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# Ocular Surface Disease

## Dry Eye Syndrome

### Aqueous Tear Deficiency Dry Eye Syndrome

#### *Evaluation and Diagnosis of Aqueous Tear Deficiency Dry Eye Syndrome*

- **Clinical findings:** decreased tear meniscus (1.0 mm is normal), epithelial keratopathy (stains help visualize), filaments
  - **Binds to intercellular junction breaks/epithelial loss:** fluorescein
  - **Stains devitalized epithelium:** rose bengal (toxic to epithelium, irritant - use with topical anesthetic), lissamine green
  - **Helpful for staining conjunctiva:** lissamine green
  - **Severe sequelae of aqueous tear deficiency dry eye:** corneal thinning/perforation, band keratopathy, keratinization

#### *Filamentary Keratopathy*

- **Features:** strands of degenerating epithelial cells strongly attached to corneal surface over mucus core, may be very painful
- **Associations:** blepharitis, meibomian gland dysfunction, **superior limbic keratoconjunctivitis**, vernal keratoconjunctivitis
- **Treatment:** **acetylcysteine** 10% drops

#### *Sjögren Syndrome*

- Aqueous tear deficiency associated **with inflammation** (10% of aqueous tear deficiency)
- **Causes**
  - Primary (idiopathic)
  - Hypergammaglobulinemia
  - Rheumatoid arthritis
  - Collagen vascular disease
  - ⊕ SS-A (Ro)/SS-B (La) or other autoantibodies
- **Pathophysiology:** T-cell mediated inflammation with lacrimal gland dysfunction eventually resulting in fibrosis of lacrimal gland
- **Associations:** 5% of primary Sjögren syndrome develop **lymphoma**
- **Treatment for Sjögren-related dry eyes:** oral cholinergic agonists, zidovudine

#### *Non-Sjögren Syndrome*

- **Causes**
  - **Primary lacrimal gland disease:** Riley-Day, congenital alacrima, anhidrotic ectodermal dysplasia, Adie syndrome, Shy-Drager syndrome
  - **Secondary lacrimal gland disease:** sarcoidosis, graft-vs-host disease, HIV, xerophthalmia, surgical ablation
  - **Lacrimal outflow obstruction:** cicatricial conjunctivitis (trachoma, SJS, chemical burns, OCP)
  - **Decreased lacrimal secretion:** anticholinergic meds, viruses, contact lens wear, peripheral neuropathy (DM, Bell's palsy), corneal surgery (LASIK, PK, cataract extraction)

### Evaporative Dry Eye Syndrome

#### *Evaluation and Diagnosis of Evaporative Dry Eye Syndrome*

- **Meibomian gland dysfunction (primary abnormality)**
- **Tear breakup time:** use fluorescein (no anesthetic) in fornix and count until dry spots appear; **≤ 10 seconds is abnormal**

### *Blepharitis*

- **Topical azithromycin:** lipophilic, reduces the production of bacterial lipases, improves meibomian lipids
- **Oral tetracyclines (doxycycline, minocycline):** **anti-inflammatory** (suppresses leukocyte migration, reduces production of nitric oxide and reactive oxygen species, inhibits matrix metalloproteinases, inhibits phospholipase A2), suppresses bacterial lipases; don't use in pregnancy/breastfeeding, children < 14 yo (permanent discoloration of teeth/bones), minocycline can deposit purple discoloration in skin/cartilage (looks like bruising), decreased efficacy of contraceptives, can **increase intracranial pressure**

### Angular Blepharitis

- **Causes:** ***Staphylococcus aureus*** (most common), ***Moraxella lacunata***
- **Clinical appearance:** crusting/ulceration in lateral canthal angle, **follicular conjunctivitis (*Moraxella lacunata*)**

### *Rosacea*

- **Pathogenesis:** cutaneous sebaceous gland dysfunction of face, neck, and shoulders (acneiform disorder)
  - **Inflammatory infiltration:** delayed hypersensitivity to lipid-producing glands/material
- **Clinical presentation**
  - **Eyelids:** increased sebum secretion, chronic blepharitis, lid telangiectasia, meibomian gland distortion, recurrent chalazia
  - **Eyes:** conjunctivitis, **marginal corneal infiltrates**, sterile ulcers, episcleritis, iridocyclitis, **peripheral ulcerative keratitis**, **symblepharon**, corneal scarring
  - **Face:** telangiectasias, recurrent papules/pustules, midfacial erythema, malar rash with flushing (triggers: alcohol - vasomotor instability, coffee, foods), rhinopehyma (nose skin/connective tissue thickening, late characteristic finding)
- **Management:** tetracyclines (1st-line), topical metronidazole (facial erythema), topical steroids

