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Autosomal dominant adult neuronal ceroid lipofuscinosis

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Chapter 7

AD-ANCL

visual

Visual symptoms in autosomal dominant adult neuronal ceroid lipofuscinosis

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Abstract

Objective: to study visual problems in six patients from three generations of a family with autosomal dominant adult neuronal ceroid lipofuscinosis (AD-ANCL).

Methods: We surveyed their records for any data related to vision.

Results: In five patients visual dysfunction was obvious, with both positive visual symptoms (sometimes in temporal relation with epileptic attacks) and decreased visual acuity with abnormal VEP and ERG. Bull's eye maculopathy was seen in one patient, who also had a hyperintense lesion of the optic radiation on MRI.

Conclusion: visual problems are common in AD-ANCL, due to retinal pathology, optic nerve atrophy, optic radiation degeneration, cortical dysfunction and epilepsy.

Introduction

Progressive loss of vision leading to blindness is one of the major manifestations in childhood forms of neuronal ceroid lipofuscinosis (NCL), which show recessive inheritance.

Adult NCL has a rare recessive form (Kufs' disease), and a very rare autosomal dominant form (Parry disease). Ophthalmological findings in recessive adult NCL are reported to be normal {Berkovic et al., 1988, Brain, 111, 27-62}, in sharp contrast to childhood forms. Here we report on visual problems in a family with the autosomal dominant adult form of NCL (AD-ANCL).

Methods

Descriptive and retrospective. We have carefully screened all medical records of our six patients from a known family with AD-ANCL {Nijssen et al., 2002, Mov Disord, 17, 482-7} for any clinical, neurophysiological, ophthalmological, and imaging data related to vision. Diagnosis was confirmed by electronmicroscopy as described previously {Nijssen et al., 2003, Brain Pathol, 13, 574-81}. The cases will be described briefly.

Results

Patient 1

This woman with tonic clonic seizures from the age of 44 years, had progressive cognitive decline, myoclonus and parkinsonism. She died at the age of 51.

No visual symptoms or signs were found in her medical records.

Patient 2

This woman is a daughter of patient 1. She had myoclonus of arms and face from the age of 46 years, followed by progressive dementia, parkinsonism, tonic clonic seizures and psychotic episodes. She died at the age of 59 years. At the age of 46 years old, she mentioned flashes in both eyes. Several months later she described seeing all kinds of colors. No other visual symptoms could be found in her extensive medical records. Neuropsychological testing showed severe difficulties in a trail making test and also in copying complex figures, but no visual problem were reported.

Visual evoked potential (VEP) at the age of 46 years old showed a P100 latency of 115 ms on both sides (normal <117 ms). Two VEP's in the next 2 years were similar.

Patient 3

This sister of patient 2 had depressive and psychotic episodes, epileptic seizures, parkinsonism, myoclonus and dementia. She died at the age of 56.

At the age of 47 she mentioned seeing flashes frequently. A year later she reported colorful optic sensations, which were hard to describe in more detail. In the next two years she complained of blurred vision, and progressively decreasing visual acuity.

VEP at the age of 48 showed delayed P100 latencies of 136 and 146 ms. Four years later VEP showed no discernable responses anymore.

Patient 4

This brother of patients 2 and 3 had myoclonic jerks of the arms since the age of 36 years. He had progressive memory impairment, depressive episodes, parkinsonism, facial dyskinesias and tonic clonic epileptic insults. He died at the age of 56 years.

He mentioned seeing stars and black patches at the age of 43. Five years later a tonic clonic epileptic seizure had a prodrome consisting of seeing stars. In the last months of his life he had an episode with visual hallucinations of persons.

Electronystagmography at the age of 54 showed saccadic pursuit movements, hypometric and overshoot saccades and absent caloric responses (indicating peripheral as well as central vestibular dysfunction). Electrooculography and electroretinography at the age of 54 showed a low normal Lp/Dt ratio, low scotopic amplitudes, while photopic responses were normal, indicating rod-dysfunction. At the age of 61 findings were similar. VEP at the age of 53 showed a delayed P100 of 145 ms at the right side, and no response at the left.

Patient 5

This daughter of patient 2 had tension-type headache and migraine attacks without aura from the age of 19 years. Neurological examination at the age of 24 years was normal. Since the age of 32, she has had progressive myoclonus and slight memory difficulties.

