GEN KÖK
Genom ve Kök Hücre Merkezi
Genome and Stem Cell Center

DEJENERATİF RETİNA VE OPTİK SİNİR HASTALIKLARINDA KÖK HÜCRE KULLANIMI

Prof.Dr. Ayşe Öner, FEBO
Erciyes Universitesi Tıp Fakültesi
Göz Hastalıkları AD KAYSERİ
TOD 52. ULUSAL KONGRE
VRC BİLEP

ERCİYES ÜNİVERSİTESİ 1978

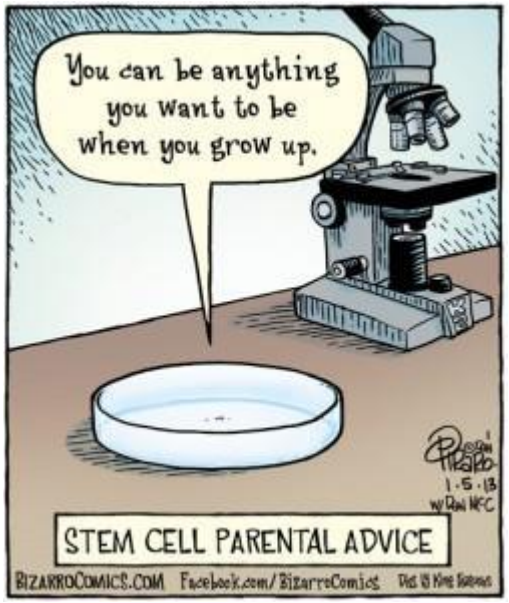
Finansal İlinti Beyanı

* Finansal ilintim yoktur.

KÖK HÜCRE NEDİR?

Kök Hücre:

* Hücrenin özelleşmemiş en temel ve saf halidir.
* Vücuttaki pek çok hücre tipine differensiye olabilir.
* Hasarlı hücre ve dokuları onarabilir.

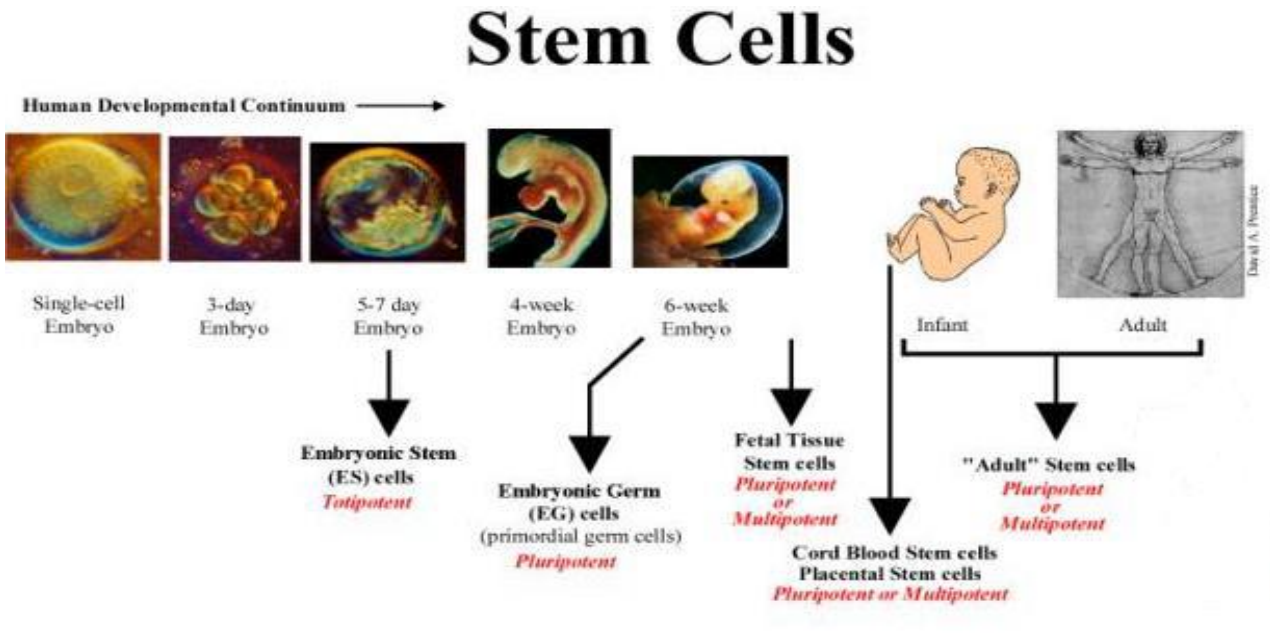


KÖK HÜCRELERİN ÖZELLİKLERİ

- Proliferasyon
- Self-renewal: Kendini yenileme
- Differensiasyon

KÖK HÜCRE TİPLERİ

1-EMBRYONİK KÖK HÜCRE
2-ERİŞKİN KÖK HÜCRE
- Mesenkimal KH
- İndüklenmiş pluripotent KH
3-KORDON KANI KÖK HÜCRESİ
4- AMNİOTİK SIVI KÖK HÜCRESİ



ÜLKEMİZDE KÖK HÜCRE UYGULAMALARI

* İnsan embriyonik kök hücre kullanımı yasaktır (2005)

* Erişkin kök hücre ve İPKH kullanımı için ise Lokal Etik Kurumdan ve Sağlık Bakanlığı'ndan (Organ ve Doku Nakli Biriminden) onay gereklidir.

