Genodermatoses

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Ichthyosis Vulgaris

- M/C sx of cornification
  - 1/200 prevalence
- Impaired cornified keratinocytes, increased TEWL, inflammation from irritants/allergens
- Aut semidominant
  - Mild w/heterozygous filagrin mutation
  - Severe if both alleles mutated
- Extensors, scalp, forehead
- Hyperlinear palms, KP, AD
Ichthyosis Vulgaris

**Treatment**

- Emollients
- Ceramides
- Humectants
- Keratolytics
  - Urea, lactic/salicylic acids

**Pathology**

Thin to absent granular layer, orthokeratosis
X-Linked Recessive Ichthyosis

• X-linked recessive
  • 1/5,000 male births

• Deletion of STS gene (arylsulfatase C)
  • Steroid sulfatase deficiency
    • Increased cholesterol sulfate
    • Decreased cholesterol
    • Low/absent estrogen in amniotic fluid
    • Failure of labor to progress

• Mild erythroderma, large translucent scales
  • Evolves to brown “dirty” scales over extremities, trunk, neck
  • Spares palms/soles, face

• A/W comma-shaped corneal opacities, cryptorchidism (increased risk of testicular CA), increased risk of ALL, rare neurological sx$s
X-linked Ichthyosis

Dx: FISH, molecular gene testing, serum lipoprotein electrophoresis (accum of cholesterol sulfate)

Tx: Humectants, keratolytics, retinoids
Lamellar Ichthyosis/Nonbullous
Congenital Ichthyosiform Erythroderma

• AR, mutation in TGM1 or ABCA12
  • Abnormal cross-linking of structural proteins in epidermis, leads to defective cornification and desquamation

• Collodion membrane at birth and erythroderma
  • Large, brown plate-like scales, prominent flexural involvement
  • Generalized, except ‘bathing suit ichthyosis’ in South African variant
  • A/W ectropion, eclabium, scarring alopecia (peripheral scalp), PPK, nail dystrophy, heat intolerance
Lamellar Ichthyosis

Treatment

• Acitretin for severe dx
• Topical retinoids and keratolytics limited used secondary to irritation
  • Possible problematic systemic absorption if keratolytics applied to an extensive area
Epidermolytic Hyperkeratosis/Bullous CIE

• AD, Keratin 1 and Keratin 10 mutations
• Occasionally offspring of parent with epidermal nevus sx
  • EHK changes in epidermal nevi
• Erythroderma, peeling skin, erosions at birth
  • Can have sepsis, dehydration, electrolyte imbalances
• Gradually evolve to widespread hyperkeratosis with corrugated ridges on flexures
  • Cobblestone pattern on extensors
• Episodic blistering, secondary infections, body odor, PPK
EHK/EI/Bullous Congenital Ichthyosiform Erythroderma

Massive orthokeratosis, cytolysis of suprabasal/granular layers, clumped tonofilaments
**Treatment**

- **Neonates**
  - Protective isolation, emollients, and monitoring
- **Children and adults**
  - Emollients, humectants
  - Mechanical exfoliation of hyperkeratosis
  - Bleach bathes
  - Antimicrobials prn
  - Avoid widespread use of salicylic acid
    - Possible toxicity

**DDx in neonates**

- Epidermolysis bullosa
- SSSS
- Superficial EI
- Ichthyosis hystrix
- Sjogren-Larsson
- KID sx
Sjogren-Larsson Syndrome

- **AR, FALDH mutation**
  - Defective conversion of fatty alcohols to fatty acids
  - Important for epidermal lipid synthesis, and catabolism of phospholipids/sphingolipids in CNS myelin
- **Generalized Ichthyosis w/erythroderma**
  - Evolves to darker scale w/out erythema
    - Flexures, lower abdomen, neck
  - Spasticity, scissor gait
Sjogren-Larsson Syndrome

