Pediatric Ophthalmology

How did eye inherit this?
Kimberley Lovelace, MD
March 2, 2019

Objectives:
1. We will better understand eye embryology.
2. We will name at least three inherited retinal disorders.
3. We will learn the craniofacial malformations and their associated problems.
   No financial disclosures.

Ocular Embryology

Day 22 – embryo develops a pair of shallow grooves on each side of the forebrain
Day 25 – anterior (cranial) neuropore closes
   Grooves form outpouching of forebrain = optic vesicles
   Vesicles contact the surface ectoderm and induce changes for lens formation
   Vesicles invaginate forming the double-walled optic cup
7th week – Invagination involves the inferior portion
   Choroid fissure fuses to make a round opening, a future pupil
   Hyaloid artery forms in the choroid fissure

Outer layer of the optic cup
   Small pigment granules appear (pigment layer of the retina)
Inner layer of the optic cup
   Posterior 4/5: pars optica retinae contains rods & cones
   adjacent layer is the mantle layer which gives rise to neurons supporting cells traverse through optic stalk (future optic nerve)
   Anterior 1/5 is one cell layer thick and forms the inner layer of the iris and helps form the ciliary body
Intraocular muscles (sphincter & dilator pupillae) are formed from the underlying ectoderm of the optic cup 5th week – eye primordium is surrounded by loose mesenchyme which differentiates into an inner layer (similar to pia mater of brain) & outer layer (dura mater)

Inner layer – choroid
Outer layer – sclera (continuous with the dura mater of the optic nerve)

Mesenchyme invades inside the optic cup to become the vitreous
7th week – choroid fissure closes repeated 2 slides previous but

Optic stalk becomes the optic nerve
Centrally, a portion of the hyaloid artery initially feeds the lens then regresses leaving only a portion within the optic nerve
Central artery

Why is embryology important?

Coloboma: failure of the choroid fissure to close leaving a cleft in the iris, lens, ciliary body, choroid, or retina

Persistent hyaloid artery
Varying degrees from mittendorf dot, bergmeister papilla, or PFV
Congenital cataracts
Often genetically determined
In 1941, Gregg observed that children of mothers who suffered from German measles (rubella) at 4-7 weeks gestation often developed cataracts, but infection after the 7th week developed deafness and no lens damage

Microphthalmia, anophthalmia, congenital aphakia, aniridia

Growth and Development of the Eye
Most growth takes place in the 1st year of life.
Power of the pediatric lens decreases dramatically over the 1st several years (IOL consideration)

Refractive state – axial length increases while cornea and lens flatten
Infants – usually hyperopic
Hyperopia increase slightly until age 7
Myopic shift toward plano until adult dimensions by age 16
If myopic prior to age 10, then higher risk of progression to -6 D or greater
Astigmatism is common in infants and often regresses
NLD obstruction spontaneously clears in 75-90% by age 1
Most iris color changes occur during first 6-12 months of life
Macula is poorly developed at first but changes rapidly until 4 years.

Congenital Anomalies

Terms:
- Agenesis: developmental failure
- Hypoplasia: developmental arrest
- Hyperplasia: developmental excess
- Dysraphia: failure to fuse
- Failure to divide or canalize
- Persistence of vestigial structures
- Malformation: morphologic defect present from an early age
- Sequence: single structural defect can lead to a cascade, or domino effect, or secondary anomalies
- Syndrome: consistent pattern of multiple malformations known to have a specific cause
- Association: defects known to occur together in a statistically significant number of patients
Two or more minor anomalies in combination significantly increase the chance of an associated major malformation

Hereditary Retinal Diseases

Leber Congenital Amaurosis
Achromatopsia
Congenital Stationary Night Blindness
Foveal Hypoplasia
Aicardi Syndrome
Oculocutaneous albinism

Leber Congenital Amaurosis (LCA)

Group of hereditary retinal diseases affecting rods & cones
Usually AR
Severe vision loss noted in infancy, nystagmus, poorly reactive pupils, extinguished ERG
Vision – 20/200–bare LP
Fundus exam varies, depending on genotype, from normal to pigment clumping in RPE
Oculodigital reflex (eye poking), photoaversion, cataracts, keratoconus, keratoglobus, high hyperopia
Dx with ERG but wait until 6 months of age
Achromatopsia