(TCK: 90 ile uygulamalar yasal olarak düzenlenmiştir.)

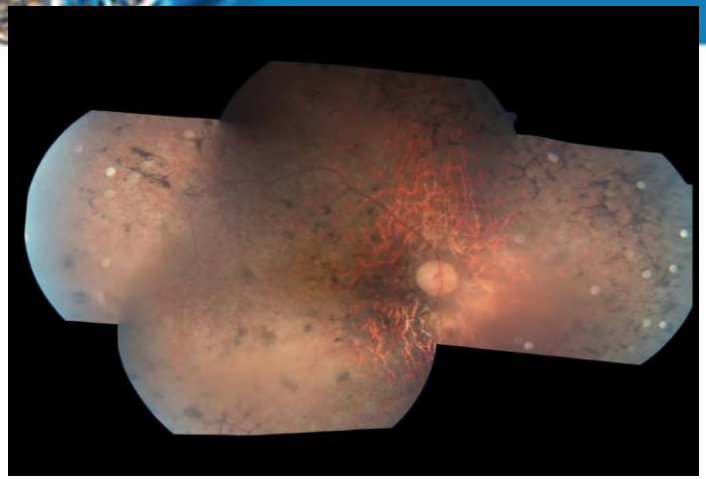
KÖK HÜCRE TEDAVİSİNİN MEKANİZMASI

* (1) Hücre Replasmanı: Sağlıklı kök hücreler dejenere hücrelerin yerini alabilir.
* (2) Nutrisyonel Destek (Parakrin etki): Sağlıklı kök hücreler salgıladıkları faktörlerle etraftaki hücrelerin yaşamlarını desteklerler.
* (3) Hücreler arası yeni bağlantılar oluşturulmasına yardımcı olurlar.

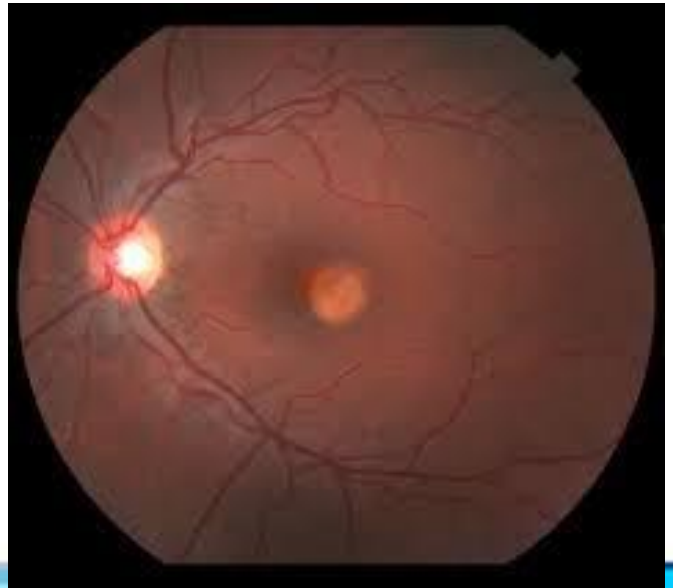
Gözde Kök Hücre Kullanımı

* Çok küçük dozlar yeterli olur.
* Cerrahi yaklaşım kolaydır.
* Nakledilen hücre kolayca izlenir.
* Gözün immün yapısı uygundur.
* Diğer göz kontrol olarak kullanılabilir.
* Ekstraoküler yayılım söz konusu değildir.

