Modern Approaches in Inherited Retinal Diseases and Low Vision Technology

Laura Windsor, O.D., F.A.A.O.
Low Vision Centers of Indiana and Eye Associates Group, LLC
315 Huggins Drive
Hartford City, IN 47348
765-348-2020
drlaura@eyeassociates.com

Course Outline

I. History of Low Vision Care and Inherited Eye Diseases
   a. Evolution of Low Vision Care in the USA
      i. 1920s-1940s was WWI and WWII Veterans with injuries
      ii. 1960s - Retinopathy of Prematurity
      iii. 1980 – Present; Macular degeneration, diabetic retinopathy, inherited rare eye diseases

II. Optometry and Genetic Testing in Rare Eye Diseases
   a. Need to be on frontline in helping patients identify their genetic mutation
   b. Confirm diagnoses and give comfort to patients

III. ID your IRD (Inherited Retinal Disease) Initiative
   a. Free DNA testing for 248+ genes of rare eye diseases
      i. Criteria for Testing:
         1. Patients suspected of having an inherited retinal disease (retinitis pigmentosa, Leber congenital amaurosis, Stargardt disease, etc)
         2. Patients who have experienced one or more of the following:
            a. Nyctalopia
            b. peripheral field loss
            c. central vision loss
            d. deterioration of color vision or
            e. photophobia
         3. Not appropriate for patients with age-related macular degeneration or ocular/oculocutaneous albinism.
   ii. Costs are underwritten by Spark Pharmaceuticals but does not link patients to company.
   iii. Quick in-office saliva or cheek swab testing, free shipping to Invitae for testing
1. Results within 2-3 weeks
   iv. www.eyewant2know.com
v. How this will help your patients?
   1. Look positive DNA results up on NHI site clinicaltrials.gov and see if there is research going on for that gene.
   2. Patients are very interested in clinical studies
   3. Results can show that many patients have multiple genetic mutations and many that have not been completely understood as pathogenic yet.
   4. Invitae offers a free 1 hour genetic counseling appointment

IV. Inheritance Patterns
   a. Autosomal Inheritance
      i. 1:4 (25%) chance for each child to be affected
      ii. 2:4 (50%) to be a carrier, non-affected
      iii. 1:4 (25%) non-carrier and non-affected
   b. Autosomal Dominance
      i. 50% chance for each child to be affected
      ii. 50% chance for each child not to be affected
      iii. Affected parent passes it down to children
      iv. Huge family history of disease: parent, uncles, aunts, cousins, grandparents, etc.
   c. X-Linked Inheritance
      i. Passed down through maternal side of the family
      ii. Look at family pedigree for clues
      iii. Will show up in uncles, male cousins, grandfathers, great uncles
   d. Scenario 1 (X-linked recessive): Dad has condition, Mom doesn’t
      i. Dad has faulty X, Mom has two normal X copies
      ii. All male sons will not be affected, have mom’s X.
      iii. All daughters will be carriers because they have the dad’s faulty X chromosome.
   e. Scenario 2 (X-linked Dominant): Mom is carrier, Dad is not
      i. Dad has normal X, Mom has one normal X and one faulty X
      ii. 50% male sons will be affected.
      iii. 50% daughters will be carriers because they have the mom’s faulty X chromosome.
iv.
V. What’s Happening in the Most Common Inherited Retinal Diseases
   a. Retinitis Pigmentosa
      i. Incidence and Genetics
         1. One of the most common inherited diseases of the retina
         2. Affects 1 in 3,500 to 1 in 4,000 people in the United States and Europe
         3. Mutations in more than 60 genes are known to cause non-syndromic RP
         4. More than 20 of these genes are associated with the autosomal dominant RP
            a. RHO gene are the most common cause of autosomal dominant RP, accounting for 20 to 30 percent of all cases
         5. At least 35 genes have been associated with the autosomal recessive form
            a. USH2A; responsible for 10 to 15 percent of all cases of autosomal recessive RP
         6. Changes in at least six genes are thought to cause the X-linked form of RP.
            a. RPGR and RP2 genes account for most cases of X-linked retinitis pigmentosa.
         7. Simplex Cases of RP
            a. 10 to 40 percent of all cases of RP, only one person in a family is affected.
            b. It can be difficult to determine the inheritance pattern of simplex cases because affected individuals may have no affected relatives or may be unaware of other family members with the disease.
            c. Simplex cases can also result from a new gene mutation that is not present in other family members.
      8. 67 Clinical Studies, Beginning, Recruiting and/or Active for RP currently worldwide.
         i. Gene Therapies
         ii. Continuous Oxygen Tx- China
         iii. Stem Cell Txs
         iv. L-Dopa Treatment-Lebanon
         v. Minocycline Tx- China
         vi. Acupuncture- Nova Southeastern University; College of Optometry
         vii. Argus II/ORCAM Device Study- Mayo Clinic
         viii. Allergan RST-001 intravitreal injection for severe RP
      ii. Vision Issues
         1. Night blindness followed by severe peripheral VF loss
         2. Progression through the macular region leading to total blindness
      iii. Treatment with Diamox when macular edema present
      iv. Vitamin A palmitate therapy
      v. Luxturna Gene Therapy
b. Leber’s Congenital Amaurosis

