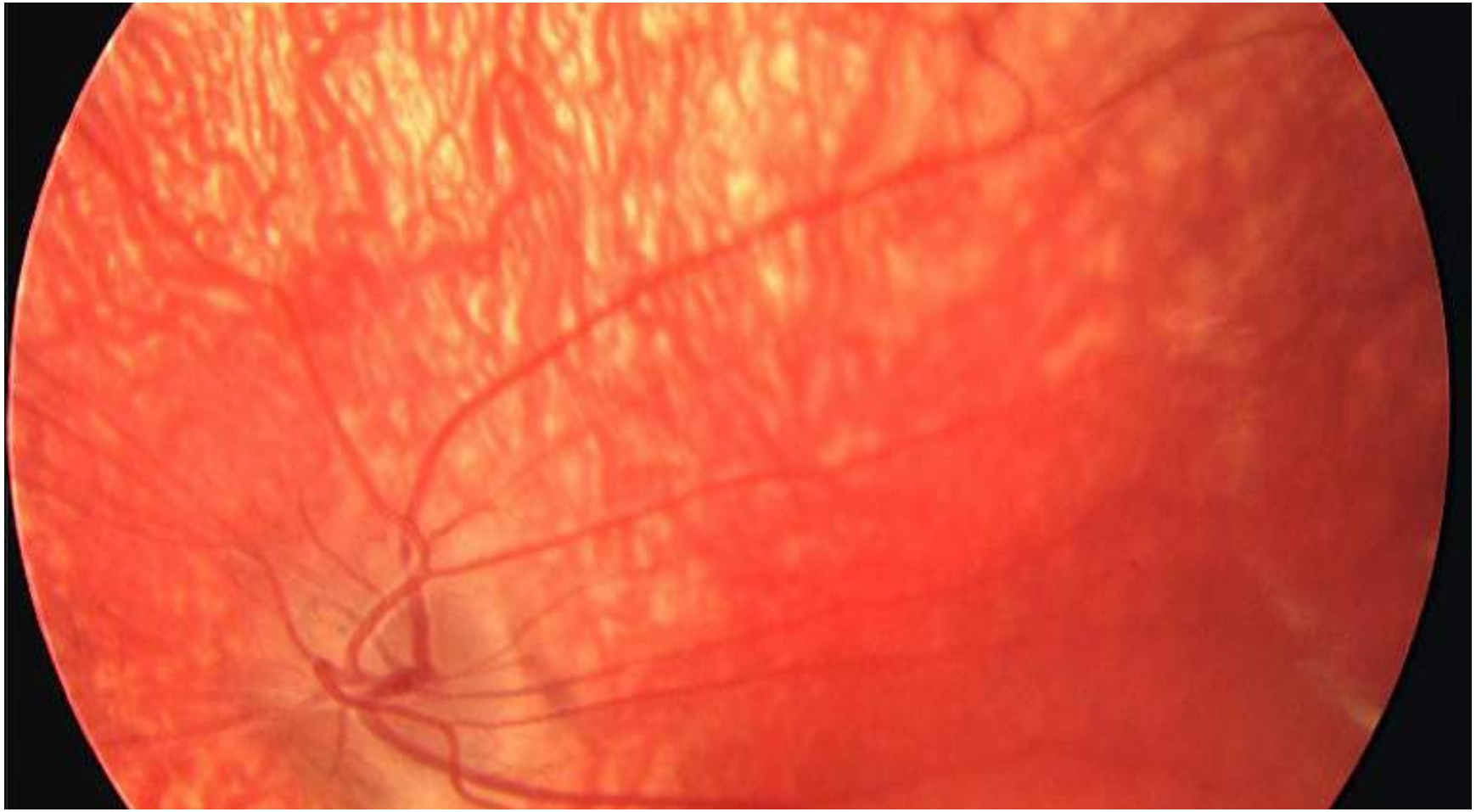
PRIMERI

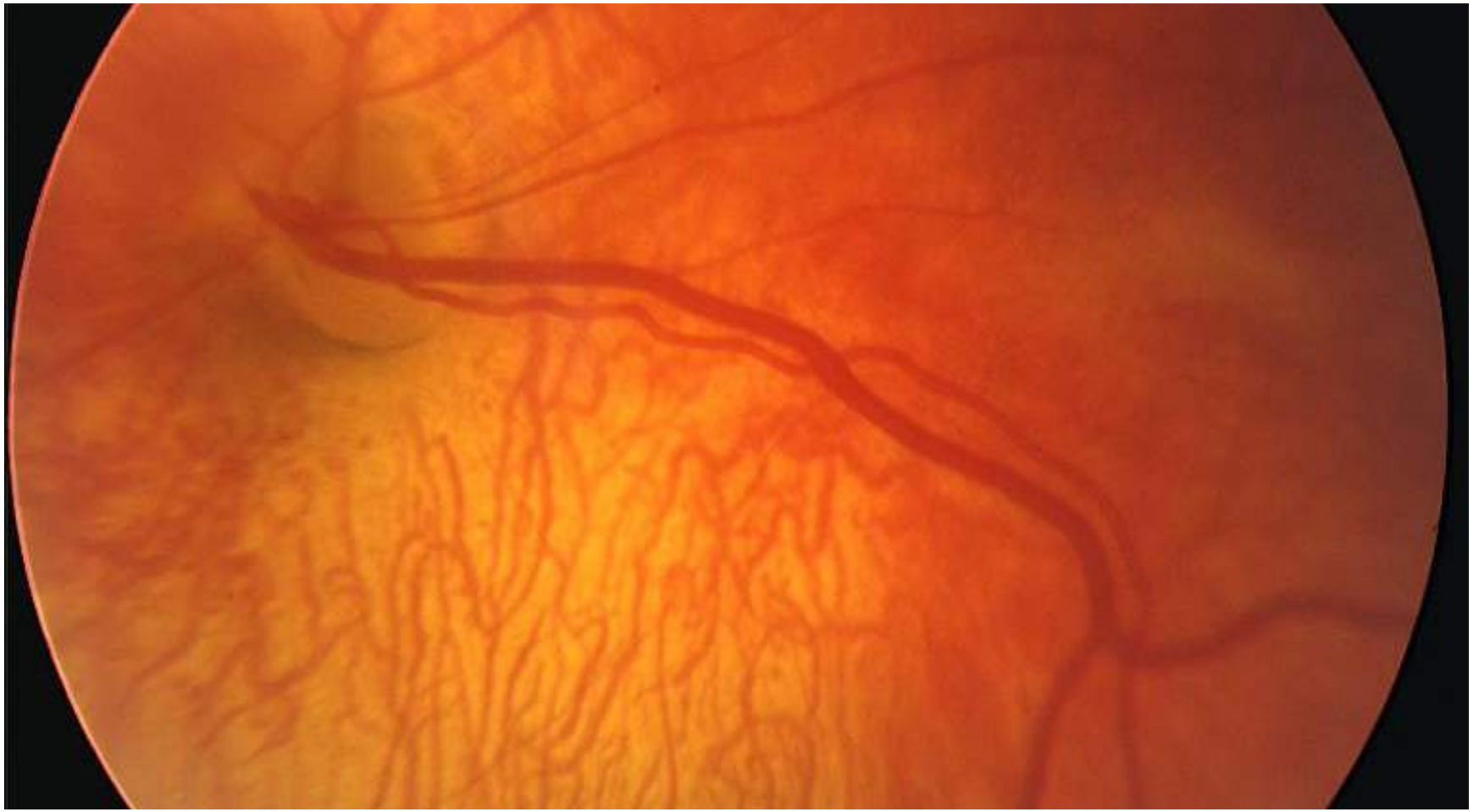
PRIMER 1

- 23 tednov 3/7, 620g