HEDEFLENEN RETİNAL HASTALIKLAR



RP, Leber KA, YBMD, BEST, STARGARDTS' OPTİK NÖROPATİLER



KÖK HÜCRE İLE İLGİLİ YAYINLAR

- Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet* 2015;385:509-16.
- Song WK, Park KM, Kim HJ, et al. Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients. *Stem Cell Reports* 2015;4:860-72.
- Limoli PG, Limoli C, Vingolo EM, Scalinci SZ, Nebbioso M. Cell surgery and growth factors in dry age-related macular degeneration: visual prognosis and morphological study. *Oncotarget* 2016;7:46913-23.
- Mandai M, Watanabe A, Kurimoto Y, et al. Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration. *N Engl J Med* 2017;376:1038-46
- Kuriyan AE, Albini TA, Townsend JH, et al. Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD. *N Engl J Med* 2017;376:1047-53.
- Kumar A, Midha N, Mohanty S, Chohan A, Seth T, Gogia V, Gupta S.Evaluating role of bone marrow-derived stem cells in dry age-related macular degeneration using multifocal electroretinogram and fundus autofluorescence imaging. *Int J Ophthalmol.* 2017;10(10), 1552-1558.
- Siqueira RC, Messias A, Messias K, et al. Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells (Reticell -clinical trial). *Stem Cell Res Ther* 2015;6:29.
- Park SS, Bauer G, Abedi M, et al. Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings. *Invest Ophthalmol Vis Sci* 2015;56:81-9.
- Satarian L, Nourinia R, Safi S, et al. Intravitreal Injection of Bone Marrow Mesenchymal Stem Cells in Patients with Advanced Retinitis Pigmentosa; a Safety Study. *J Ophthalmic Vis Res* 2017;12:58-64.
- **Oner A, Gonen ZB, Sinim N, Cetin M, Ozkul Y. Subretinal adipose tissue-derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: a phase I clinical safety study. *Stem Cell Res Ther* 2016;7:178.**
- Weiss JN, Levy S. Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of retinitis pigmentosa. *Stem Cell Investig*. 2018 Jun 6;5:18.
- Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study (SCOTS): bone marrow-derived stem cells in the treatment of Leber's hereditary optic neuropathy. Neural Regen Res 2016;11:1685-94.
- Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of non-arteritic ischemic optic neuropathy (NAION). Stem Cell Investig 2017;4:94.
- Cell Physiol Biochem. 2018;49(1):40-52.

Original Article

Stem Cell INVESTIGATION

Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of Retinitis Pigmentosa

Jeffrey N. Weiss[1], Steven Levy[2]

2018-Haziran

Results: Following therapy in SCOTS or SCOTS 2, 11 patients (64.7%) showed improved binocular vision averaging 10.23 lines of Snellen acuity per eye over pre-treatment acuity; 8 patients (35.3%) remaining stable over the follow up period; no patients experiencing loss of overall acuity. In 33 treated eyes, 15 eyes (45.5%) improved an average of 7.9 lines of Snellen acuity, 15 eyes (45.5%) remained stable, and 3 eyes (9%) worsened by an average of 1.7 lines of Snellen acuity. Improvements ranged from 1 to 27 lines of vision. Using the LogMAR Scale and calculating delta as a ratio to pre-treatment vision in improved eyes, acuity improvement ranged from 23% to 90% with an average of 40.9% visual acuity improvement over baseline vision. Evaluation of all patients and eyes capable of LogMAR vision showed an average of 31% improvement in vision over baseline. Findings were of statistical significance (P=0.016). There were no surgical complications.

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RESEARCH ARTICLE

Stem Cell Ophthalmology Treatment Study (SCOTS): bone marrow-derived stem cells in the treatment of Leber's hereditary optic neuropathy

Jeffrey N. Weiss[1], Steven Levy[2, *], Susan C. Benes[3]

1 Retina Associates of South Florida, 5800 Colonial Drive, Suite 300, Margate, FL, USA
2 MD Stem Cells, 3 Sylvan Road South, Westport, CT, USA
3 The Eye Center of Columbus, The Ohio State University, Columbus, OH, USA

Abstract

The Stem Cell Ophthalmology Treatment Study (SCOTS) is currently the largest-scale stem cell ophthalmology trial registered at ClinicalTrials.gov (identifier: NCT01920867). SCOTS utilizes autologous bone marrow-derived stem cells (BMSCs) to treat optic nerve and retinal diseases. Treatment approaches include a combination of retrobulbar, subtenon, intravitreal, intra-optic nerve, subretinal, and intravenous injection of autologous BMSCs according to the nature of the disease, the degree of visual loss, and any risk factors related to the treatments. Patients with Leber's hereditary optic neuropathy had visual acuity gains on the Early Treatment Diabetic Retinopathy Study (ETDRS) of up to 35 letters and Snellen acuity improvements from hand motion to 20/200 and from counting fingers to 20/100. Visual field improvements were noted. Macular and optic nerve head nerve fiber layer typically thickened. No serious complications were seen. The increases in visual acuity obtained in our study were encouraging and suggest that the use of autologous BMSCs as provided in SCOTS for ophthalmologic mitochondrial diseases including Leber's hereditary optic neuropathy may be a viable treatment option.

Key Words: *nerve regeneration; Leber's hereditary optic neuropathy; mitochondrial disease; optic neuropathy; bone marrow derived stem cells; blindness; visual loss; neural regeneration*

Original Article

Stem Cell INVESTIGATION

Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of non-arteritic ischemic optic neuropathy (NAION)

Jeffrey N. Weiss[1], Steven Levy[2], Susan C. Benes[3]

Background: Ten patients with bilateral visual loss due to sequential non-arteritic ischemic optic neuropathy (NAION) underwent autologous Bone Marrow Derived Stem Cell (BMSC) therapy within the Stem Cell Ophthalmology Treatment Study (SCOTS). SCOTS is an Institutional Review Board approved clinical study utilizing autologous BMSC in the treatment of optic nerve and retinal diseases that meet inclusion criteria.

Methods: The average age of the patients treated was 69.8 years. The average duration of visual loss in eyes treated was 9.8 years and ranged from 1 to 35 years. Affected eyes were treated with either retrobulbar, subtenons and intravenous BMSC or, following vitrectomy, intra-optic nerve, subtenons and intravenous BMSC. The primary outcome was visual acuity as measured by Snellen or converted to LogMAR.