• Atypical retinitis pigmentosa w/ glistening white dots
• Pruritus is unique
  • Responds to Zileuton
    • Reduces leukotriene B4 levels
• Variable prognosis dependent on CNS complications/mobility
  • Physical therapy can prevent spasticity progression
Netherton Syndrome

• AR, SPINK5 mutation
  • Serine protease inhibitor may be associated with downregulating inflammatory pathways

• Congenital erythroderma, failure to thrive

• Classic triad
  • Ichthysosis linearis circumflexa - serpiginous plaques with double-edged scale
  • Trichorrhexis invaginata – “bamboo hair”
    • Examine eyebrow/eyelash hair if scalp hair sparse
  • Atopic diathesis
Netherton Syndrome

• Topical calcineurin inhibitors for pruritus and erythema
  • Limit use, potential for high absorption and toxicity

• Oral retinoids
  • Often have adverse effects

• Allergy referral
  • RAST testing

• May improve at puberty
Nevoid Basal Cell Carcinoma Syndrome (NBCCS)

• AKA Gorlin Syndrome
• Autosomal dominant
• Due to mutations in PTCH or PTCH1 gene
  • Most due to premature termination & production of shortened gene product or long arm deletions on chromosome 9q22
  • Some people carrying the genetic mutation do not meet diagnostic criteria
• Diagnosis based on major and minor criteria (varies by source)
  • 2 Major
  • 1 Major + 2 Minor
  • 1 Major + molecular confirmation
Major Criteria

1. Development of multiple BCC’s (>5) or a BCC before age 30
2. Odontogenic keratocysts of the jaw - mandible or maxilla
3. Pitted depressions of hands and feet (palmar plantar pits) 2 or more
4. Lamellar calcification of the falx <20 YOA
5. 1st degree relative with NBCCS
1) Skin Tumors--BCC

- Usually appear between ages 17-35
- Marked tendency towards central facial area
- Type 1 fair skin & prior UV exposure particularly prone to multiple BCC’s
- 1-10mm, hyperpigmented or skin-colored, dome-shaped papules
- Striking resemblance to typical compound or intradermal nevi; polypoid bcc or acrochordon-like BCC in childhood.
2) Jaw Cysts

- Occur in ~ 90% of patients
- Occur as early as age 5, rarely after 30
- Both mandible (2x mc) and maxilla show cystic defects on x-ray
- Occur as painless swelling
- Have a keratinized lining but uncommonly a cyst may be an ameloblastoma
3) Pits of Palms & Soles

• Unusual pitting of palms and soles is distinguishing feature of Gorlin’s
• Occurs in 87% of pts
• Usually apparent in 2nd decade
• Histo: basaloid proliferation, but lesions don’t progress or behave like BCC
4) Lamellar calcification of falx

5) 1\textsuperscript{st} degree relative
Minor Criteria

1. Childhood medulloblastoma
2. Lympho-mesenteric or pleural cysts
3. Macrocephaly (97th percentile)
4. Cleft lip/palate (5% of patients)
5. Vertebral/rib abnormalities—bifid, fused, missing or splayed ribs; scoliosis; kyphosis
6. Preaxial or postaxial polydactyly
7. Ovarian/cardiac fibromas
8. Ocular abnormalities
Jaw cysts, rib abnormalities, palmar pits
Gorlin Syndrome

Clinical findings are dependent on 2 characteristics:

• Race

• Form of the mutation (point mutation vs deletion)
  • Pt’s with NBCCS due to deletions of chromosome 9q22 have all stigmata of typical NBCCS and in addition often have severe MR, hyperactivity, overfriendliness with strangers, short stature, and less commonly, neonatal hypotonia, epicanthic folds, short neck, scoliosis, and epilepsy.
HISTO—solid & superficial mc types
Further Consultations/Work-up

• Ophthalmology—numerous ocular findings
• X-rays—oral, spine
• Genetic counseling
• Oral surgeon
• Routine skin checks/surveillance
Management