- ROP III. – IV.









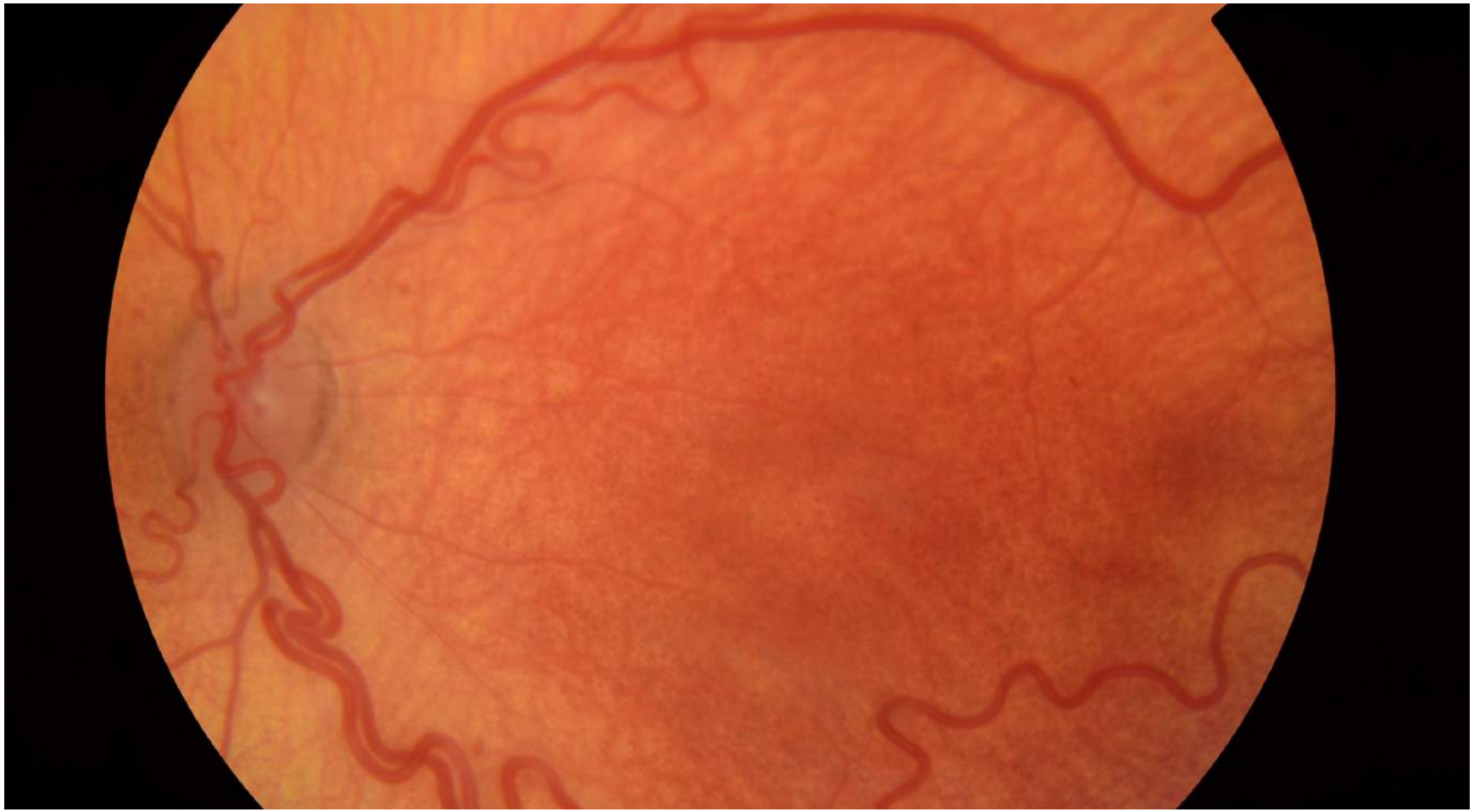
- v starosti 36.-38. tednov kriokoagulacija o.u.