Since the age of 37 she had frequent attacks of colorful visual sensations, which were described as caleidoscopic speckles in the whole visual field, without impairing vision. The sensations were often the first symptoms of an epileptic attack with loss of consciousness. She saw hundreds of yellow or orange dots in a week of not taking her antiepileptic drugs. During a psychotic episode she saw spiders and magicians. She had several short attacks seeing indefinable colorful objects, which diminished after addition of levetiracetam. Since the age of 45 she complains of progressively worsening visual acuity, which decreased to 0.7 vs 0.5 at age 46. Fluorescein fundus angiogram showed slightly altered macular pigment distribution, but no Bulls eye maculopathy. Optical coherence tomography (OCT) was normal.

Patient 6

This son of patient 4 has had myoclonus of the thumb and arms from the age of 25, and frequent tonic clonic seizures since age 31.

Pattern VEP at the age of 31 showed delayed P100 latencies of 132 ms (right) and 134 ms (left). Six years later responses were extremely delayed (239 and 242 ms).

At the age of 38 he reported blurred vision, when visual acuity of the right eye was 3/6, 1/30 at the left. He then had attacks for 10 minutes, three times a week, seeing colorful images. A year later he reported an attack where he saw images of melting snow, blue patches, lots of hair, greyish faces, and a parade of people passing by. Visual acuity was 0.1 vs 0.16. Fluorescein fundus angiogram showed a Bull's eye maculopathy (fig. 2). Cerebral MRI showed optic nerve atrophy, and paraventricular T2 hyperintensity, extending in a thin line (cross-sectioning a plane parallel to the lateral ventricle wall) into the optic radiation (fig. 3). Later he had several attacks with images of hundreds of black hairs randomly scattered like mikado sticks on a white background, stripes in different colors, or more complex images like dolphins in an aquarium. After levetiracetam was added to his anti-epileptic drug regimen, positive visual sensations vanished. At age 44 visual acuity had decreased to 0.05 vs 0.01.

Optical coherence tomography (OCT) (fig 4A) showed severe retinal abnormalities, consisting of an atrophic retina on an intact Bruch membrane, with disturbed retinal layer morphology, merely due to thinning of the outer nuclear layer and outer segment layer (along with its hyperintense borders), and maybe also retinal pigment epithelium atrophy. Where the outer segment layer and retinal pigment epithelium were expected, granular bead-like structures were seen with a diameter of 20 to 50 μm .

Discussion

Visual dysfunction is a hallmark of most NCL forms, but not in Kufs' disease.

In Infantile NCL (CLN1) visual symptoms occur in the first 2 years {Wisniewski et al., 1988, Am J Med Genet Suppl, 5, 27-46}, with retina degeneration, involution of retinal vessels, brownish macula discoloration and optic atrophy. VEP amplitudes decrease from the age of 2.5 years old, and extinction of VEP and Electroretinography (ERG) occur before the age of 4 years {Vanhanen et al., 1997, Dev Med Child Neurol, 39, 456-63}.

In classic Late Infantile NCL (CLN2) onset between age 2 and 4 progresses to blindness at the age of 5 or 6 years old, with retina atrophy and centrifugally progressive loss of photoreceptors. ERG is diminished early, and finally extinguishes. Giant VEP (with amplitudes of around 350 V) is persistent, only to diminish in a preterminal stage {Pampiglione and Harden, 1977, J Neurol Neurosurg Psychiatry, 40, 323-30}.

In CLN3 visual failure presenting between 4 to 7 years old is often the presenting symptom, with rapid progression due to diffuse retinal pigment epithelium atrophy with stippled hyperfluorescence {Hainsworth et al., 2009, Retina, 29, 657-68} and optic nerve atrophy. Bull's eye maculopathy occurs in 1 in 4 {Hainsworth et al., 2009, Retina, 29, 657-68}{Collins et al., 2006, Br J Ophthalmol, 90, 1119-24}. VEP shows markedly reduced amplitudes, and early extinction {Tackmann and Kuhlendahl, 1979, Eur Neurol, 18, 234-42}.

