

Cutaneous Manifestations of Genetic Diseases

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Disclosure

- Novartis pharmaceuticals (clinical trial)
- Taro pharmaceuticals (previously a speaker and consultant)
- Sciele pharmaceuticals (consultant)
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Objectives

- Recognize the different patterns of mosaicism as it relates to cutaneous manifestations of genetic diseases in children.
- Recognize the cutaneous manifestations of selected genetic conditions
- Be able to identify the course of action for the cutaneous manifestation of selected genetic conditions in children

Cutaneous Mosaicism

- The definition of Mosaicism
 - “an organism composed of 2 or more genetically different population of cells originating from 1 genetically homogenous zygote” (Happle and Konig, p.368)
 - Skin is often a reflection of these conditions

Types of Cutaneous Mosaicism

- Blaschko lines
 - Checkerboard pattern
 - Phylloid pattern
 - Patchy pattern without midline separation
 - Lateralization
 - It is probable that others will be defined in the future

Lines of Blaschko

- The lines can be narrow or broad
- The configuration is based on the outgrowth of embryonic cells from the neural crest
- There is a characteristic pattern that arises as a result of the growth of the embryo in conjunction with this proliferation of cells

May be further defined....

- Functional X chromosome mosaicism
- Autosomal epigenetic mosaicism
- Genomic mosaicism

Case 1

- 4 year old male is referred to your clinic with a history of brown adherent scaly skin that waxes and wanes depending on the weather
- The child was born by C-section after failure to progress
- Reported cradle cap as an infant

X linked Recessive Ichthyosis

- There is an absence of steroid sulfatase due to a gene deletion (Xp22.32) or contiguous gene deletion syndrome
- In female carriers this absence leads to perinatal problems such as delayed onset of labor and failure to progress
- May be diagnosed prenatally
- The neonates often present with a diffuse erythema and exfoliation
- Usually present at 2-6 weeks of age

Diagnostic features in children

- Brown adherent scale
- May affect the eyes (comma shaped corneal opacities)
- Males may have cryptorchidism (20%)
- Cutaneous involvement waxes and wanes throughout life-may be worse in the dry weather

Management

- Newborns
 - -monitor fluid and electrolytes, protein intake and temperature
 - -more at risk for infection
- Dermatology referral (usually managed with topical treatment)
- If needed refer to pediatric urology
- Referral to pediatric ophthalmology
- Advise OB-GYN in future pregnancies

Case 2

- A female is born with a rash that is partially vesicular on an erythematous base
- It is primarily in a linear pattern on the child's leg
- The child was born after a term healthy pregnancy and does not appear ill

Incontinentia Pigmenti (Bloch-Sulzberger syndrome)

- This is an X linked dominant disorder that is usually lethal to males
 - -male survivors may also have Klinefelter syndrome
- Presents in a Blaschko line distribution which distinguishes it from other newborn rashes

4 stages

- I-Vesicular
 - occurs in the first few weeks to about 4 months of life
 - may present at birth
 - Appears as blisters or pustules on an erythematous base or erythematous macules and papules in the Blaschko line distribution
- II-Verrucous
 - Usually seen about 1 month of age and consists of warty lesions that are usually red brown and scaly
 - Resolves by 4-6 months

- III-Hyperpigmentation
 - Usually 3-6 months
 - Linear and whorls and swirls hyperpigmentation that may persist for years along Blaschko lines
- IV-Hypopigmentation
 - Hypopigmented atrophic streaks (adulthood) may be associated with or without follicular atrophy

Diagnosis and Treatment

- Biopsy confirms the diagnosis
- Consult ophthalmology and genetics and eventually dental
- Additional evals pending symptoms
- Symptomatic treatment as needed for the lesions
- Prognosis is a normal life span

Case 3

- Child presents to clinic for evaluation of increasing numbers of café au lait macules
- Family history suggests that no other members of the family have multiple lesions
- Child is otherwise well and developmentally normal

Neurofibromatosis

- There are 3 types of NF
- Type 1 and 2 are autosomal dominant and occur spontaneously 50% of the time
- Types 3-8 appear to be partial forms of type 1 and 2

Neurofibromatosis

- Type 1 (von Recklinghausen Disease)
- The gene responsible is on chromosome 17 (17q11.2) and encodes the protein neurofibromin (90%)
 - Usually appears in young children
- Type 2 is (Acoustic Neuroma Syndrome)
- The gene responsible is located on the long arm of chromosome 22 (22 q 11-13.1) and encodes the protein merlin
 - Usually appears in teens and young adults
 - Bilateral vestibular Schwannomas

Neurofibromatosis Type 1

- Clinical features:
 - Café au lait macules (increase in size and number in the first 5 years of life)
 - Two or more neurofibromas (any type) or 1 or more plexiform neurofibromas
 - Axillary or inguinal freckling (90%)
 - Bilateral Optic nerve glioma
 - 2 or more Lisch nodules (iris hamartomas)
 - Osseous lesions (skeletal dysplasia)
 - First degree relative with NF

Neurofibromatosis type 1 other features

- Macrocephaly
- Short stature
- Scoliosis
- Hypertension
- Learning disabilities
- ADHD
- Mental retardation (rare about 5%)
- Increased risk of malignancy

Diagnosis and Treatment

- Made on clinical criteria
- AAP has issued a policy statement on NF that may assist in providing care for these children and offer guidance for health maintenance
- Management depends on symptoms but children should be referred to genetics and ophthalmology, neurology and other specialists as needed for SX
- Prognosis is dependant on involvement

Monitor for....