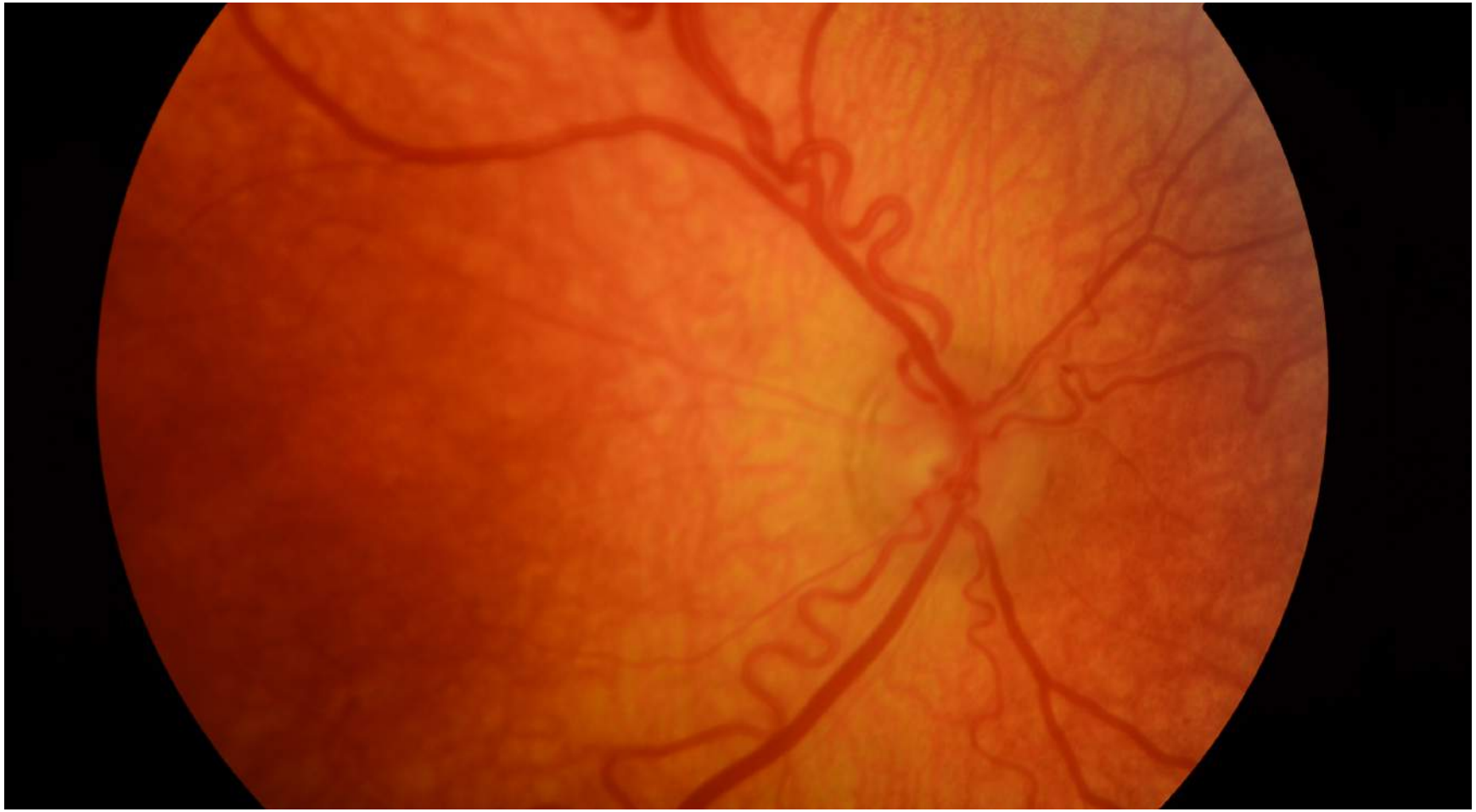
- ERG: z desnega in levega očesa so prisotni znaki za prizadetost funkcije mrežnice