In CLN5 (Finnish v LINCL) giant VEPs are seen at 7-10 years of age {Lauronen et al., 2002, Clin Neurophysiol, 113, 1491-500}, while in CLN6 diminished or absent VEP were reported {Williams et al., 1999, The neuronal ceroid lipofuscinoses, 102 - 13}. In Northern epilepsy

visual evoked potentials were abnormal in 44% {Lang et al., 1997, *Acta Neurol Scand*, 95, 1-8}.

Despite evident retinal abnormalities in a member of our ANCL family and other NCL forms, some studies indicate that other factors than retinal pathology may contribute to visual deterioration in NCL. In a mouse PPT-1 gene knockout model progressive accumulation of autofluorescent storage material in all layers of the retina was observed, but only a modest loss of nucleated cells in the outer and inner nuclear layers. Retinal function was severely impaired by 8 months, despite only modest changes in retinal morphology {Lei et al., 2006, *J Neurosci Res*, 84, 1139-49}. In *Cln3*(-/-) mice decreased optic nerve axonal density and decreased nerve conduction were found, with loss of neurons in the dorsal lateral geniculate nucleus (LGNd). Reduced transport of amino acids from the retina to the LGN suggested an impediment in communication between the retina and projection nuclei {Weimer et al., 2006, *Neurobiol Dis*, 22, 284-93}.

The granular bead-like structures with a diameter of 20 to 50 nm which were seen on OCT in the outer segment layer and retinal pigment epithelium in patient 6 may represent degenerated retinal cells or clustered aggregates of storage material. It is not likely that these beads represent individual GRODs, since the size of ultrastructural granular osmiophilic deposits (GRODs) in *CLN1* is usually up to 0.5 μm , forming aggregates of up to 5 μm {Elleder et al., 1999, *The neuronal ceroid lipofuscinoses*, 5-15}. GRODs found in neurons throughout the CNS in this family varied from 0.5 to 2.5 μm $\varnothing$, while glial inclusions up to 4 μm $\varnothing$ were seen filled with numerous dense osmiophilic granules {Nijssen et al., 2003, *Brain Pathol*, 13, 574-81}. Early ultrastructural studies of the retina in human childhood NCL showed storage material in almost every type of retinal cells, loss of photoreceptors, atrophy of pigment epithelium and displacement of melanin into inner layers of the retina

{Goebel et al., 1974, *Am J Ophthalmol*, 77, 25-39} {Goebel, 1977, *Fortschr Med*, 95, 2432-6}.

In Kufs' disease, the autosomal recessive adult NCL form, vision remains normal, and no retinal pigmentary degeneration occurs {Berkovic et al., 1988, *Am J Med Genet Suppl*, 5, 105-9} {Berkovic et al., 1988, *Brain*, 111, 27-62}. A few case reports focus on the exceptions to this rule. Martin et al. reported storage in retinal ganglion cells in a single Kufs case {Martin et al., 1987, *Clin Neuropathol*, 6, 231-5}. Goebel et al. found granular lipopigment storage in nerve cells in different layers of the retina of a 33-year-old woman with biopsy-proven Kufs' disease who had never had visual impairment, nor electroretinographic abnormalities {Goebel et al., 1998, *Acta Anat (Basel)*, 162, 127-32}. Ikeda et al. report a case of Kufs' disease with retinal lesions which resulted in total blindness, with retinal thinning with severe loss of rods, cones, and outer nuclear and outer plexiform layers. Ganglion cells of the retina were ballooned and contained lipopigments {Ikeda et al., 1984, *Clin Neuropathol*, 3, 237-9}. Armstrong et al. reported abnormal functioning of the amacrine and horizontal cell systems of lateral inhibition in a patient with Kufs' disease {Armstrong et al., 1985, *Int Ophthalmol*, 8, 37-42} {Dawson et al., 1985, *Doc Ophthalmol*, 60, 163-71}. Charles et al. found asymptomatic pigmentary retinal degeneration in a patient with questionable Kufs' disease {Charles et al., 1990, *Rev Neurol (Paris)*, 146, 752-6}. Alonso-Navarra observed a single case of Kufs' disease with probable visual agnosia, hypermetamorphopsia {Alonso-Navarro et al., 2005, *Rev Neurol*, 40, 93-8}. Zini described a case of Kufs' disease with focal occipital seizures with visual hallucinations where MRI showed cortical atrophy and, on T2-weighted images, hyperintensity and reduction of the deep white matter {Zini et al., 2008, *Neurology*, 71, 1709-12}. However, according to Berkovic, the reported diagnosis of Kufs' disease is often doubtful after critical reassessment (including