Results: Following therapy in SCOTS, 80% of patients experienced improvement in Snellen binocular vision (P=0.029) with 20% remaining stable; 73.6% of eyes treated gained vision (P=0.019) and 15.9% remained stable in the post-operative period. There was an average of 3.53 Snellen lines of vision improvement per eye with an average 22.74% and maximum 83.3% improvement in LogMAR acuity per eye. The average LogMAR change in treated eyes was a gain of 0.364 (P=0.0089). Improvements typically manifested no later than 6 months post procedure.

FAZ II ÇALIŞMAMIZ

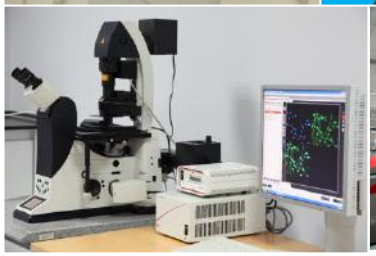
* Çalışma için kurumun etik kurulundan (No:2017/480) ayrıca T.C Sağlık Bakanlığı bünyesinde bulunan Organ Doku ve Diyaliz Hizmetleri Daire Başkanlığı'ndan
  (No: 56733164/203) onay alınmıştır.

* 20 olgu opere edildi. (YBMD, RP, Stargardt MD, optik atrofi)

* Suprakoroidal olarak adipoz dokudan derive edilmiş allojenik mezenkimal KH kullanıldı.

* Proje dışında Sağlık Bakanlığı onayı alınarak ilave 23 hasta opere edilmiştir.

GENKÖK VE EÜTF



GMP (Good manufacturing practice) (İyi Klinik Uygulamalar)

ADMKH ler uluslar arası standartlarda üretildi

SONUÇLAR

* 20 olgunun 6 aylık takipleri tamamlanmıştır.
* Hiçbir olguda sistemik komplikasyon olmadı.
* Hiçbir olguda okuler komplikasyon olmamıştır.

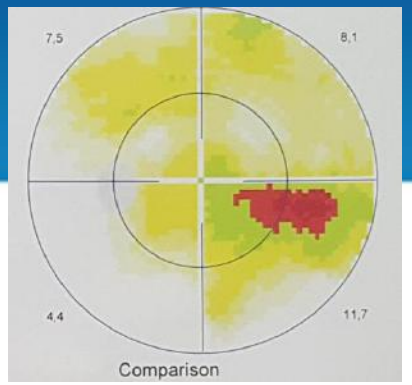
SUPRAKOROİDAL KÖK HÜCRE UYGULAMASI GÜVENLİ

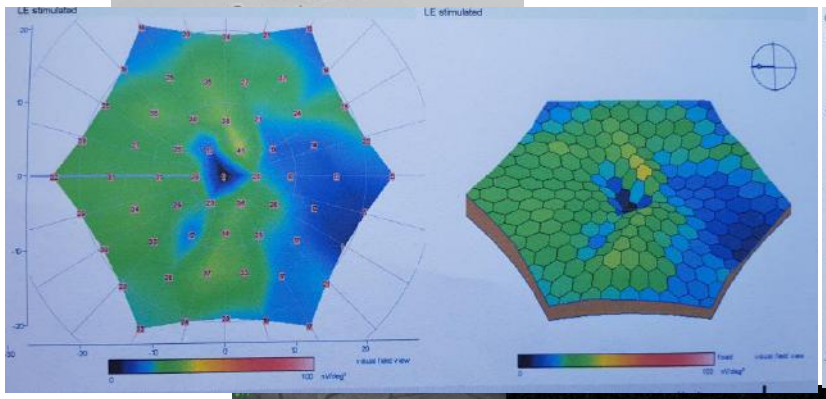
SONUÇLAR

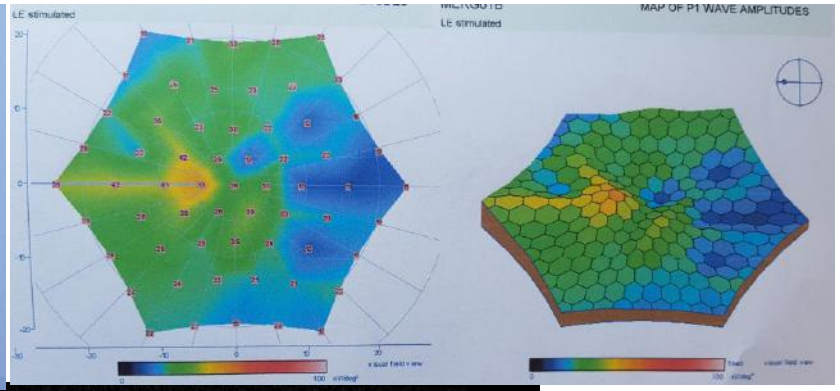
- Olguların % **85'inde** değişen düzeylerde görme keskinliği ve görme kalitesi artışları saptanmıştır. %15'i stabil seyretmiştir.
- Görme artışı en iyi olan olgular preop görmesi iyi olan olgulardır.
- En az gören olgu **p+'den 1meh'ne** yükselmiştir.
- En iyi gören olgu **0.05'den 0.3'e** yükselmiştir.
- Görme artışı 1. ay kontrolünde başlamış, 6 ay kontrolünde daha da belirginleşmiştir.
- Olguların hepsinde mf ERG ve PGA testlerinde iyileşme saptanmıştır.
- Çalışmanın makula hastalarını içeren kısmı yayınlanmak üzere 'Cellular Reprogramming' dergisinde kabul edilmiştir.