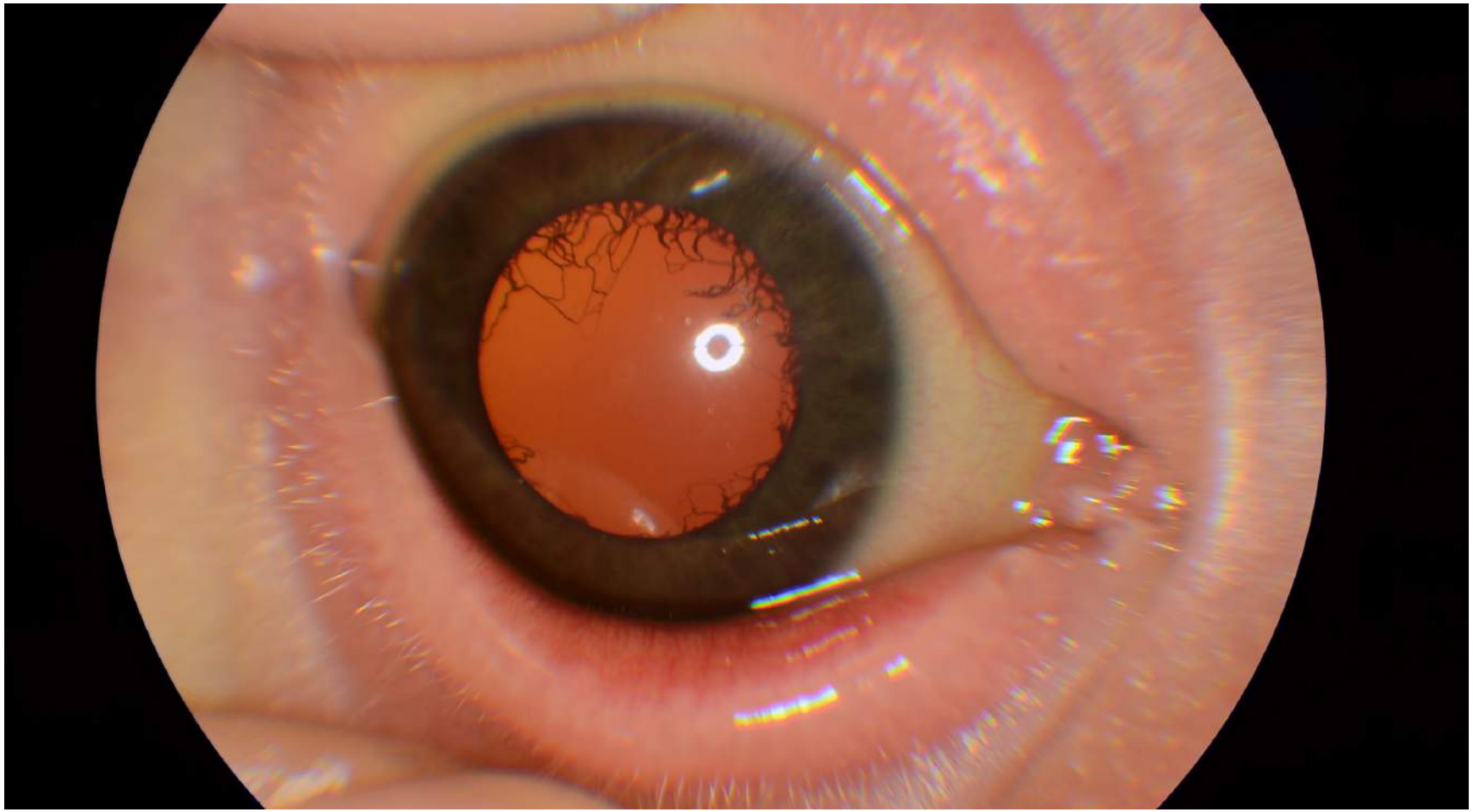
PRIMER 2

- 25 tednov 3/7, 860g
- Stanje po nekrozantnem enterokolitisu