Dawson's case) {Berkovic et al., 1988, Am J Med Genet Suppl, 5, 105-9}{Berkovic et al., 1988, Brain, 111, 27-62}. In the autosomal dominant ANCL family described by Boehme, no sensory disturbances were seen, but their patient IV/2 presented with 'a faint preceded by a visual aura of "bright spots"' {Boehme et al., 1971, Brain, 94, 745-60}. The single patient from an AD-ANCL family reported by Ferrer et al. had no reported visual problems {Ferrer et al., 1980, J Neurol, 222, 183-90}. In the AD-ANCL family described by Josephson et al. one patient had visuospatial deficits, one had 'a spell with micropsia' and visual hallucinations, in 3 others ophthalmologic examination was normal {Josephson et al., 2001, J Neurol Sci, 188, 51-60}. In the AD-ANCL family from Alabama, 2 patients saw flashing lights as an aura to their seizures. None had optic atrophy or retinal degeneration on fundoscopic examination {Burneo et al., 2003, Epilepsia, 44, 841-6}.

In our autosomal dominant ANCL family visual problems were frequent and diverse. Abnormal ERG's and Bulls eye maculopathy indicate retinal pathology. Bilaterally delayed VEP's may also indicate retinal, optic nerve, chiasma, tract or radiation dysfunction. Optic nerve atrophy was seen on MRI of patient 6, where cerebral MRI also showed optic radiation hyperintensity and atrophy of the visual cortex.

Abundant positive visual signs in patient 3,4,5 and 6 were most likely of temporo-occipital epileptic origin, because of a temporal relation with epileptic seizures and response to anti-epileptic drugs. In patient 6 more complex images occurred in later stages with severely impaired vision, which may resemble Charles-Bonnet syndrome.

The widespread visual pathology in this family with AD-ANCL is in contrast with the normal or minimal visual findings in Kufs' disease. This supports our view that the autosomal dominant and the recessive form of ANCL should be considered separate nosological entities.

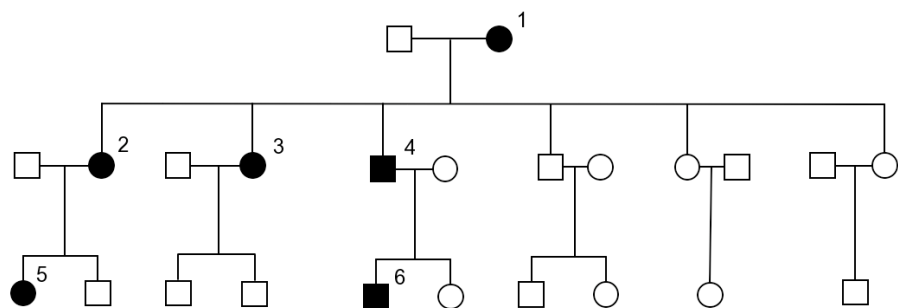


Fig.1: Family pedigree.