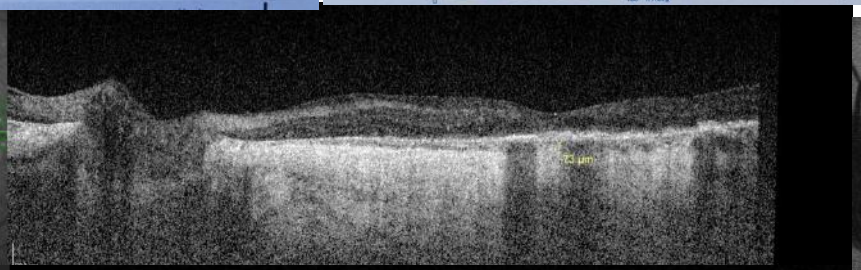
OLGU- YBMD

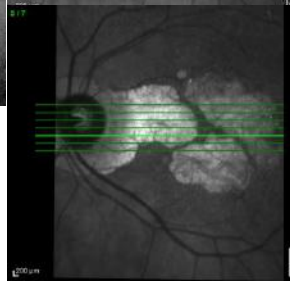
65 y erkek olgu
GK: 1 MPS'den 0.05

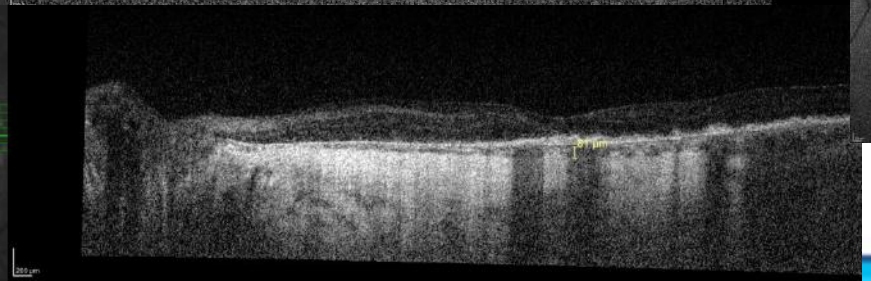




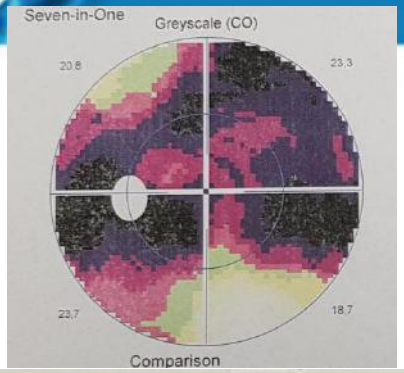


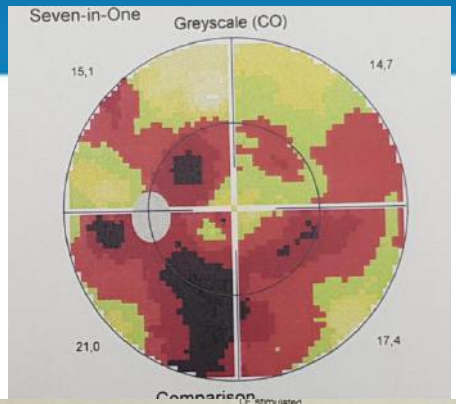




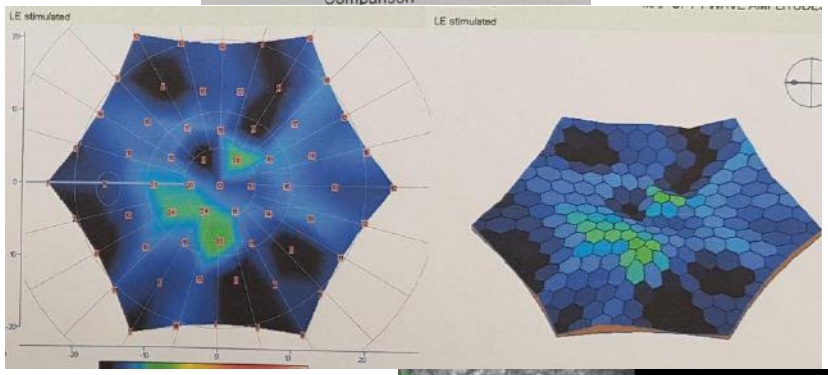


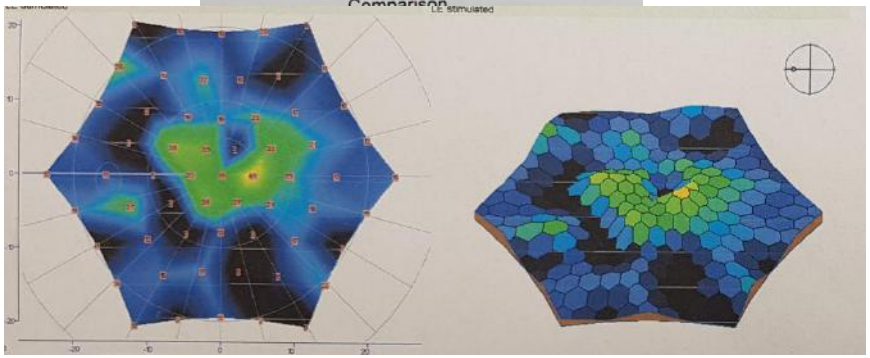