i. Incidence and Genetics

1. 13 types of LCA distinguished by their genetic cause, patterns of vision loss, and related eye abnormalities.
2. 2 to 3 per 100,000 newborns
3. 1/50,000 - 1/33,000 live births
4. Accounts for 5% of all retinal dystrophies
5. 20% of blindness in school age children.
6. Mutations in at least 14 genes (GUCY2D (17p13.1), CEP290 (12q21.33), RPGRIP1 (14q11.2), RDH12 (14q24.1), SPATA7 (14q31.3), AIPL1 (17p13.1), RD3 (1q32.3), CRB1 (1q31-q32.1), CRX (19q13.3), IMPDH1 (7q31.3-q32), IQCB1 (3q21.1), KCNJ13 (2q37), LCA5 (6q14), NMNAT1 (1p36.22), and TULP1 (6p21.3).
7. These mutations cause severe functional impairment or are mostly related to retinal dystrophies.
8. Mutations in CRX or IMPDH1 genes may cause an early and severe onset disease.
9. Patients with GUCY2D mutations present with very slow progressive morphological degeneration and a mostly functional defect.
10. CEP290, CRB1, GUCY2D, and RPE65 genes are the most common
11. 30% of cases are still unknown
12. Mostly autosomal recessive
13. CRX or IMPDH1 gene- autosomal dominant condition

ii. Vision

1. Severe dystrophy of the retina, typically becomes evident in the first year of life.
2. Nystagmus,
3. Sluggish or near-absent pupillary responses in early life
4. Photophobia,
5. High hyperopia
7. Visual acuity is rarely better than 20/400.
8. Franceschetti’s oculo-digital sign, comprising eye poking, pressing, and rubbing.
9. Fundus is extremely variable. May initially appear normal, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood.
10. ERG is characteristically "nondetectable" or severely subnormal.
11. Total blindness by third or fourth decade of life.

iii. Gene Therapy
1. Luxturna
2. NHI Trials
   a. GUCY2D
   b. CEP290
   c. RPE65 Natural History Study

c. Cone – Rod Dystrophies
   i. Incidence and Genetics
      1. Often occurs in childhood
      2. 30 known genetic causes for cone-rod dystrophy
      3. Inheritance Patterns: autosomal recessive, autosomal dominant, and X-linked. Additionally, it can occur as part of a syndrome.
      4. Affects 1 in 30,000 to 40,000 individuals.
      5. Four most commonly mutated genes are ABCA4 (1p22.1) responsible for 30 to 60% of autosomal recessive CRDs,
      6. CRX (19q13.33) and GUCY2D (17p13.1) responsible for many reported cases of autosomal dominant CRDs,
      7. RPGR (Xp11.4) responsible for X-linked CRDs.
   ii. Vision
      1. Primary cone involvement or, occasionally, by concomitant loss of both cones and rods.
      2. Decreased visual acuity, color vision defects, and light sensitivity are first.
      3. Followed by central visual field loss and scotomas, later followed by progressive loss in peripheral vision and night blindness.
      4. Can develop nystagmus as condition progresses