• Genetic counseling
• Strict sun avoidance and maximum skin protection
• Avoid ionizing radiation (radiation tx for medulloblastoma, BCC or other CA)
• Regular monitoring and biopsy of suspicious lesions
• Topical tazarotene or imiquimod to prevent and treat superficial tumors
• Oral retinoids may reduce frequency of new BCCs & slow growth of small BCC’s
  • However, once D/C’d, lesions again begin to grow
Management

• Vismodegib—hedgehog pathway inhibitor
  • Reduces BCC tumor burden & prevents growth of new BCCs
  • Poor tolerability leads to high d/c rate
  • Topical smoothened inhibitor appears effective & better tolerated

• Surgical tx used for most lesions – Mohs, Excision or ED&C
  • Megasessions—general anesthesia with removal of several lesions

• PDT - beneficial to tx areas that have had multiple BCC’s in the past
Gorlin Syndrome

• Can be physically and emotionally devastating
  • Support groups
  • Conferences for patients
Other syndromes with multiple BCCs

• Bazex-Christian-Dupre Syndrome
• Rombo Syndrome
• Brooke-Spiegler Syndrome
• Xeroderma Pigmentosum
• Schöpf-Schulz-Passarge Syndrome
• Infundibulocystic BCC syndrome
• Unilateral nevoid BCC with comedones
Bazex-Christian-Dupre Syndrome

• X-linked dominant
• Multiple BCCs of face at early age
• Follicular atrophoderma of extremities
• Hypotrichosis and localized/general hypohidrosis of face & head
Rombo Syndrome

- Multiple BCCs
- Atrophoderma vermiculatum
- Hypotrichosis
- Milia

• Infundibulocystic BCC syndrome
  • AD inheritance
    • palmar pits and jaw cysts with multiple trichoepitheliomas
    • Skin-colored pearly papules affecting central face and accentuated in nasolabial folds

• Unilateral nevoid BCC with comedones
  • Linear arrangement of close-set papules sometimes interspersed with comedones
    • Present at birth.
  • Bx reveal basal cell epitheliomas which don’t increase in size with age of patient
Neurofibromatosis Type I

• AKA Von Recklinghausen’s disease
• AD inherited syndrome manifested by nervous system, bones and skin.
• NF-1 (neurofibromin) responsible for 85% of cases
  • Neurofibromin → protein that negatively regulates signals transduced by Ras proteins
  • High rate of spontaneous postzygotic mutation
  • Both alleles must be affected for pt to grow a neurofibroma
  • Early post-zygotic mutation affecting the 2nd allele in fetal life resulting in LOH affecting entire Blaschko segment
• Gene locus 17q11.2; 50% are new mutations
• Birth incidence 1/3000
Neurofibromatosis Type I

Diagnostic criteria = 2 or more of the following:
• -> 6 café au lait macules (> 5mm prior to puberty or > 15mm after puberty)
• 2 or more NFs or 1 plexiform NF
• Pathognomonic “button-hole” sign
• Axillary or inguinal freckling (Crowe’s sign)
• 2 or more Lisch nodules
• Optic gliomas
• Osseus lesion: Sphenoid wing dysplasia, thinning of long bone cortex with or without pseudoarthrosis
• First degree relative with NF-1

** Nevus anemicus (neck & upper chest), xanthogranuloma (cephalic or genital), and glomus tumors are strongly a/w NF-1. Prevalence is high during first 2 yrs of life, when other diagnostic criteria may be absent.
Café-au-lait macule and axillary freckling

- Oval-shaped light-brown patch
- Multiple small 1–2 mm lentigines in the axilla
  - Crowe’s sign
Cutaneous Neurofibromas

• Small, soft, skin-colored to pink polypoid papules that characterize NF1

• Can be pressed down into the panniculus by light pressure and spring back when released
  • “button-holing”
Lisch nodules

- Multiple yellow-brown papules on iris
- Late finding, usually seen in older patients
Plexiform Neurofibromas

- Soft tissue swelling of the left hand, note the overlying hyperpigmentation
- Feels like “bag of worms”
Neurofibromatosis Type II