OLGU- STARGARDT HASTALIĞI

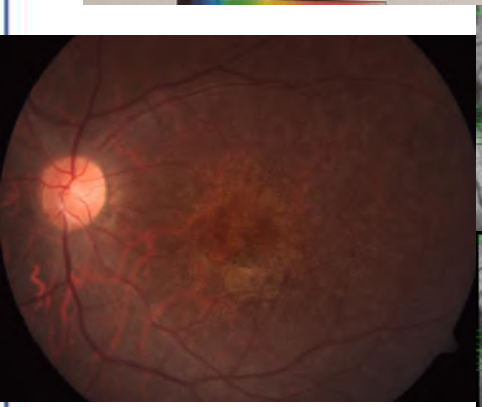


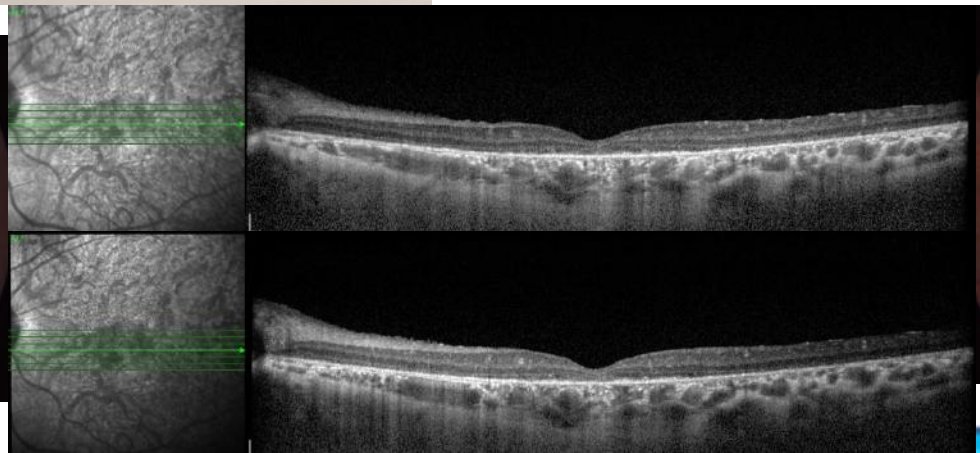


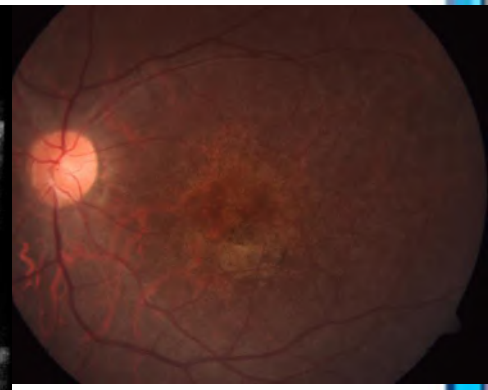
27 y kadın hasta
GK: 1 MPS DEN 0.05



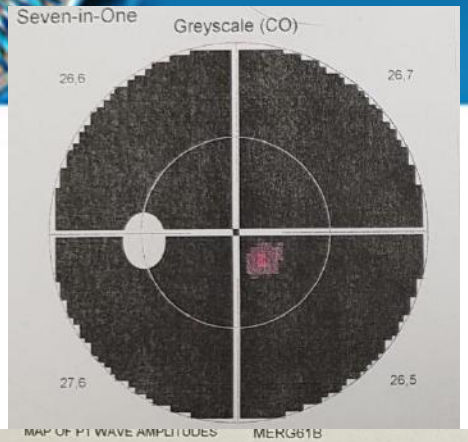




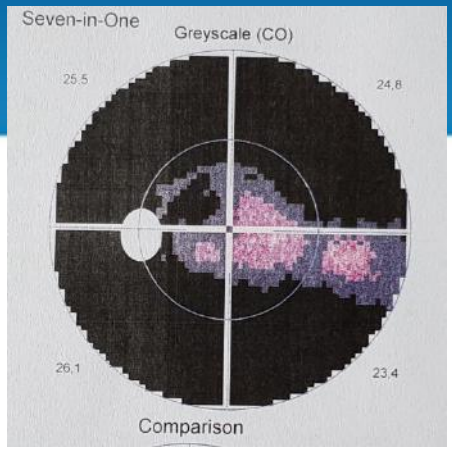


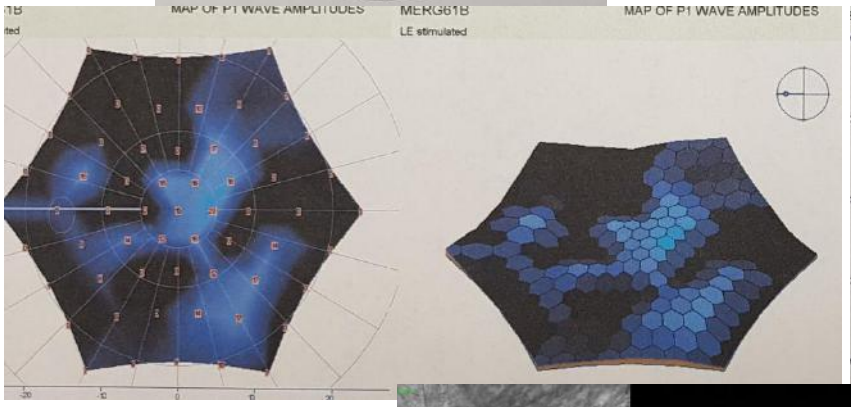


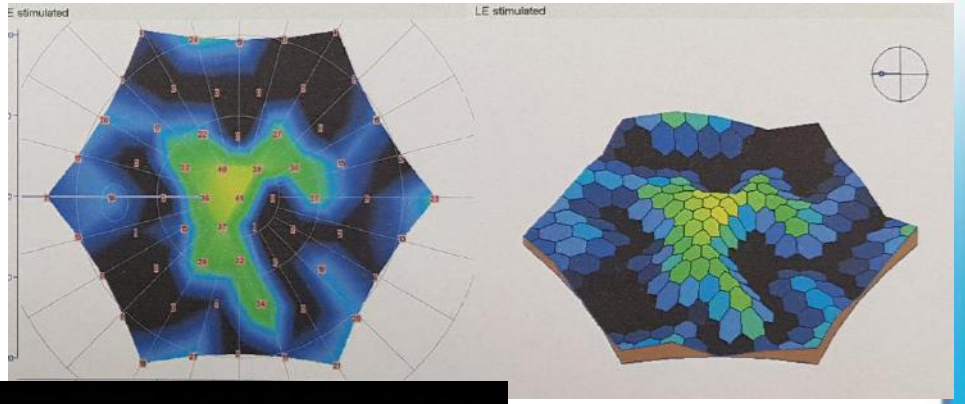