d. Stargardt Macular Degeneration
   i. Incidence and Genetics
      1. most common form of juvenile macular degeneration
      2. 1 in 8,000 to 10,000 individuals
      3. ABCA4 (most common gene) and ELOVL4 genes provide instructions for making proteins that are found in photoreceptor cells.
      4. ABCA4 protein transports potentially toxic substances out of photoreceptor cells
         a. Toxic substances build up and form lipofuscin in the photoreceptor cells and the surrounding cells of the retina, eventually causing cell death.
         b. Autosomal Recessive Inheritance Pattern
      5. ELOVL4 protein plays a role in making a group of fats called very long-chain fatty acids.
a. Formation of ELOVL4 protein aggregates build up and may interfere with retinal cell functions, ultimately leading to cell death
b. Autosomal Dominant Inheritance Pattern

ii. Vision
1. Central vision loss, decreased color vision, and light sensitivity.
2. Can progress later in life.

iii. New Treatments
1. Emixustat Study for ABCA4 Gene
   a. A visual cycle modulators (VCMs) oral medicine,
   b. First synthetic medicinal compound shown to affect retinal disease processes when taken by mouth.
   c. Currently in Phase 3 trials for dry, age-related macular degeneration (AMD).
   d. The compound is also being investigated as a potential therapy for proliferative diabetic retinopathy and diabetic macular edema.
   e. In Phase I/II FDA trial and recruiting patients
      i. Criteria
         1. 16 Years and older
         2. Macular atrophy measured to fall within a defined size range
         3. Two mutations of the ABCA4 gene. If only one mutation, a typical STGD appearance of the retina.
         4. Visual acuity in the study eye of at least 20/320

2. ALK-001
   a. Administered orally for 24 months
   b. C20-D3-Retinyl Acetate
   c. Defective ABCA4 gene, leads to the formation of toxic vitamin A dimers in the eye. Vitamin A dimers are thought to contribute to vision loss in Stargardt disease.
   d. ALK-001 is a chemically-modified vitamin A designed as a replacement of vitamin A that has been changed specifically to prevent the formation of toxic vitamin A dimers in the eye, without altering the normal processing of vitamin A to enable vision.
   e. 2 and 60 years old (inclusive), with any visual acuity
f. Six Stem Cells studies are active, but not all are recruiting patients at this time.
g. Injections of autologous bone marrow derived stem cells
h. Embryonic stem cells

3. SAR422459 Study
   a. Sub-retinal Injection
   b. 6 Years and older
   c. At least one pathogenic mutant ABCA4 allele on each chromosome.
d. Different Treatment Groups being studied
e. France has completed recruitment, Oregon, Texas, Florida and Iowa are still recruiting for study
f. Omega-3 treatment Study
   i. Enrolling currently

e. Achromatopsia
   i. Incidence and Genetics
      1. 1 in 30,000 people worldwide
      2. Island of the Colorblind: Pingelap (Eastern Caroline Islands of Micronesia).
         a. Between 4 and 10 percent of people in this population have a total absence of color vision.
   3. Autosomal recessive and X-linked patterns
   4. 6 known genes (CNGA3, CNGB3, GNAT2, PDE6C, PDE6H and ATF6)
      a. CNGB3 gene mutation accounts for about 50% of all cases,
      b. CNGA3 gene mutation accounts for about 25% of cases.
      c. % are other 4 genes and 21% still unknown
   5. Two types of achromatopsia
      a. rod monochromatism (RM)
         i. Visual acuities from 20/125-20/300
         ii. Complete versus incomplete color vision loss
      b. blue cone monochromatism (BCM)
         i. Sex Linked condition
         ii. Blue cones are functioning
         iii. Better Acuities, less hemeralopia
            1. Visual acuities 20/60-20/100