• NF-2 resembles NF-1 but it has Bilateral Acoustic Neuromas and the affected gene is MERLIN or SCHWANNOMIN, mutation in SCH gene on 22q11-q13
• NF-3 (mixed) and NF-4 (variant) have higher risk of optic neuromas, neurilemmomas, meningiomas
• NF-5 segmental (dermatomal)
• NF-6 only café au lait, no neurofibromas
• NF-7 late onset
Neurofibromatosis II Diagnosis

Requires either of the following:

• Bilateral 8th cranial nerve masses, seen on CT or MRI
• 1st degree relative with NF-2 and either unilateral 8th nerve mass or two of the following:
  • A neurofibroma, meningioma, glioma, schwannoma, and juvenile posterior subscapular lenticular opacity
Neurofibromatosis TX

• Treatment of NF requires a team approach
  • Neurology
  • Ophthalmology
  • Dermatology
  • Endocrinology
  • Orthopedics
  • Oncology

• Neurofibromas that are bothersome can be excised

• Progressive deterioration w/ loss of hearing, ambulation, & sight. Death resulting from CNS tumor.

• Recommended screening:
  • CT or MRI at diagnosis in high-risk patients
  • Yearly exam with problem focused workup

• Trials of targeted therapy to reduce the growth of cutaneous NFs are ongoing
Disorders of pigmentation

- Oculocutaneous Albinism
- Chédiak-Higashi Syndrome
- Hermansky-Pudlak Syndrome
- Gricelli Syndrome
- Hypomelanosis of Ito
- Incontinentia Pigmenti
- Piebaldism
- Waardenburg Syndrome
Oculocutaneous albinism

- Seven genetic forms
  - Main types are 1-4
  - Most common is OCA2
- All are autosomal recessive
- Variable pigmentary dilution of skin, hair, and eyes
Oculocutaneous albinism type 1

- Accounts for around 40% of OCA worldwide
  - Prevalence – 1:28,000 blacks; 1:39,000 Caucasians
- Presents at birth
- Divided into two types: 1a and 1b
- Pathogenesis
  - Mutations in the TYR gene on chromosome 11q
  - Leads to an absence (OCA type 1a) or reduction (OCA type 1b) of tyrosinase activity (and therefore melanin biosynthesis)
OCA type 1a

• Complete loss of tyrosinase function = no melanin
• White hair and skin
• Pink irides, turn blue-grey over time
  • Decreased visual acuity (20/400)
  • Photophobia
• No pigmented lesions develop
OCA type 1b

• Retain some tyrosinase function
• May develop some pigment over time
  • Eyes can turn tan or light brown
  • Hair can turn yellow
  • Pigmented lesions can develop
• Visual acuity not as severely affected as type 1a
• Temperature sensitive variant
  • Enzyme with limited activity below 37°C and none above
  • Melanin pigment only in cooler areas (ie acral)
OCA type 2

- “Yellow mutant albinism”
- Accounts for about 50% of OCA
- Tyrosinase positive
- Defect in OCA2 gene (previously P gene)
  - Decreased eumelanin synthesis
- Mild to moderate pigment dilution
  - Light brown hair and skin
  - Develop pigmented nevi/lentigines over time
OCA type 3

• More common in South Africa

• Mutation in tyrosinase-related protein 1 (TYRP1) gene
  • Important in maintenance of melanosome structure
  • Affects melanocyte proliferation and cell death
  • Essential cofactor for tyrosinase activity

• Patients have red hair and reddish brown skin
  • AKA “rufous” or red OCA

• Decreased visual acuity, but may be minor/undetectable
OCA type 4

- Very rare, except in Japan (where it accounts for 25% of OCA)
- SLC45A2 mutation (formerly MATP)
- Resembles OCA2
  - Distinguished by molecular studies
Chédiak-Higashi Syndrome

