Antioxidant treatment in patients with SLOS

Ellen Roy Elias, MD, FAAP, FACMG
Professor, Pediatrics and Genetics
CU School of Medicine
Director, Special Care Clinic
Children's Hospital Colorado

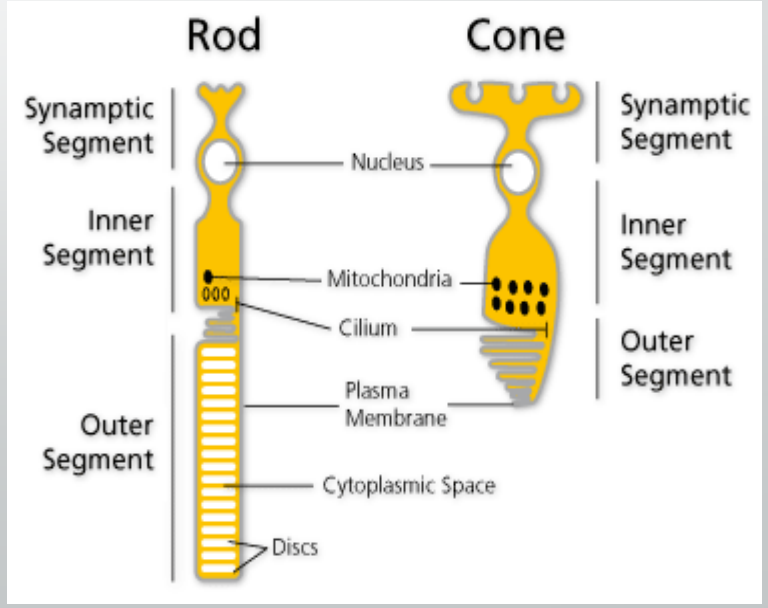
Review Of Antioxidant Protocol with Updates: 2008-2019

Retinal Studies:

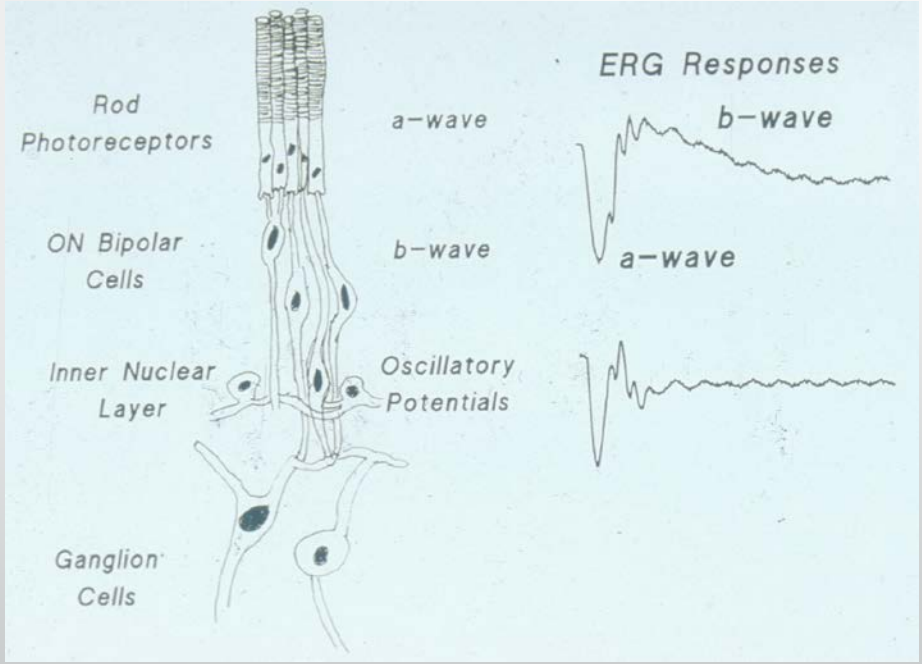
- Historically, patients with SLOS followed with serial eye exams between 1994-2007 were noted to have progressive loss of vision and abnormal eye findings.
- Earlier studies had shown two retinal issues:
  - Pigmentary retinopathy: abnormal pigment deposits of the retina which worsened over time
  - Abnormal retinal function on ERG consisting of reduced amplitude of the wave, and an increased implicit time (IT); ie. it took a greater amount of light energy a longer period of time to produce a retinal response

Difference between Rods and Cones

- Rods and Cones are two different types of photoreceptors used to process light. **In patients with SLOS, both rods and cones are affected, but rods are affected more severely than cones.** In a human eye, an estimated number is felt to be about 5-7 million Cones and 110-130 million Rods. Cones are found mainly in the central area of the Retina (Fovea), while Rods are found in the Peripheral Retina. When Photoreceptors respond to light, it causes the activation and consequent breakdown of a photo-sensitive pigment, bound in large quantities to the membranes of the outer segment.