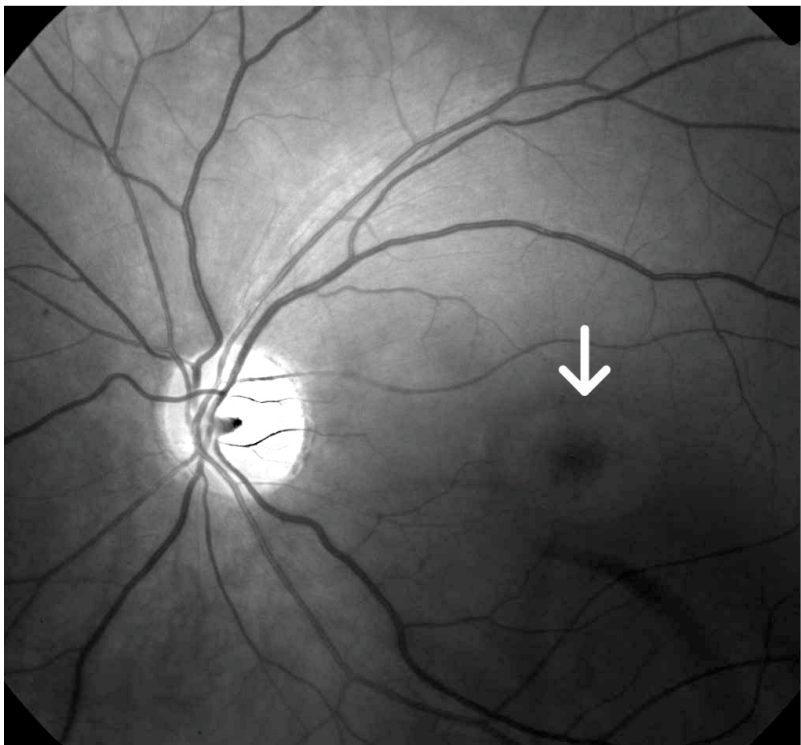


Fig. 2: fluorescein fundus angiogram of patient 6, showing a Bull's eye maculopathy (arrow).