- ROP II bilateralno + PLUS







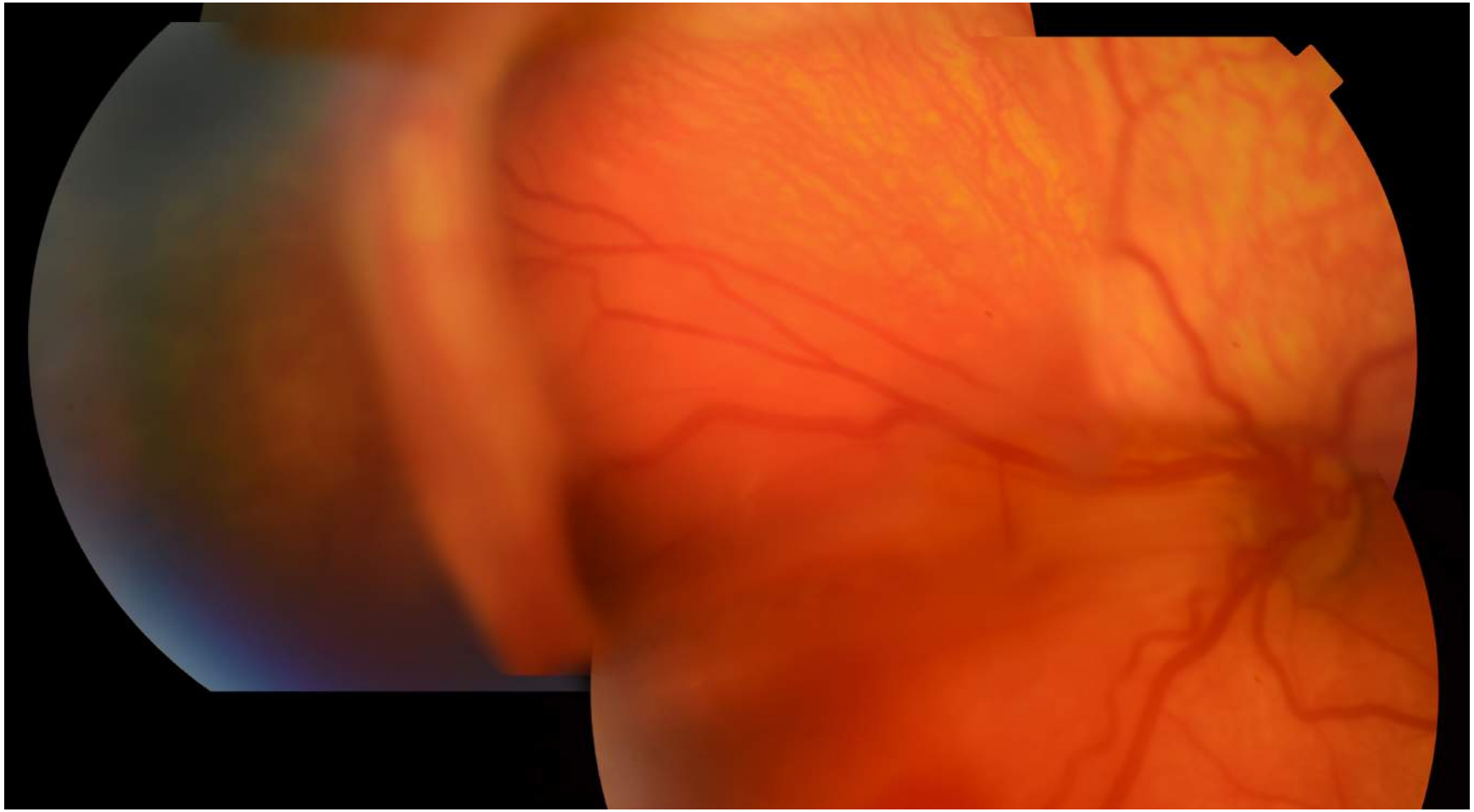
PRIMER 3

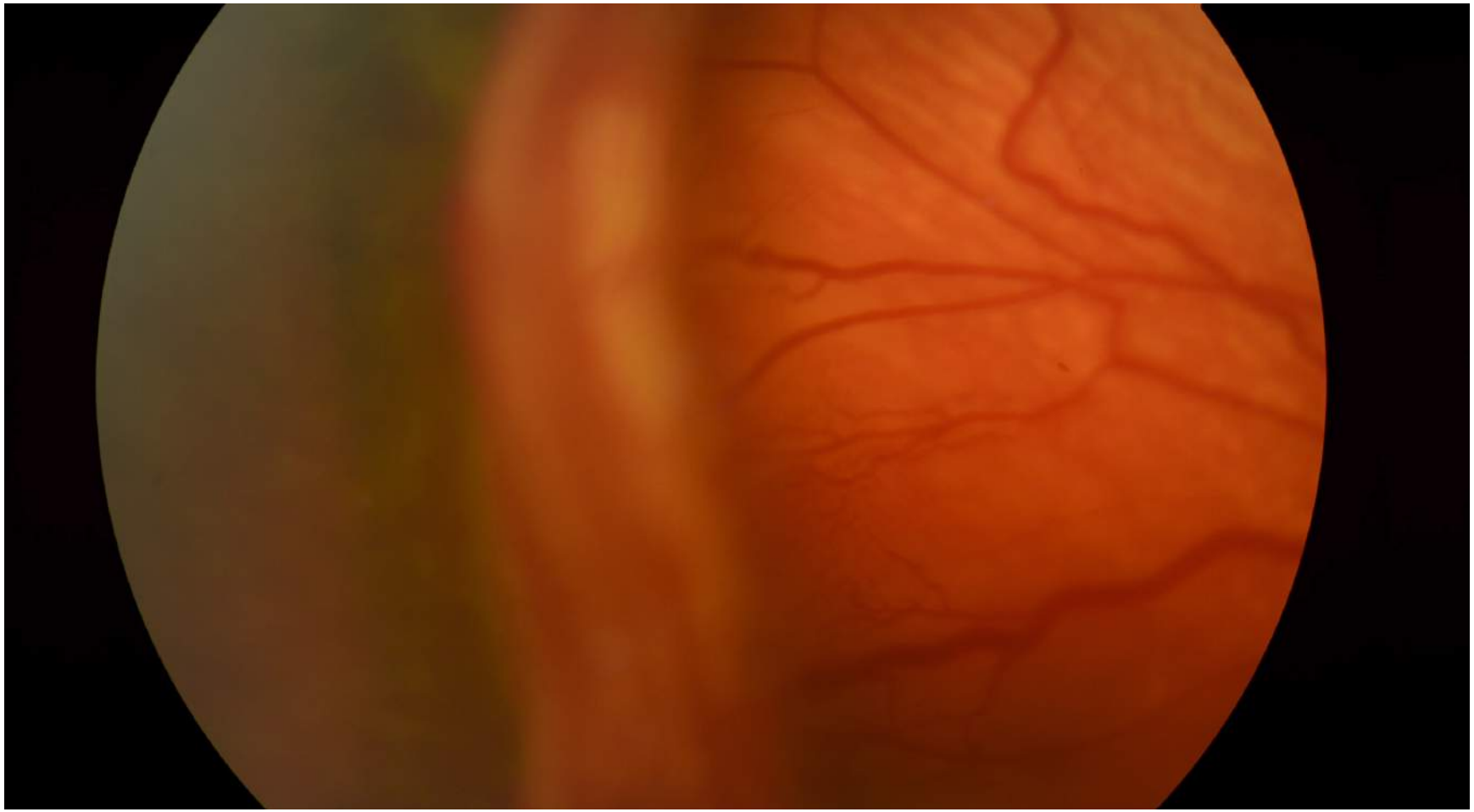