OLGU: RETİNİTİS PİGMENTOSA

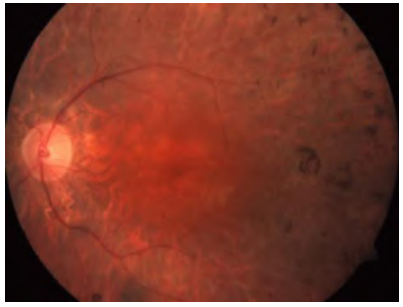


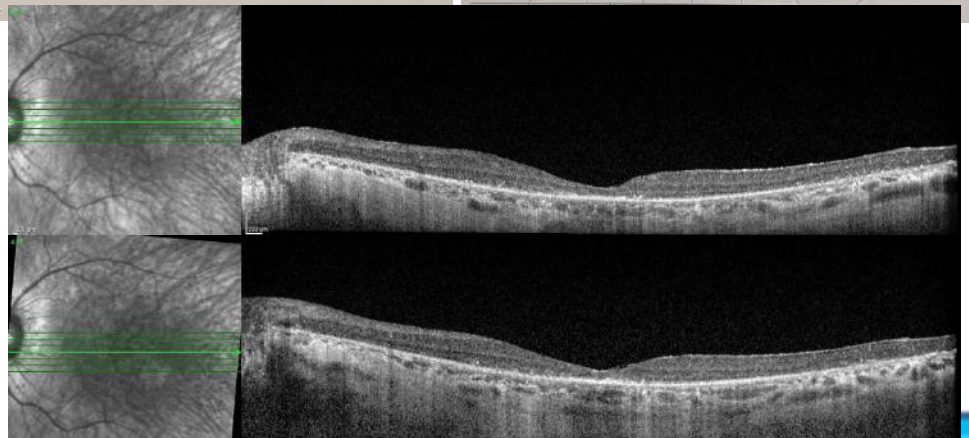
57 y kadın olgu
GK: 1 meh'den 2 mps'ye

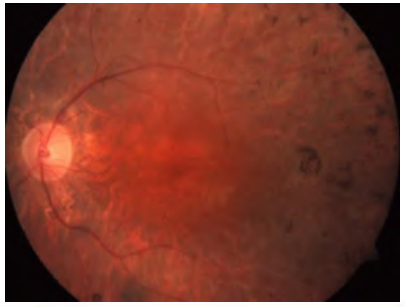




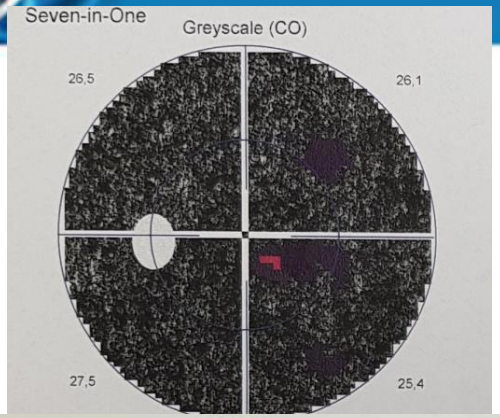




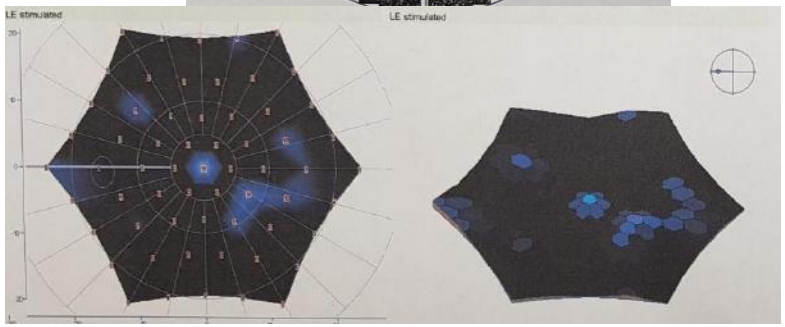


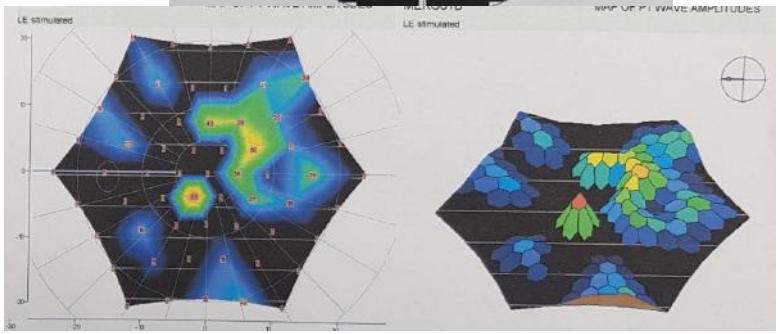