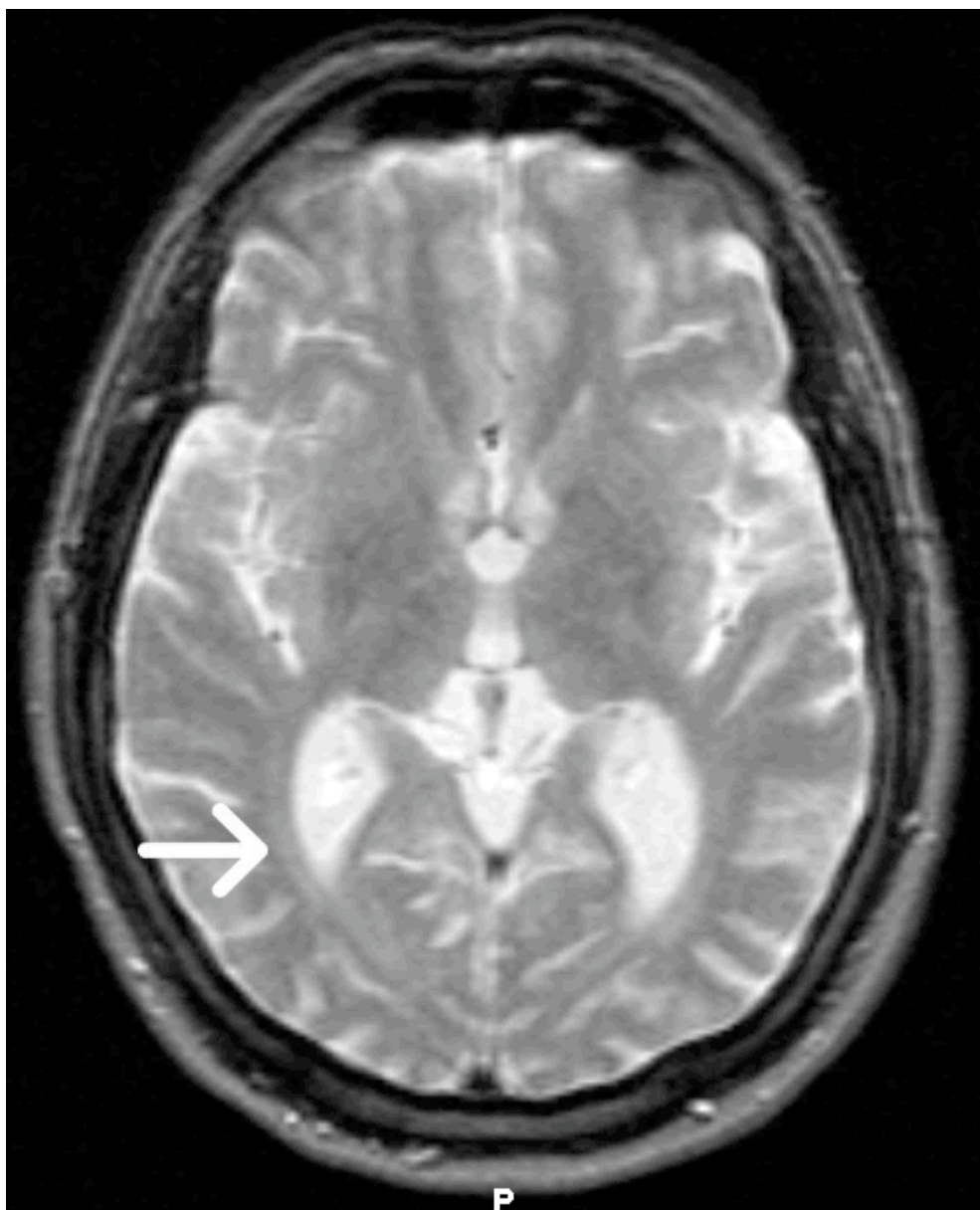


Fig. 3: T2 weighted cerebral MRI of patient 6, showing bilateral periventricular hyperintensity in the optic radiation (arrow).

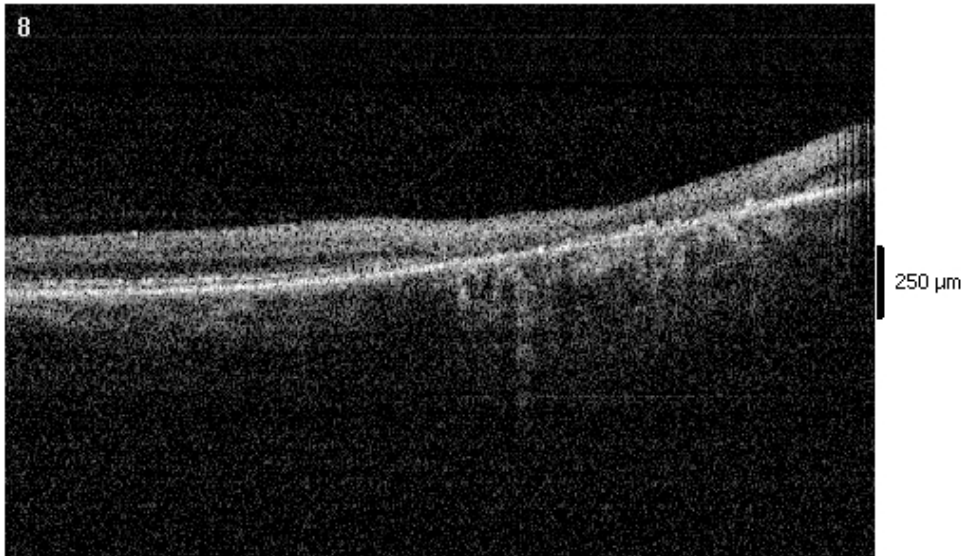
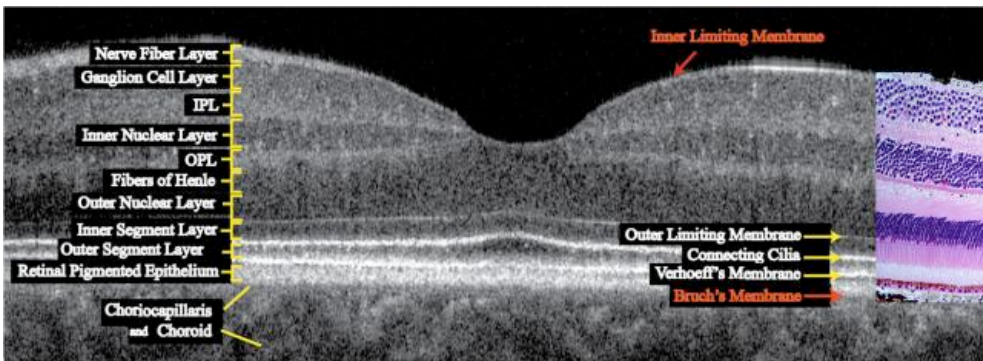


Fig. 4A: Optical coherence tomography (OCT) of patient 6. Retinal atrophy due to thinning of the outer nuclear layer and outer segment layer, and maybe also retinal pigment epithelium atrophy. Where the outer segment layer and retinal pigment epithelium were expected, granular bead-like structures were seen with a diameter of 20 to 50 m.



4B: normal OCT and normal retinal histology

(from <http://vsri.ucdavis.edu> , adapted from Optics ExpressNs, 2005; Expert Review of Ophthalmology, 2007)

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