### *Ichthyosis*

- Excessively dry skin and scaly accumulation, phenotype with multiple systemic causes (see chart)
- **Management:** hydrate skin, unresponsive to steroids

| Disease | Inheritance | Features |
|---|---|---|
| **Ichthyosis vulgaris (most common)** | AD | • Lid scaling<br>• Cicatricial ectropion<br>• Conjunctival thickening |
| **X-linked ichthyosis** | XLR | • **Corneal opacities (50%)**<br>• Dots/filament-shaped opacities in pre-Descemet membrane or deep stroma more apparent with age but not visually significant<br>• Posterior embryotoxon |
| **Sjögren-Larsson** | AR | • Defect in fatty aldehyde dehydrogenase<br>• Paralysis + mental retardation + ichthyosis<br>• **Crystalline retinopathy** |
| **KID (congenital keratitis-ichthyosis-deafness)** | | • Vascularizing keratitis that worsens with isoretinoin<br>• **Primary limbal stem cell deficiency** |
| **Refsum** | AR | • **R**etinopathy (RP-like bone spiculing, nyctalopia common)<br>• **E**ar (deafness) / **E**nlarged corneal nerves<br>• "**F**"ytanic (phytanic) acid accumulation<br>• **S**kin (ichthyosis) / **S**mell (anosmia)<br>• **U**ncoordinated (ataxia and polyneuropathy)<br>• **M**yopathy (cardiomyopathy) |

## Nutritional Disorders

### *Vitamin A Deficiency*

- **Pathogenesis:** vitamin A is fat-soluble, stored in liver - important for photoreceptor (**rhodopsin**) and goblet cell function (**mucin**)
  - **Stressors (measles, diarrhea, HSV, bacteria, etc.):** trigger vitamin A deficiency-related disease if liver reserves are low
- **Risk factors:** malnourishment, **cystic fibrosis**, biliary cirrhosis, **bowel resection**, unusual diets, **chronic alcoholics** (may present as persistent epithelial defect/ulceration unresponsive to treatment)
- **Clinical presentation**
  - **Nyctalopia (earliest symptom)**
  - **Loss of mucus production by goblet cells**
  - Xerosis (corneal/conjunctival dryness)
  - **Bitôt spot:** metaplastic keratinization + inflammation + debris + ***Corynebacterium xerosis***
  - Keratomalacia (diffuse corneal necrosis)
  - Xerophthalmic fundus (rare, peripheral yellow-white spots in retina)

**Causes of Decreased Goblet Cells**

- Vitamin A deficiency
- Mucous membrane pemphigoid
- Pseudopemphigoid (topical β-blockers, miotics)
- Superior limbic keratoconjunctivitis
- Trachoma

- **Testing:** ERG abnormal, VF constriction, low serum vitamin A or retinol-binding proteins
- **Treatment:** lubrication + systemic vitamin A (PO/IV/IM) + protein/calorie replacement
- **Prognosis:** guarded (untreated mortality of 50%)

## Structural Disorders

### *Exposure Keratopathy*

- **Pathogenesis:** limited eyelid closure from lagophthalmos or proptosis
- **Treatment:** lubrication, taping lids shut, tarsorrhaphy, gold weights (MRI-safe, can induce astigmatism), horizontal lid tightening

### *Floppy Eyelid Syndrome*

- **Pathophysiology:** eye rubbing/eversion of upper lid with pillow or clothes with floppy upper tarsus, upper lid papillae
- **Associations:** obesity, **obstructive sleep apnea**, **keratoconus**
- **Treatment:** shield/taping lids shut at night, eyelid tightening surgery

### *Superior Limbic Keratoconjunctivitis (of Theodore)*

- **Epidemiology:** women, 20-70 yo, bilateral (asymmetric)
- **Clinical presentation:** staining and injection/thickening of superior bulbar conjunctiva, **filamentary keratopathy**
- **Histopathology:** nuclear pyknosis ("snake nuclei," condensation of nuclear chromatin), karyorrhexis (fragmentation of cell nucleus after pyknosis), **keratinization** of superior conjunctiva with **loss of goblet cells** and **acanthosis** (thickened epithelium)
- **Associations:** **thyroid eye disease** (20-65% of SLK patients have thyroid dysfunction - order TSH, $T_3$/$T_4$, anti-thyroid antibodies)
- **Treatment:** reduce inflammation/friction between upper tarsal and bulbar conjunctiva