The Retina and ERG waves



Since late 2008, the SLOS Retinal protocol is as follows:

—An Ophthalmology Exam (EUA) and an ERG are preformed at baseline under Anesthesia

—Patients undergo serial ERG's and EUA's while on both Cholesterol and Antioxidants (AquADEKS or DEKAS plus)

—A Pediatric Ophthalmologist is examining all patients and obtaining good photos during the EUA with a special Retcam to follow the pigmentary changes

—**Treatment** – started at enrollment

Cholesterol suspension (200 mg/ml and/or other cholesterol sources) with doses of 150-250 mg/kg/day divided three times a day

AquADEKs™	
or	Vitamins A, D, E, K
DEKAS plus	Vitamin C
	B Vitamins
	Selenium
	Coenzyme Q10

Participants

- 25 patients with biochemically and/or genetically confirmed SLOS were enrolled in the COMIRB approved protocol at Children's Hospital Colorado between 2003 and 2019, and had at least one ophthalmologic exam under anesthesia (EUA) and Electroretinogram (ERG).
- Patients treated prior to 2008 were on Cholesterol alone and since 2008 were on both cholesterol and antioxidants.
- Average age was 10 years (range 13 days to 49 years)

Average sterol labs at diagnosis grouped by sterol ratio severity

	Mild N=7	Moderate N=11	Severe N=7
Serum Cholesterol (mg/dL)	152.6 (93-193)	129 (88-191)	47.9 (12-83)
Serum 7-DHC (mg/dL)	1.1 (0.04-3.3)	5.2 (2.0-13.0)	21.3 (3.2-46.0)
Serum 8-DHC (mg/dL)	0.9 (0.0-2.9)	4.51 (2.1-7.2)	14.3 (3.4-27.5)
Sterol Ratio (%)	0.9 (0.03-3.3)	7.8 (3.9-15.0)	186.1 (17.6-551.7)

- Sterol ratio ranges:
  - Mild (0-3.5), Moderate (3.6-17), Severe (>17).
  - Sterol Ratio : (7-DHC+ 8-DHC)/ cholesterol x 100
  - 7-DHC reference range: 0.004-0.036mg/dL. (Ranges listed in parentheses)

Results:

Mild patients: (sterol ratio < 3.5)

- N=7 patients with at least 1 ERG
- ERG results:
  - Mild patients showed increased implicit times in both rods and cones
  - Rods were affected more than cones:
    - rods showed mild/moderate decrease in amplitude
    - cones showed normal to mild changes.
  - 4 patients with serial studies, all showed improved amplitudes and decreased implicit times.
- EUA studies:
  - 2 patients showed mild pigmentary retinopathy which improved on follow-up testing
  - No progression of RPE seen in any patient
  - 1 patient showed hypoplastic discs and abnormal pigment with tortuous vessels
  - (1 patient died of unrelated issues, 3 lost to follow-up, 1 recently enrolled)

Results:

- Moderate patients
  - N=11 (Sterol ratio 3.6-17) with at least 1 ERG
- ERG results
  - All 11 moderate patients showed increased implicit times in both rods and cones
  - Amplitudes showed rods affected more than cones
    - rods showed a mild-moderate decrease in amplitude
    - cones showed normal to mild to decrease in amplitude
    - In the 8 patients with serial studies, 6 patients improved and 2 were stable *(1 patient recently enrolled and is awaiting follow-up studies)*
  - EUA studies:
    - 4 patients showed mild pigmentary retinopathy which improved on follow-up testing
    - No progression of RPE seen in any patient
    - optic nerve hypoplasia seen in 2 patients, and 1 of these also had tortuous vessels
    - 1 patient developed a cataract and severe retinal detachment

Results:

Severe patients

- N=7 (Sterol ratio >17), 6 with at least 1 ERG and 3 with follow-up studies; *(3 patients died of severe disease,1 lost to follow-up, and 1 too medically unstable to undergo procedures under anesthesia)*