Difficult to distinguish from LCA but develop better visual function in infancy
AKA: rod monochromatism
AR with at least 3 genes identified, non-progressive
NO color vision, poor central vision, nystagmus, photophobia (desire to avoid bright light, rather than pain, manifest by squinting or rapid fluttering in normal indoor light)
Hemeralopia = day blindness
Normal retinal exam or possibly absent foveal reflex
ERD: normal rod response, extinguished cone response

Congenital Stationary Night Blindness

Group of non-progressive retinal disorders with abnormal rods
Most commonly X-linked, but can be AD or AR
Present in early infancy with nystagmus & normal fundus
Vision usually 20/200 but can be normal
Abnormal ERG is diagnostic
Other forms: Oguchi dz (yellow sheen after exposure to light) & fundus albipunctatus (yellow-white dots)

Foveal Hypoplasia

Incomplete development of fovea
Often associated with albinism or aniridia

Aicardi Syndrome

X-linked or AD
Clinical triad: widespread round or oval depigmented chorioretinal lacunae, infantile spasms, agenesis of the corpus callosum
Lethal in males
Albinism

Group of various conditions involving melanin system of skin and eye (oculocutaneous albinism, OCA) or eye alone (ocular albinism, OA)
- Iris transillumination, foveal aplasia or hypoplasia, lacking pigment in retina
- Nystagmus, light sensitivity, high refractive errors, Va 20/25 – 20/200
- OCA: group of 4 AR disorders, tyrosinase gene inactive or minimally active
- OA: X-linked > AR
- Part of broader syndrome: Hermansky-Pudlak &

Stargardt Disease

Aka juvenile macular degeneration
- Most common hereditary macular dystrophy
- AR>AD (mutation of ABCR gene)
- Bilateral, symmetric, progressive to Va of 20/70-20/100
- Deterioration begins between 8-15 years of age
- Stages: normal fundus → loss of foveal reflex → macular bull’s eye atrophy with surrounding round or pisciform yellow flecks, beaten bronze (light reflecting quality)
- Fundus flavimaculatus: yellow flecks throughout fundus “Dark choroid” on FA, ERG initially normal

Hereditary Macular Dystrophies

Stargardt Disease
- Best Disease

Best Disease

AKA: juvenile-onset vitelliform macula dystrophy
- AD, variable penetrance and expressivity
- Stages: normal appearing retina
- Vitelliform stage - age 4-10, yellow-orange cyst (egg yolk), usually in macula, 1.5-5.0 disc diameters in size, good central vision
- Scrambled egg stage ~ 20/30 vision, unless the 20% who develop subretinal neovascularization & serous detachment with vision deterioration to 20/100 or worse
- EOG abnormal, ERG normal
**Hereditary Vitreoretinopathies**

- Juvenile Retinoschisis
- Stickler Syndrome
- Familial Exudative Vitreoretinopathy
- Norrie Disease
- Goldmann-Favre Vitreoretinal Dystrophy

**Juvenile Retinoschisis**

X-linked (males), RS1 gene – encodes retinal adhesion protein essential to health of Muller cells

Foveal retinoschisis – star-shaped or spokelike, OCT shows schisis in middle layers of macula

50% have peripheral retinoschisis in nerve fiber layer

Vitreous veils prominent

Va drops to CF range

**Stickler Syndrome**

Flat midface, progressive hearing loss, cleft palate, Pierre Robin sequence, mitral valve prolapse, progressive arthropathy w/ spondyloepiphyseal dysplasia

High myopia, high incidence of retinal detachment 2/2 retinal breaks, lattice degeneration & proliferative vitreoretinopathy (PVR), vitreous liquefaction = “optically empty vitreous”

Less frequent: anterior chamber anomalies, ectopia lentis, cataracts, ptosis, strabismus