### *Recurrent Corneal Erosion*

**DDx of Recurrent Erosions**

- Trauma
- Diabetes mellitus
- Corneal dystrophies (epithelial and stromal)
  - EBMD (most common)

- **Pathogenesis**
  - **Initial event:** sudden sharp abrading/shearing injury (fingernail, branch), EBMD, PRK (small superficial injuries rarely cause recurrent erosions)
  - **Recurrent event:** eyelid movements (early morning) peel off epithelium; poor epithelial adhesion (**disorganized hemidesmosomes**) + upregulation of gelatinase activity (MMP-2 and -9, cleaves collagen IV, V, VII, X)
- **Clinical presentation**
  - Sudden onset eye pain + redness + photophobia + tearing at night or first waking, pain out of proportion to findings, lasts 30 minutes to hours up to days
  - Topical anesthetics relieve symptoms
  - Examine contralateral eye to look for epithelial basement membrane changes
- **Treatment**
  - **Acute:** lubrication (antibiotics for prophylaxis), cycloplegia, debridement, topical NSAIDs, bandage contact lens
  - **After epithelial defect healed:** NaCl 5% (lubrication + transiently affects osmotic gradient), prophylactic lubricant, tetracyclines/topical steroids (**inhibits local MMPs**)
  - **Recurrent/refractory disease:** anterior stromal micropuncture, epithelial debridement, phototherapeutic keratectomy

### *Neurotrophic Keratopathy*

- **Pathogenesis:** damage to CN V (corneal hypesthesia/anesthesia), increased tear film osmolarity
- **Causes**
  - **Surgical:** trigeminal ablation, PK, AK/LRI, LASIK
  - **Neurological disease:** CVA, aneurysms, MS
  - **Tumors:** acoustic neuroma, neurofibroma, angioma
  - **Infections:** **herpes keratitis (most common)**, leprosy
  - **Hereditary:** Riley Day
  - **Topical medications:** anesthetics, NSAIDs, β-blockers, carbonic anhydrase inhibitors
  - **Diabetes mellitus:** diabetic neuropathy
- **Treatment:** eliminate aggravating topical medications, lubrication, promote re-epithelialization medically or surgically

## Toxic Ocular Surface Disease

### *Topical Anesthetic Abuse*

- **Toxicity:** inhibits epithelial migration and division
- **Histopathology:** loss of microvilli, decreased desmosomes, mitochondrial/lysosomal swelling
- **Clinical presentation:** early punctate keratopathy, neurotrophic ulcer, late neovascularization/keratic precipitates/hypopyon, diffuse stromal edema, dense infiltrates, **ring opacity**

### *Contact Lens Ocular Surface Disease*

- **Sattler's veil:** central epithelial edema after RGP overwear due to hypoxia with lactate accumulation and impaired $CO_2$ efflux
- **Microcystic epitheliopathy:** fine epithelial cysts (best seen with retroillumination) associated with extended wear SCLs
- **Toxic conjunctivitis:** reaction to BAK, chlorhexidine, $H_2O_2$
- **Thimerosal delayed hypersensitivity:** contact lens-induced SLK
- **Neovascularization:** superficial pannus (reversible), deep stromal neovascularization (irreversible)

### *Topical Ophthalmic Medications*

- **Pathogenesis:** dose-dependent cytotoxicity; preservatives (usually **benzalkonium chloride** [BAK]) retained in epithelium
- **Clinical presentation:** punctate staining, **subepithelial corneal infiltrates**, conjunctival injection, **papillary or follicular conjunctivitis**, **diffuse/whorled (vortex, hurricane) keratopathy**, epithelial defects, neovascularization, **limbal stem cell deficiency**, **drug-induced pemphigoid (see conjunctival inflammations)**
- **Management:** discontinue offending agent (may take months to resolve), preservative-free artificial tears/ointment
  - **Drug-induced pemphigoid:** conjunctival biopsy with negative immunofluorescence (Michel fixative)

| Clinical presentation | Offending Agents |
|---|---|
| **Limbal stem cell deficiency** | Preserved topical agents, fibrin formation blockers (**mitomycin C**) |
| **Peripheral corneal infiltrates** | Aminoglycosides, antiviral agents, BAK- or thimerosal-containing medications |
| **Chronic follicular conjunctivitis** | Atropine, antiviral agents, miotics, sulfonamides, epinephrine (including dipivefrin), α-adrenergic agonists (e.g., apraclonidine, brimonidine tartrate), vasoconstrictors |
| **Conjunctival scarring (symblepharon)** | Miotics, β-blockers |