- ERG results
  - All 6 severe patients showed increased implicit times in both rods and cones
  - Amplitudes showed rods affected more than cones
    - rods showed moderate/severe decrease in amplitude
    - *Cone amplitudes were normal!*
  - In the 3 patients with serial studies, rod function varied over time, and cone function remained stable. THERE WAS NO LOSS OF FUNCTIONAL VISION IN ANY PATIENT
  - EUA studies:
    - 3 patients showed stable pigmentary retinopathy
    - No progression of RPE seen in any patient, but also no improvement
    - 1 patient showed marked retinal hypopigmentation

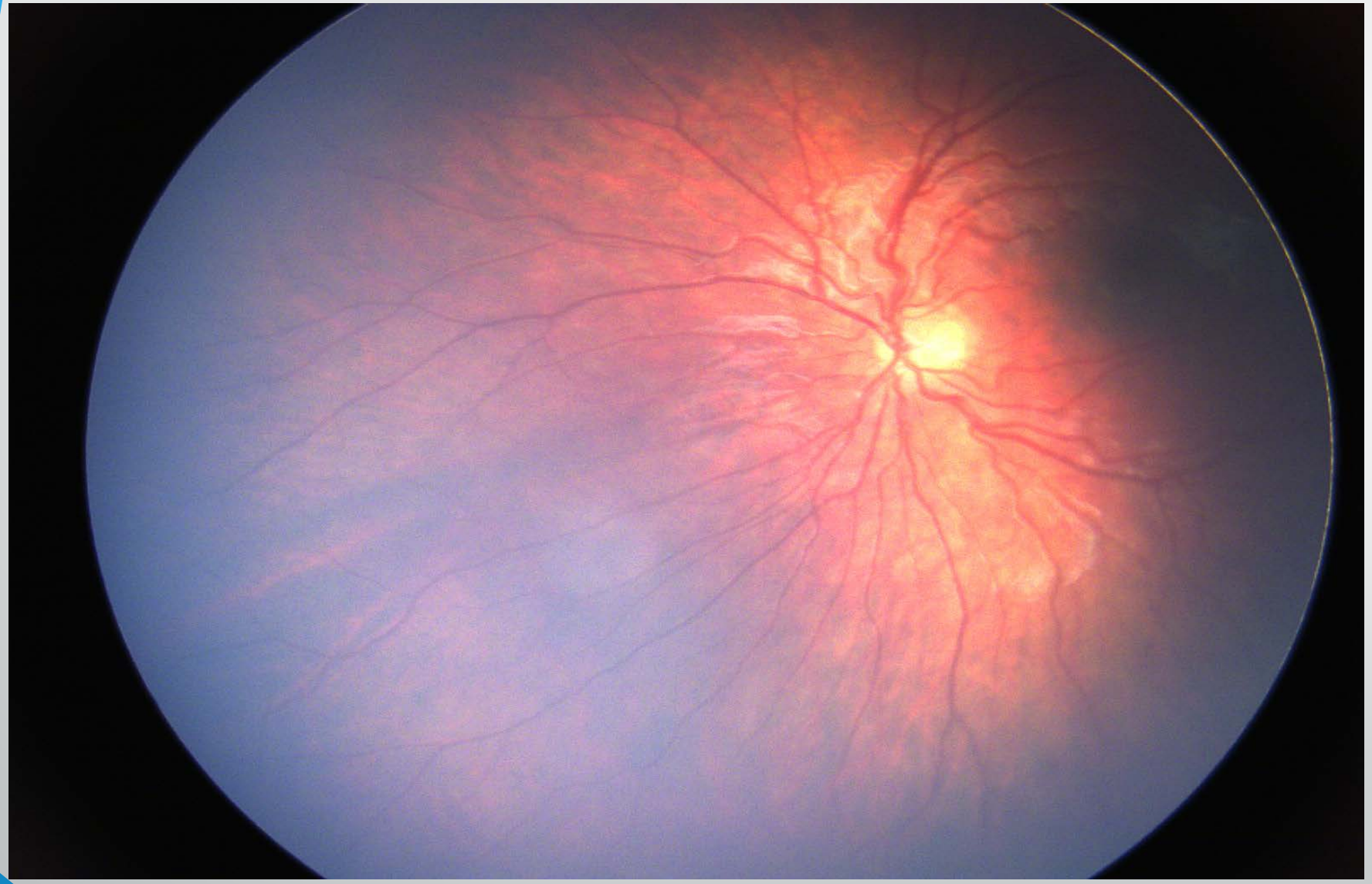
Summary – ERG findings at baseline

- Patients with Smith-Lemli-Opitz syndrome demonstrate abnormalities of retinal function detected on Electroretinogram (ERG)
- The abnormalities demonstrated include:
  - Prolonged implicit times in all patients, regardless of severity of disease
  - Decreased wave amplitudes in Rod cells were seen in all patients, with a greater change found as disease severity worsened.
  - Rod cell amplitudes were affected more than cone cells in mild and moderately affected patients
  - Cone cell amplitudes were NORMAL in severely affected patients – unclear why!!