- 22. teden

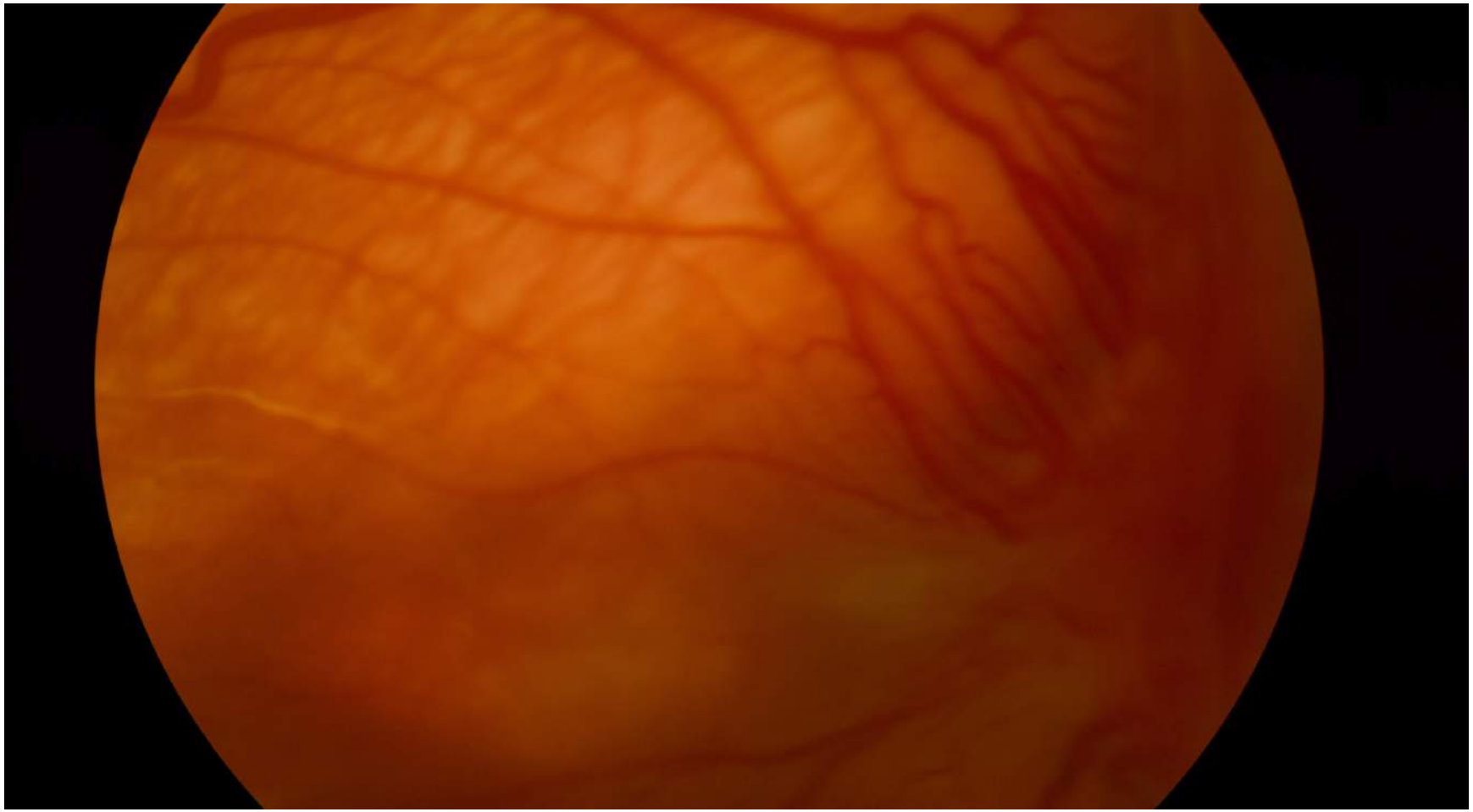
- ROP IV desno + PLUS
- ROP III levo + PLUS