## Limbal Stem Cell Deficiency

- **Pathogenesis: 25-33% of limbus must be preserved** to prevent stem cell deficiency
  - **Conjunctival stem cells:** uniformly distributed on bulbar surface or in fornices
  - **Corneal stem cells:** basal cell layer of limbus
- **Pathophysiology:** ↓ wound healing, irregular ocular surface, epithelial breakdown
- **Clinical presentation**
  - **Symptoms:** recurrent corneal ulceration, blurred vision (irregular cornea)
  - **First sign:** wavelike irregularity of epithelium (noted on fluorescein stain)
  - **Increased epithelial permeability:** fluorescein entering anterior stroma
  - **"Conjunctivalization of cornea":** goblet cells on corneal impression cytology
- **Treatment**
  - **1 eye (e.g., pterygium):** autograft from ipsilateral or fellow eye
  - **Both eyes (Stevens-Johnson syndrome, bilateral chemical burns, etc.):** allograft with systemic immune suppression

**Select Causes of Limbal Stem Cell Deficiency**

- Anterior segment ischemia
- Antimetabolites (5-FU, **MMC**)
- **Atopic keratoconjunctivitis**
- **Cicatrizing disease:** SJS, OCP
- **Iatrogenic:** surgery/cryo/radiation
- **Infections: herpes**, **trachoma**
- **PAX6 mutations (aniridia)**
- Prolonged contact lens use
- **Pterygium**
- PUK/Fuchs marginal keratitis
- **Sclerocornea**
- Trauma (chemical/thermal burns)

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# Congenital and Developmental Abnormalities of the Anterior Segment

## Primary Congenital Abnormalities of the Cornea

### Anomalies of Shape and Size of the Cornea

| Dimensions | Normal | Microcornea | Megalocornea | Cornea Plana |
|---|---|---|---|---|
| **Horizontal corneal diameter at birth** | 9.5-10.5 mm | < 9 mm | > 12 mm | Variable |
| **Horizontal corneal diameter after 2 years old** | 10.5-12.5 mm | < 10 mm | > 13 mm | Variable |
| **Keratometry** | 43 D | Flat | Steep | Flat (30-35 D) |

#### *Cornea Plana*

- Very flat corneal curvature (**keratometry 30-35 D**; normal 43 D); **corneal curvature same as adjacent sclera is pathognomonic**
- **Inheritance/genetics:** autosomal dominant and recessive; *KERA* gene (keratan sulfate proteoglycans)
- **Ocular associations:** **high hyperopia (> 10.00 D)**, colobomas, angle-closure glaucoma (from shallow AC) or open-angle glaucoma (angle dysgenesis), **sclerocornea**, **microcornea**
- **Systemic association:** **Ehlers-Danlos syndrome**

#### *Megalocornea*

- Bilateral, nonprogressive enlargement of the cornea; **horizontal diameter > 13 mm** (> 12 mm at birth)
- **Inheritance: X-linked recessive** (90% males); carriers have larger corneas (example of lyonization)
- **Ocular associations:** **myopia** (steep cornea) and **with-the-rule astigmatism** are common, iris translucency (diaphanous), pigment dispersion, miosis, goniodysgenesis, cataract, **ectopia lentis**, arcus juvenilis, glaucoma

**Megalocornea Associations: "HARD CLIMB"**

- **H**ypertelorism / **H**ypotonia / facial **H**emiatrophy
- **A**lport
- **R**etardation
- **D**own syndrome
- **C**raniosynostosis / **C**entral cloudy dystrophy of François
- muco**L**ipidosis type II
- **I**mperfecta (osteogenesis)
- **M**arfan
- **B**ossing (frontal)

#### *Microcornea*

- Clear cornea, normal thickness, **horizontal diameter < 10 mm** (< 9 mm at birth)
- **Inheritance: autosomal dominant** (most common), autosomal recessive
- **Ocular associations: hyperopia** (flat cornea); **↑ incidence of angle-closure glaucoma, 20% develop open-angle glaucoma later**; persistent fetal vasculature (PFV); congenital cataracts; anterior segment dysgenesis; **optic nerve hypoplasia**
- **Systemic associations (FAME):** **F**etal alcohol syndrome, **A**chondroplasia, **M**yotonic dystrophy, **E**hlers-Danlos syndrome

#### *Sclerocornea*

- Nonprogressive, noninflammatory scleralization of cornea; ill-defined limbus; **90% are bilateral**
- **Inheritance: sporadic** (most common)
- **Ocular associations:** **cornea plana** (80% of cases, **most common ocular finding**); angle malformations (**↑ glaucoma risk**), **limbal stem cell deficiency**