Summary – ERG findings on treatment with Antioxidants

- Serial studies were done on patients treated with both Cholesterol and Antioxidants (AquADEKS or DEKAS plus)
- ERG findings showed:
  - Improvement in amplitude of both rods and cones in all 3 mild patients
  - Improvement in implicit times in all 3 mild patients
  - Improvement in rods and cones in 6/8 moderate patients
  - Improvement in implicit times in 6/8 moderate patients
  - 2/6 moderate patients showed stable results
  - Rod function was variable in 3/3 severe patients with serial studies
  - Improvement in implicit time in 3/3 severe patients
  - Cone function remained normal
  - 1 patient showed stable results

  - **NO patient showed worsening of retinal function while on treatment, which is promising compared to historical eye findings prior to the use of antioxidants.**



Summary of Ophthalmological Exam under Anesthesia (EUA) findings

- **Pigmentary Retinopathy worsened over time in patients with SLOS treated with cholesterol alone from 1994-2008 (historical finding)**
- Pigmentary Retinopathy was only seen in a subset of patients
  - 2/7 mild patients
  - 3/11 moderate patients
  - 3/7 severe patients
- Pigmentary Retinopathy was present in the periphery (where the rods live) and when subtle, required a good exam under anesthesia to document it.
- On Antioxidant treatment, Pigmentary Retinopathy improved or remained stable
  - 2/7 mild patients with RP – both improved over time
  - 3/11 moderate patients – both improved over time
  - 3/7 severe patients – 2 improved and 1 stable
  - **No Patient had worsening Pigmentary Retinopathy while receiving both Cholesterol and Antioxidants**

Auditory findings in Smith-Lemli-Opitz syndrome (SLOS)