AD, 4 different types, mutations in genes encoding collagen

**Familial Exudative Vitreoretinopathy (FEVR)**

Type 1 – mutation on chromosome 11, AD

Type 2 – mutation on NDP gene, X-linked recessive

Retinal traction, folds, breaks & detachment 2/2 vitreous traction, PVD, avascular peripheral retina, thick peripheral intraretinal & subretinal exudates
Norrie Disease

X-linked recessive, mutation in NDP gene encoding protein norrin
Globular, severely dystrophic retina with pigmentary changes in the avascular periphery
Congenital blindness, Hearing impairment, Mental retardation
Males typically born blind, 1st days/weeks of life – yellowish RD OU, followed by white mass behind clear lens, later lens and cornea opacify, phthisis bulbi by 10 years of age
Female carriers – peripheral retinal abnormalities

Goldmann–Favre Vitreoretinal Dystrophy

AR
Vitreous strands & veils + foveal & peripheral retinoschisis
Nummular (circular) pigmentary changes
Decreased central vision & night blindness – 2nd decade of life, complicated cataracts later

Craniosynostosis

Premature closure of 1 or more cranial sutures
Plagiocephaly – “oblique head”
Acrocephaly – “tower head”
Brachycephaly – “short head”
Scaphocephaly – “boat head”
Syndromes: many have overlapping features, mutations in fibroblast growth factor receptor found in 50%
Crouzon
Apert
Pfeiffer syndrome

Crouzon

Most common
AD, over 30 mutations identified
Synostosis of both coronal sutures = broad, retruded forehead, brachycephaly & acrocephaly
Mid-face retrusion, hypertelorism, proptosis, inferior scleral show
Normal intelligence
Findings limited to head
Hydrocephalus is common
**Apert Syndrome**

AD
- Multiple fused calvarial sutures
- Syndactyly (extreme with all digits of hands and feet completely fused)
- Internal organ malformations (cardiovascular & urinary), mental retardation

**Pfeiffer Syndrome**

AD
- Similar to Apert but more severe craniosynostosis, resulting in cloverleaf skull (Kleeblattschadel)
- Less syndactyly
- Short, broad thumbs & toes

**Saethre-Chotzen**

AD
- Milder than the other syndromes, often underdiagnosed
- Ptosis, low-hairline, ear abnormalities
- Brachydactyly (short digits on hands and feet)
- Normal intelligence

**Ocular Complications of Craniosynostosis**

- Proptosis
- Corneal exposure
- Globe luxation (shallow orbits)
- Vision loss
- Amblyopia
- Strabismus (V-pattern XT)
- Optic nerve abnormalities (papilledema, optic atrophy)
- Hypertelorism, telecanthus, NLDO
Nonsynostotic Craniofacial Conditions

Goldenhar syndrome
Treacher Collins syndrome
Pierre Robin Sequence

Branchial Arch Syndromes

Disruptions in the embryonic development of 1st two branchial arches
Form the maxillary and mandibular bones, ear and facial muscles
Oculoauriculovertebral (OAV) spectrum – hypoplasia of eye, ear & vertebrae, often neurologic, cardiovascular & genitourinary abnormalities
includes hemifacial microsomia, Goldenhar syndrome and Treacher Collins syndrome

Goldenhar Syndrome

Sporadic
Ocular hallmarks:
Epibulbar or lipodermoids – occur inferotemporally
Limbal dermoids – bilateral in 25%, can cause astigmatism
Can also have eyelid coloboma, microphthalmia, cataract and iris abnormalities
Duane syndrome common

Treacher Collins Syndrome

AKA Mandibulofacial dysostosis
AD
Underdevelopment or agenesis of zygoma and malar eminences bilaterally
Cheeks and lateral orbital rims are depressed and palpebral fissures slant downward
Absent meibomian glands & sometimes cilia of lower eyelids
Hypoplastic mandible – micrognathia (undersized jaw)
Normal intelligence
Pierre Robin Sequence

- Respiratory problems
- Micrognathia, glossoptosis, cleft palate
- Ocular anomalies: RD, microphthalmos, congenital glaucoma, cataracts, high myopia
- Frequent finding in Stickler syndrome