- AR; lysosomal transport (LYST) gene defect
- Presents in infancy with pigmentary dilution (sun-exposed sites may be hyperpigmented) and “silvery hair”
- Immunodeficiency
- Bleeding diathesis
- Neurologic degeneration
- Death typically by age 10 from infection or an accelerated lymphoma-like phase

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Hermansky-Pudlak syndrome

• AR; 9 associated gene defects described
• Most common in Puerto Rico, especially HSP1
• Main features
  • Tyrosinase-positive OCA
  • Bleeding diathesis
    • Absence of dense bodies in platelets
  • Lysosomal ceroid accumulation
    • Pulmonary fibrosis, cardiomyopathy, granulomatous colitis, renal failure
  • Immunodeficiency (HSP2)
Incontinentia pigmenti

- X-linked dominant (lethal in males)
- NFκβ essential modulator (NEMO) gene mutation
- 4 stages:
  - Vesicular
  - Verrucous
  - Hyperpigmented
  - Hypopigmented
- Cutaneous lesions follow lines of Blaschko
Vesicular stage

- Occurs in 87% of cases
- Onset within first 6 weeks of life
- Vesicles in linear or whorled erythematous plaques
Verrucous stage

- Onset age 2-6 months
- Usually resolve within first year of life
- Some cases reported to last several years
Hyperpigmented stage

- Onset after age 6 months
- Linear/whorled hyperpigmentation following lines of Blaschko
- May last years then fade with no sequelae
Hypopigmented stage

- May be seen in some adults
- Subtle hypochromatic or atrophic linear lesions
Other cutaneous manifestations

• Patchy alopecia

• Atrophic changes of hands
• Onychodystrophy, painful subungual keratotic tumors
Extracutaneous manifestations

• Teeth (90%): delayed eruption, partial anodontia, microdontia, peg- or cone-shaped teeth
• Bones (40%): syndactyly, skull deformities, dwarfism, spina bifida, etc.
• Eyes (35%): strabismus, cataracts, retinal detachment
• CNS (33%): seizures, mental retardation, spastic paralysis, microcephaly
Histology

- Varies with clinical stage

Eosinophilic spongiosis with dyskeratotic keratinocytes

Pigment incontinence
Genodermatoses with EYE Findings

- Richner-Hanhart Syndrome—Painful keratitis, dendritic corneal ulcers (pseudoherpetic)
- Waardenburg Syndrome—heterochromia iridis (2 different eye colors in same individual)
Genodermatoses with EYE Findings

- KID syndrome - photophobia, severe keratitis, neovascularization, blindness
- Pseudoxanthoma elasticum (& lead poisoning) - angioid streaks
Genodermatoses with EYE Findings

- X-Linked Ichthyosis—comma-shaped corneal opacities
- Fabry disease—whorl-like corneal opacities
- Gardner Syndrome—congenital hypertrophy of retinal pigment epithelium (CHRPE)
Genodermatoses with EYE Findings

- Homocystinuria - ectopia lentis (lens dislocation), downward
- Marfan Syndrome - ectopia lentis, upward
Genodermatoses with EYE Findings

- Goltz Syndrome - coloboma (defect in iris)
Genodermatoses with EYE Findings

• Neurofibromatosis - Lisch nodules (pigmented hamartomatous nevi in iris)
• Tuberous Sclerosis—retinal phakomas (hamartomas)
Genodermatoses with EYE Findings

- Sjogren-Larsson syndrome - perifoveal glistening with white dots in ocular fundus
- Cocakyne syndrome, Refsum disease—retinitis pigmentosa (salt/pepper)
Genodermatoses with NOSE & EAR Findings

- Trichorhinophalangeal syndrome - bullous pear-shaped nose
- Rubinstein-Taybi syndrome, progeria - beaked nose
Genodermatoses with NOSE & EAR Findings

- Beckwith-Wiedemann Syndrome - circular depression (posterior rim of helices), ear lobe crease
- Congenital contractural arachnodactyly - crumpled ears
Genodermatoses with NOSE & EAR Findings

Hyper-IgE Syndrome
- broad nasal bridge