## Anterior Segment Dysgenesis Syndromes

### *Posterior Embryotoxon*

- **Thickened and anteriorly displaced Schwalbe line** visible on external examination (up to 30% of normal eyes); typically bilateral
- **Schwalbe line/ring:** junction of trabecular meshwork and termination of Descemet membrane
- **Inheritance:** autosomal dominant
- **Associations:** **Axenfeld-Rieger syndrome**, Alagille syndrome (arteriohepatic dysplasia), X-linked ichthyosis, familial aniridia

### *Axenfeld-Rieger Syndrome*

- **Genetics/inheritance:** autosomal dominant (75%), homeobox genes (***FOXC1***, ***PITX2***)
- **Ocular features: posterior embryotoxon,** attached iris strands, iris hypoplasia, corectopia, pseudopolycoria, **glaucoma** (50%)
- **Systemic features:** teeth defects, facial bone defects, **redundant periumbilical skin**, **pituitary abnormalities**, **hypospadias**

### *Peters Anomaly (Kerato-Irido-Lenticular Dysgenesis) and Peters-Plus Syndrome*

- Congenital central corneal opacity due to localized absence of corneal endothelium and Descemet membrane; bilateral (80%)
- **Genetics/inheritance:** sporadic; ***PAX6***, ***PITX2***, ***FOXC1***, CYP1B1
- **Ocular features:** glaucoma (50%), microcornea, aniridia, retinal detachment, persistent fetal vasculature
  - **Peters anomaly type 1:** iridocorneal adhesions, avascular opacity
  - **Peters anomaly type 2:** failure of lens vesicle to separate from surface ectoderm; corneolenticular adhesions, cataract, vascularized opacity
  - **Major indication for corneal transplant** (penetrating keratoplasty)
- **Peters-plus syndrome:** Peters anomaly with systemic abnormalities
  - Cleft lip/palate, short stature, external ear abnormalities and hearing loss, intellectual disability, **heart defects**, central nervous system deficits, gastrointestinal and genitourinary defects, skeletal defects

# Secondary Congenital Abnormalities of the Cornea

## Congenital Masses

### *Congenital Corneal Keloid*

- Reactive fibrous proliferation, appears as white raised mass; typically bilateral
- **Histopathology:** thick collagen bundles haphazardly arranged, focal areas of myoblastic proliferation
- **Ocular associations:** cataract, aniridia, glaucoma
- **Systemic associations**
  - **Lowe (oculocerebrorenal) syndrome:** X-linked recessive; cataract, renal failure, intellectual disability, seizures
  - **Rubinstein-Taybi syndrome:** cutaneous keloids
  - **ACL syndrome:** autosomal dominant; acromegaly, cutis verticis gyrata, corneal leukoma

### *Limbal (Epibulbar) Dermoid*

- Congenital **choristoma** containing hair, sebaceous glands, sweat glands, muscle, bone, or teeth
- **Clinical appearance:** well-circumscribed, white round/oval mass most commonly at **inferotemporal limbus**
  - **Corneal astigmatism:** can cause **anisometropic amblyopia**; **flattest meridian adjacent to dermoid**
- **Systemic associations:** **Goldenhar-Gorlin syndrome**, trisomy 8 mosaicism syndrome, linear nevus sebaceous syndrome

## Acquired Congenital Corneal Edema

### *Primary Congenital Glaucoma*

- **Corneal findings in primary congenital glaucoma**
  - **Buphthalmos:** > 12 mm horizontal diameter during first year of life (normal 9.5-10.5 mm)
  - **Corneal edema:** due to increased intraocular pressure; 25% at birth, > 60% by 6 months
  - **Haab striae:** tears in Descemet from corneal stretching, lines are **H**orizontal or concentric to limbus

### *Birth Trauma*

- Ruptures of Descemet membrane and corneal endothelium during childbirth
  - Vertical or oblique posterior striae; ruptures usually heal but leave hypertrophic ridge of Descemet membrane
- **Corneal edema:** progressive, begins during first few days of life, can recur anytime; left eye > right eye
- **Sequelae: high astigmatism, amblyopia**

## Congenital Anomalies of the Sclera

### *Blue Sclera*

- **Pathogenesis:** increased thinning of sclera with visibility of uvea
- **Management:** hearing evaluations, bone strengthening

**Associations with Blue Sclera**

- Osteogenesis imperfecta type I and IIA
- Ehlers-Danlos type VI
- Hurler syndrome (MPS type I)
- Turner syndrome
- Marfan syndrome
- Werner syndrome (adult progeria)