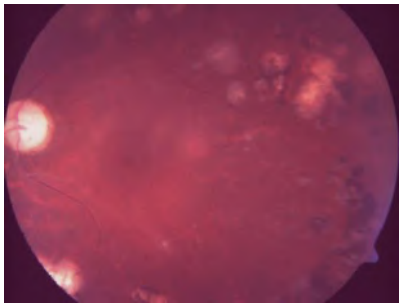
OLGU: OPTİK ATROFİ

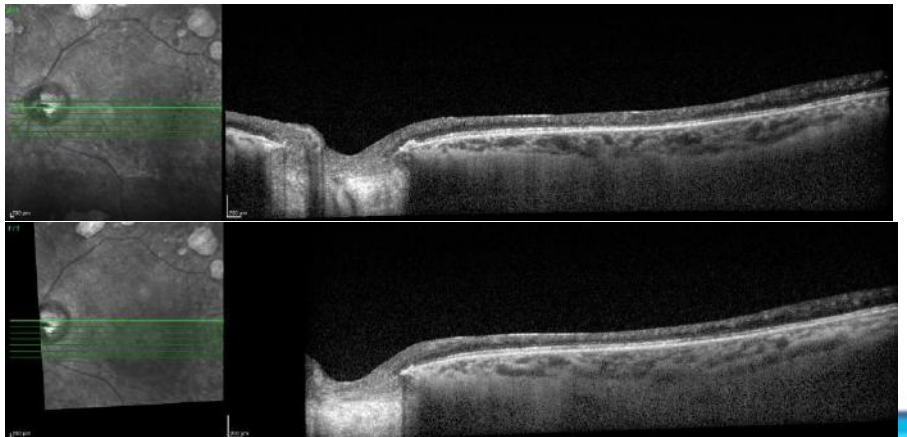


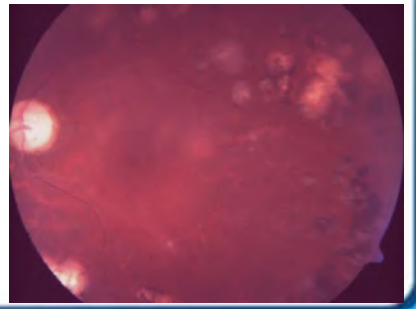
60 y erkek oldu
Diabete bağlı OA
30cmeh'den 1 mps











STANDART PROTOKOL?

* Hangi KH'yi kullanmalı?
* Hangi dozda kullanmalı?
* Hangi şekilde uygulamalı: Subretinal, intravitreal, suprakoroidal, intravenöz?