   ii. Vision Issues
1. Nystagmus begins 8-12 weeks of life
   a. Almost diminishes by teenage years
2. Severe hemeralopia (day blindness)
3. Colorblindness
4. Macula and retinal appearance is normal.
   iii. New Treatments
   1. Gene Therapy Trials
      a. CNGB3 and CNGA3 both in FDA phase ½ trials
      b. Adeno-associated virus (AAV) as the vector
      c. Delivered by a transretinal injection
      d. Works by allowing treatment to give a new complete copy of
         the gene to produce the protein needed.
      e. Studies being done in US, Israel and UK.
   2. Medication Trial New
      a. Just beginan October 2019 for ATF6 gene
      b. ATF6 is responsible for coding a protein that acts in response to
         endoplasmic reticulum (ER) stress.
      c. PBA administered - glycerol phenylbutyrate (PBA), a fatty acid
         compound that facilitates protein folding
      d. 2 participant study
   VI. CRISPR-cas9 Gene Editing
      a. Clustered Regularly Interspaced Short Palindromic Repeats
      b. Allows researchers to target specific stretches of genetic code and edit DNA at precise
         locations, modifying select gene functions
      c. New therapeutic modality for the treatment of non-hereditary degenerative diseases
      d. Conventionally used to correct mutations causing hereditary diseases or cancer
      e. RP
         i. Institute for Genomic Medicine and Institute of Engineering in Medicine, both at
            UC San Diego School of Medicine,
         ii. Used CRISPR/Cas9 to deactivate a master switch gene called Nrl and a
             downstream transcription factor called Nr2e3.
         iii. Deactivating either Nrl or Nr2e3 reprogrammed rod cells to become cone cells.
         iv. Cone cells are less vulnerable to the genetic mutations that cause RP
         v. “Strategy was to use gene therapy to make the underlying mutations irrelevant,
            resulting in the preservation of tissue and vision.”
         vi. Tested in two different mouse models of RP.
vii. Used adeno-associated virus (AAV) to perform the gene therapy
viii. In both cases, they found an abundance of reprogrammed cone cells and preserved cellular architecture in the retinas.
ix. Electroretinography testing of rod and cone receptors in live mice show improved function.

f. Wet AMD
i. Editing the VEGF gene, can achieve a longer-term cure?
ii. Treatment to suppress CNV by inactivating the VEGF gene
iii. Initially found that the delivery of the pre-assembled CRISPR-Cas9 complex is more efficient that the delivery of the same components in a plasmid form in mice models.
iv. Secondly, the complex disappeared after just 72 hours.

VII. Stem Cell Ophthalmology Treatment Study II (SCOTS2)
   a. Autologous bone marrow derived stem cells (BMSC) for the treatment of retinal and optic nerve damage or disease.
   b. Treated with a combination of injections of autologous bone marrow derived stem cells isolated from the bone marrow using standard medical and surgical practices
   c. Retinal conditions may include: degenerative, ischemic or physical damage (examples may include macular degeneration, hereditary retinal dystrophies such as retinitis pigmentosa, Stargardt, non-perfusion retinopathies, post retinal detachment
   d. Optic Nerve conditions may include degenerative, ischemic or physical damage (examples may include optic nerve damage from glaucoma, compression, ischemic optic neuropathy, optic atrophy).
   e. Done by injections may include retrobulbar, subtenon, intravitreal, intraocular, subretinal and intravenous.
   f. Patients are followed for 1 year after surgery.
g. Coral Springs, FL and Westport, CT are study sites
h. Dry Macular Degeneration
i. OpRegen - human embryonic stem cell-derived retinal pigment epithelial (RPE)cells
j. Administered as a cell suspension either in ophthalmic Balanced Salt Solution Plus (BSS Plus) or in CryoStor® 5 (Thaw-and-Inject, TAI).

VIII. Other Stem Cell Studies
   a. CRVO- bone marrow stem cells, California
   b. RP, human progenitor cells, California
c. RP, hRP cells, Arizona and Mass Eye & Ear
d. Diabetic Retinopathy, Alabama
e. China has many stem cell studies for various eye diseases in progress.