Tiffany Pointon, MD

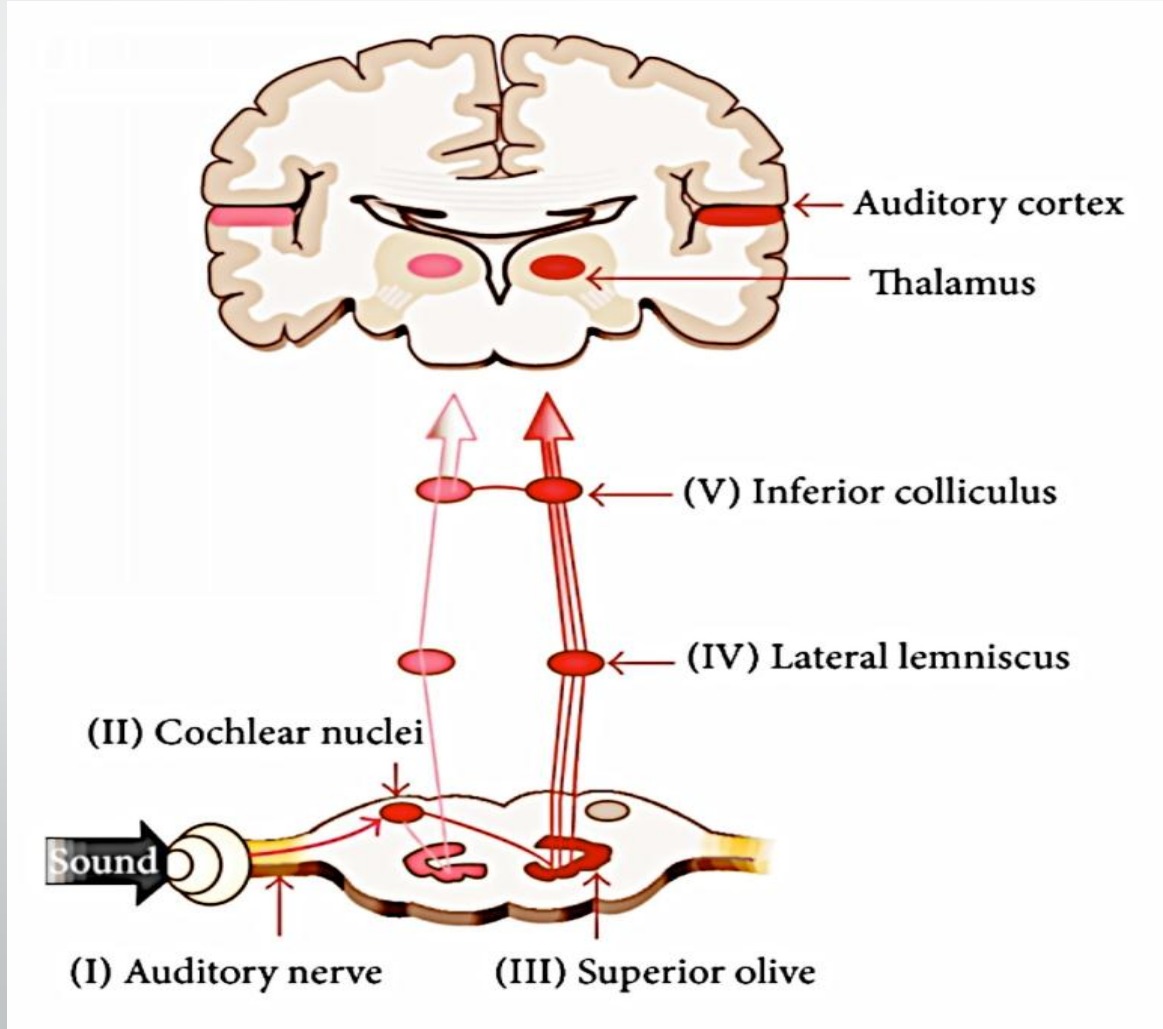
Deborah Hayes, PhD

Ellen Roy Elias, MD

The goal of this study was:

1. Analyze hearing status and auditory pathway function in SLOS
2. Determine if treatment with cholesterol and the antioxidant preparation AquADEKs™ has an effect on auditory outcomes over time

Methods
Auditory Brainstem Response (ABR)



ABR results

- Wave I-V intervals measure conduction time through the auditory brainstem pathway, from the auditory nerve to the inferior colliculus
- 36% (17/47 ears) had a prolonged wave I-V interval at baseline
- Of those with prolonged intervals, 59% had normal hearing and 29% had sensorineural hearing loss
- There was no consistent change on serial testing in ABR results

- **Prolonged conduction in the auditory pathway is likely associated with SLOS, and it is not limited to individuals with hearing loss**

Discussion

No clear evidence that treatment with cholesterol and AquADEKs™ improves auditory outcomes over time

- Potential explanations
  - Oxysterols may not play a role in auditory changes and AquADEKs™ may not have an effect on auditory outcomes
  - Also possible that AquADEKs™ may stabilize auditory outcomes from worsening over time, but not improve outcomes
  - Changes on ABR may not be sensitive enough to show effects of treatment

New Study about to start: Cholic acid treatment in patients with SLOS

- Cholic acid is a bile acid which helps with absorption of fats in the intestine.
- Cholic acid was successfully used in patients with SLOS in the mid 1990's to help increase cholesterol levels and decrease precursors
- Cholic acid was not available from late 1990's til recently, when a new drug company bought the rights to make it and would like to explore its use in patients with SLOS

Design of new Cholic Acid Study

- A pilot study will be done to evaluate both safety and efficacy. Cholic acid will be used for an 8 week treatment trial. Blood tests including Cholesterol and precursor levels will be closely followed as well as safety labs, particularly liver function tests
- Up to 15 patients with SLOS who have cholesterol levels <125 mg/dL will be eligible for enrollment
- Patients will be between the ages of 2 and 25 yr's
- Two levels of < 125 mg/dL will be obtained in the month prior to enrollment
- Patients will be seen at a STAIR site at the start of Cholic acid treatment and then 8 weeks later, with lab draws done locally. A last lab draw will be obtained 4 weeks off treatment, done locally.

Goal of Cholic Acid Study

- The goals of the new cholic acid study will be to:
  - Show that it is safe and well tolerated by patients
  - Help to improve absorption of Cholesterol so that the serum cholesterol levels can increase and levels of precursors 7-DHC and 8-DHC will fall.

Future thoughts for Cholic Acid

- If the Pilot study shows that Cholic acid is safe and effective, then the future plans would be:
  - Use Cholic acid in all patients with SLOS, especially those with very low cholesterol levels
  - Use cholic acid in infants and toddlers younger than 2 years
  - Use in conjunction with cholesterol supplementation and antioxidants
  - We will need to find a funding source for this in the future