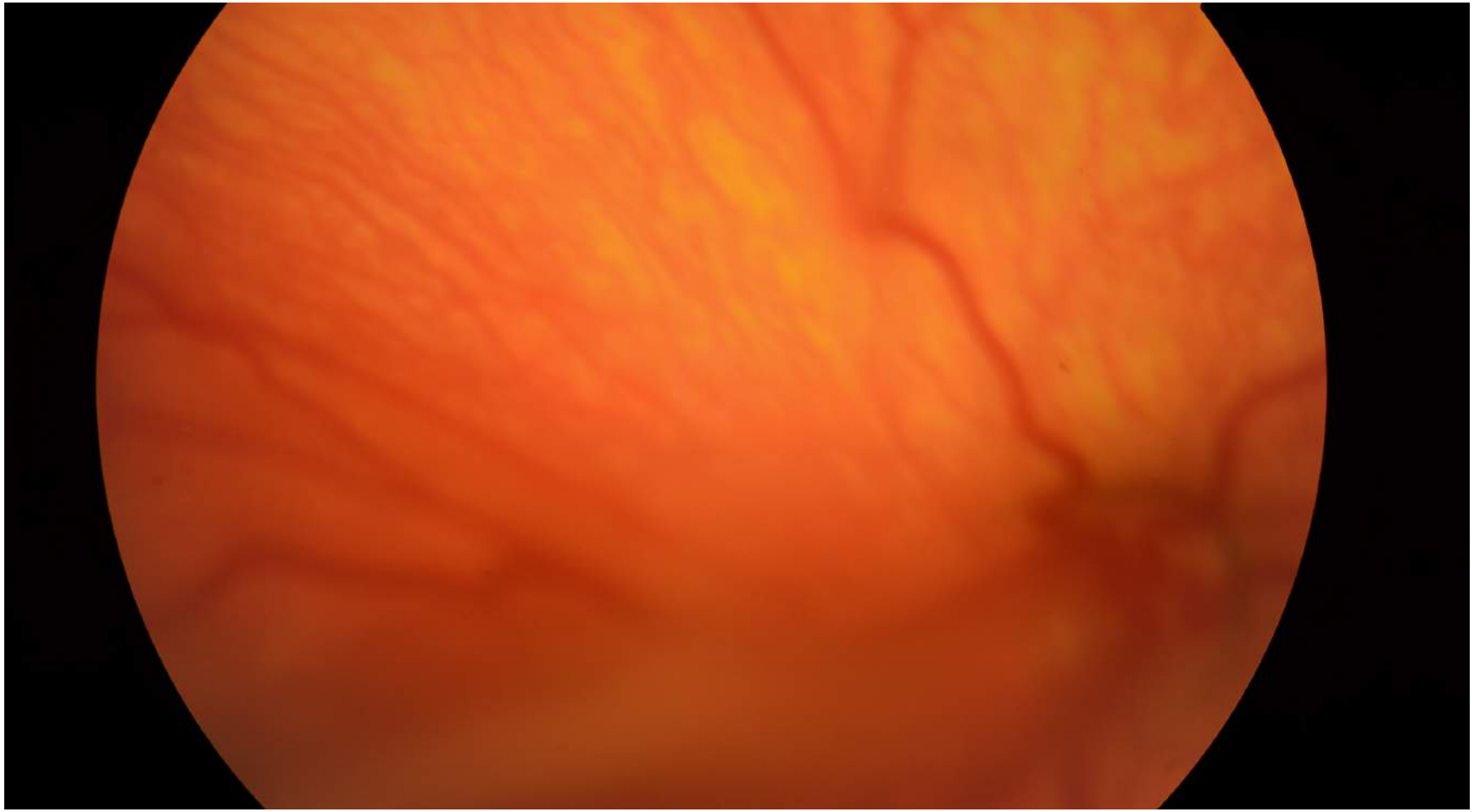
- V 35. tednu LFK obojestransko
- V 42. tednu se razvije odstop mrežnice desno, nato še levo

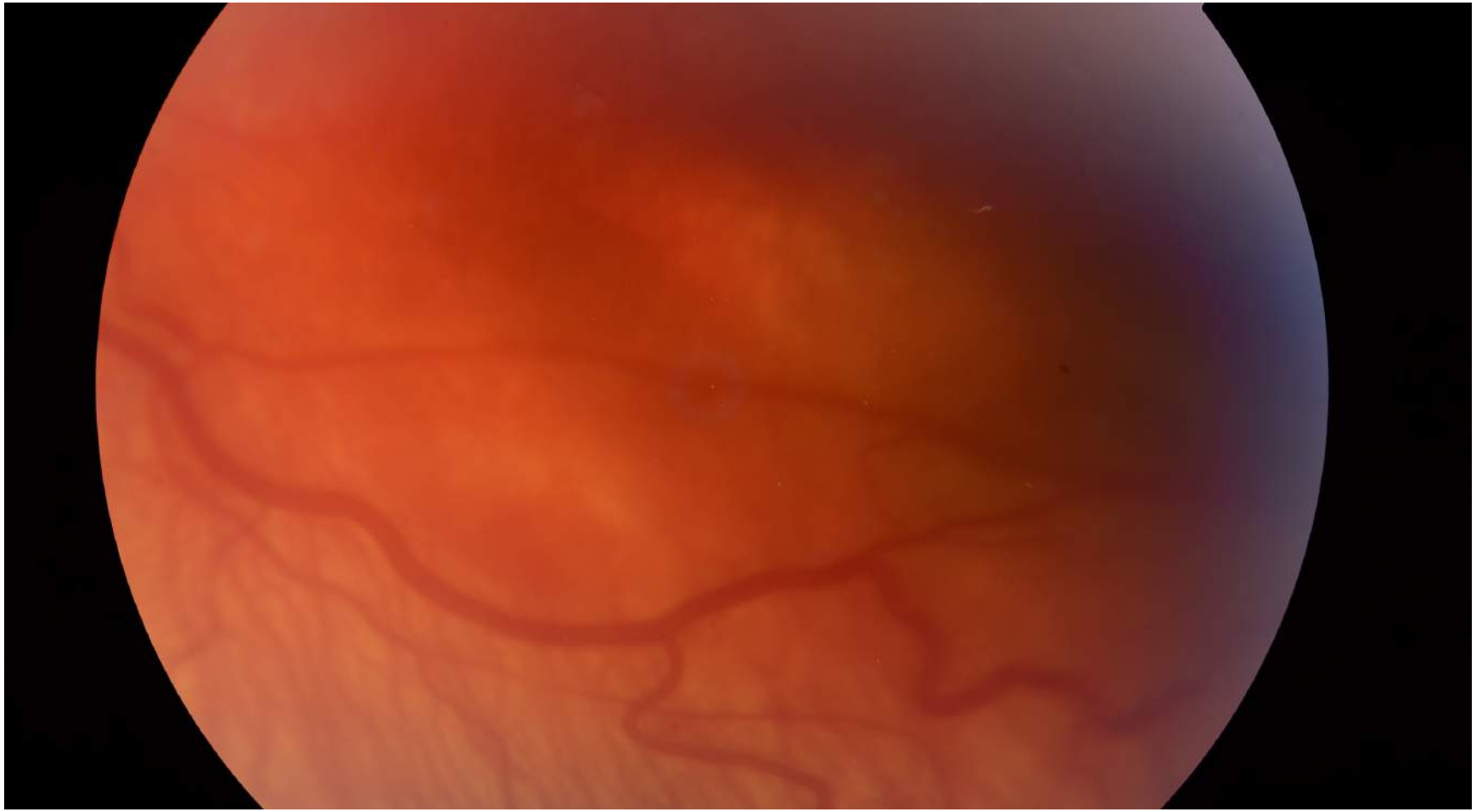
- Poslan na zdravljenje v Antwerpen
- Avastin v desno oko
- Kriokoagulacija levo
- Vitrektomija desno