IX. My Retinal Tracker
   a. Registry for people affected by an inherited retinal degenerative disease.
   c. Affected individuals and genetically related, unaffected, family members who create entries are guided to create a profile that captures the participants' perspective on their disease and its progress;
      i. family history;
      ii. genetic testing results;
      iii. preventive measures; and
      iv. interest in participation in research studies.
   d. The participants may also choose to ask their clinician to add clinical measurements and results at each clinical visit.
   e. Participants are urged to update the information regularly to create longitudinal records of their disease, from their own perspective, and their clinical progress.
   f. The overall goals are:
      i. to better understand the heterogeneity of the inherited retinal degenerative diseases;
      ii. to understand the prevalence of the different diseases and gene mutations;
      iii. to assist in the establishment of genotype-phenotype relationships;
      iv. to help understand the natural history of the diseases;
      v. to help accelerate research and development of clinical trials for treatments; and
      vi. to provide a mechanism that facilitates more rapid recruitment for research studies and clinical trials.
   g. Foundation Fighting Blindness Registry, My Retina Tracker is the official name of study.
   h. Began in 2014 and will end in June 2037.
   i. Observational prospective study hoping to have 20,000 participants and 20 years of data
   j. Study Population
      i. Affected individuals and close unaffected and genetically related family members
         1. Inclusion Criteria:
            a. Diagnosed with an inherited retinal degenerative disease OR
               Genetically-related to a person diagnosed with an inherited retinal degenerative disease
            b. Achromatopsia, Bardet-Biedl Syndrome, Bassen-Kornzweig Syndrome, Batten Disease, Best Disease, Choroidal Dystrophy,
Choroideremia, Cone Dystrophy, Cone-Rod Dystrophy, Cellular Stationary Night Blindness, Enhanced S-Cone Syndrome, Fundus Albipunctatus, Goldmann-Favre Syndrome, Gyrate Atrophy, Juvenile Macular Degeneration, Kearns-Sayre Syndrome, Leber Congenital Amaurosis, Refsum Syndrome, Retinitis Pigmentosa, Retinitis Punctata Albescens, Retinoschisis, Rod-Cone Dystrophy, Rod Dystrophy, Rod Monochromacy, Stargardt Disease, Usher Syndrome

2. Exclusion Criteria:
   a. Glaucoma
   b. Diabetic retinopathy
   c. Non-retinal disease,
   d. Not heritable retinal disease

X. NEI's eyeGENE Study and Network
   a. National Ophthalmic Genotyping Network
   b. Created a national DNA and blood repository for inherited eye diseases
   c. 33 study locations across the country
   d. Recruits patients to participate in the study by providing a blood sample and undergo a standard eye examination.
   e. NEI tests, processes and stores in the tissue repository
   f. Patients are given the option to receive results back and/or to be re-contacted in the event of future clinical studies.
   g. Stored samples will be made available to researchers once enough stored
   h. https://eyegene.nih.gov

XI. Low Vision Care
   a. Low vision care to make them more functional is the key to quality of life.
   b. Near Vision and Reading
      i. Microscopes, High Powered Reading Glasses
      ii. Magnifiers
      iii. Handheld Video Magnifiers
      iv. Desktop CCTVs
      v. Head-worn systems for reading
   c. Distance Vision
      i. Watching television, programs, sports events, concerts
         1. Handheld telescopes
2. Max Glasses
3. Bioptics
d. Other Tasks
   i. Computer Adaptations
   ii. Cellphone Apps
e. Driving and Vision Loss
   i. Waivered Drivers
      1. In Indiana, up to 20/80 vision in one eye can be considered for licensure. Must have 120 degrees of VF.
      2. Submit a VF to the BMV along with the Certificate of Vision form.
         a. Listed below are the acceptable visual fields:
         b. Humphrey 120 full field point screener
         c. Esterman Monocular
         d. HVF Kinetic
         e. Goldman III 4E
         f. An equivalent test that will obtain a 60 degree range or larger temporally from “Point of Fixation”. This test is required on each eye.
   ii. Bioptic Driving
      1. VA: Up to 20/200 in one eye, VFs 120 degrees of VF
      2. Up to 4X Bioptic
      3. Stable or slowly progressive conditions are best