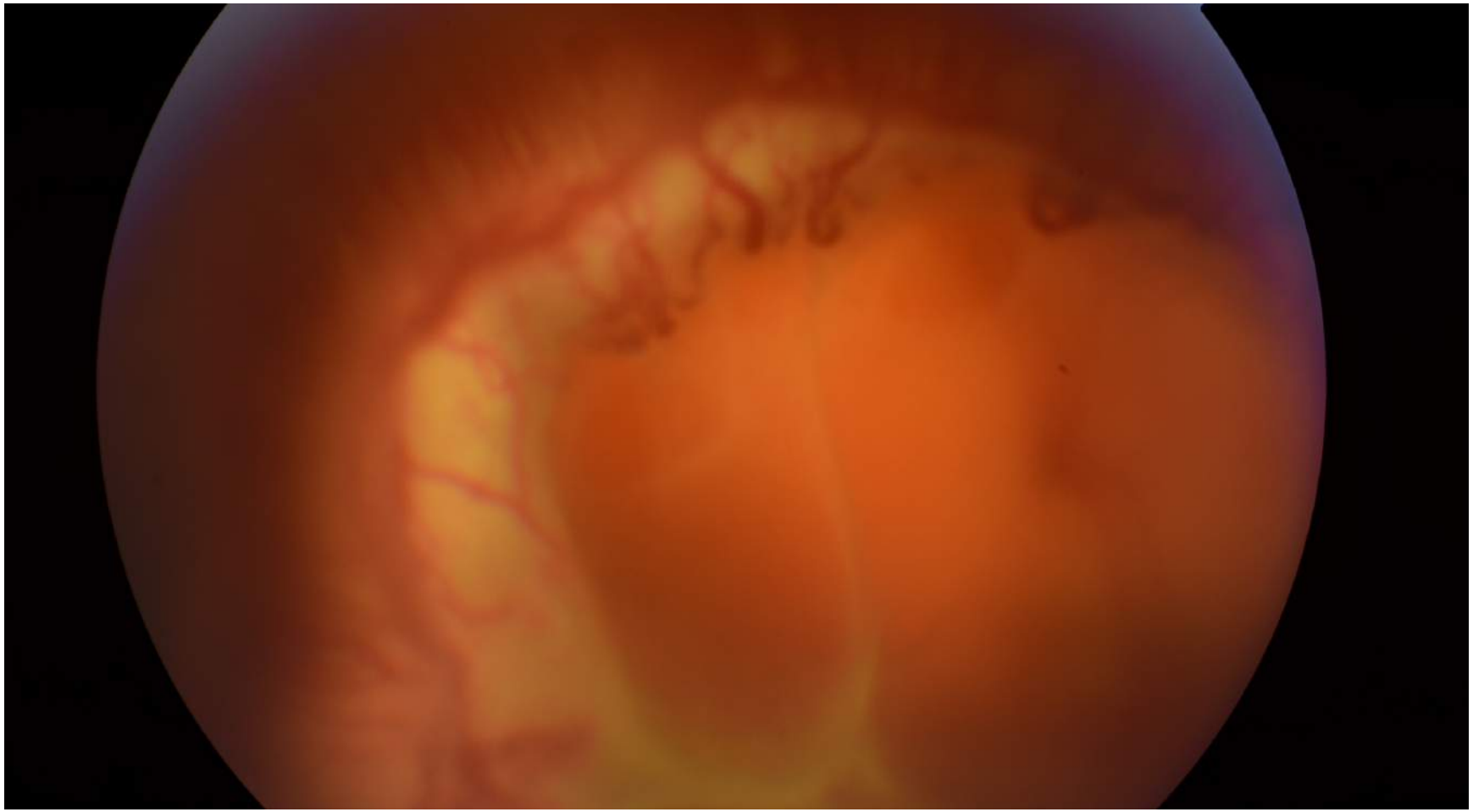












Zahvala

- doc. dr. Manci Tekavčič Pompe
- Barbari Klemenc


That's all Folks!