- Pain
- Plexiform neurofibromas
- Changes in visual acuity
- HA
- Hypertension
- Scoliosis
- Abnormalities of long bones
- Refer as needed

Case 4

- Infant presents to clinic with multiple hypopigmented macules and multiple café au lait macules
- Family history is non-contributory
- Infant is otherwise healthy and appears normal

Tuberous Sclerosis Complex (Bourneville's Syndrome)

- Neurocutaneous syndrome
- Mutations on 2 genes
 - TSC1 on chromosome 9 (9q34)
 - TSC2 on chromosome 16 (16p13)
- Transmitted as an autosomal dominant trait, may be a spontaneous mutation and parent may be asymptomatic
- May be diagnosed prenatally if the mutation is known
- May also note rhabdomyoma if fetal echo is performed

Manifestations

- Hypomelanotic macules appear usually early in life (ash leaf macule)
- Facial angiofibromas usually in nasolabial folds, cheeks or chin
- Shagreen patch
- Fibrous facial plaques
- Periungual fibromas
- Café au lait macules

Other manifestations

- Neurological component
- Eyes (retinal hamartomas)
- Kidney
- Cardiac (rhabdomyoma)
- Oral
- Musculoskeletal
- lungs

Diagnosis and Treatment

- Requires the presence of 1 major and 2 minor features
- Treat symptomatically (ie. Sz)
- Genetic counseling
- Includes multiple specialties
 - Neurology (MRI), neurodevelopmental testing
 - Ophthalmology
 - Cardiology (EKG, ECHO)
 - Renal U/S
 - Pulmonology if symptomatic

Prognosis

- Depends on organ involvement
- CNS, cardiac and renal complications are the leading cause of morbidity and mortality

Case 5

- Child presents to clinic with sparse hair, abnormal dentition, frontal bossing, saddle nose, supraorbital ridging and absent eyebrows, hyperpigmentation in the orbital area and thick lips. On history mother reports this child does not sweat much.

Ectodermal dysplasia

- More than one type
 - Hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine Syndrome)
 - Hidrotic ectodermal dysplasia (Clouston syndrome)
 - EEC syndrome (Ectrodactyly-Ectodermal Dysplasia-Cleft lip palate syndrome)
 - AEC syndrome (Ankyloblepharon filiforme adenatum-Ectodermal Dysplasia-Cleft Palate-Hay Wells Syndrome)

Anhidrotic Ectodermal Dysplasia

- Usually X linked recessive (ectodysplasin (EDA) gene (Xq12-q13))
- May be diagnosed prenatally
- Ectodysplasin –defective regulation in the ectodermal structures
- Hypohidrotic ED
 - Autosomal dominant
 - 2q11-q13

Multiple structures affected

- Skin
- Hair
- Nails
- Craniofacial
- Teeth

Prognosis and nursing care

- Very important to avoid overheating and treat infections and temps
- May have dry mucosa and skin-treat with emollients
- Referrals to dental and plastic surgery
- ENT-prn
- Wig
- Usually have normal life span

Case 6

- Nursery consult of an infant born with large blisters after a vaginal delivery
- Negative for infectious disease
- Not currently ill or on any medications

Epidermolysis Bullosa

- Rare genetic skin disease
- Vesicles and bullae in response to friction
- 3 general categories
 - Epidermolysis bullosa simplex
 - Weber-Cockayne
 - Köebner
 - Dowling-Meara
 - Junctional EB (JEB)
 - Dystrophic EB

Epidermolysis Bullosa Simplex

- Autosomal dominant
- Defect in the keratin gene (K5 12q, K14 17q)
- Weber-Cockayne
- Koebner
- Dowling-Meara

Junctional EB

- Herlitz
- Junctional EB with pyloric atresia
- Non—Herlitz JEB
- Other variants

Dystrophic EB

- Dominant (Cockayne-Touraine's Disease)
- Recessive (Hallopeau-Siemens variant)

Diagnosis and Treatment

- Biopsy to make diagnosis—sent for histopathology, immunomapping and electron microscopy
- DNA analysis
- Prenatal diagnosis is possible
- Treatment is supportive
 - Pain control
 - Wound management
 - Nutritional support
 - Social support
- Prognosis depends on the type

Summary

- Role of genetics in recognizing cutaneous manifestations of selected conditions
- Suggestion of resources for further information
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References

- Dermatlas.com
- Fitzpatrick, T.B., Johnson, R.A., Wolff, K., & Suurmond, D. (2001). *Color Atlas and Synopsis of Clinical Dermatology* (4th ed.) New York: McGraw Hill.
- Happle, R. *Cutaneous Mosaicism* (2003). In L.A. Schachner & R.C. Hansen (eds.) *Pediatric Dermatology* (3rd edition). Edinburgh: Mosby.
- Itin, P.H., Burgdor, W.H.C., Happle, R., Paller, A., Konig, A., Pierini, A., Lenane, P., Krafchik, B., Korf, B., Orlow, S., Mallory, S., Eady, R., & McGrath, J. (2003). *Genodermatoses*. In L.A. Schachner & R.C. Hansen (eds.) *Pediatric Dermatology* (2003). (3rd edition). Edinburgh: Mosby.

More references...

- Krowchuk, D.P. & Mancini, A.J. (Eds.), *Pediatric Dermatology: A Quick Reference Guide*. American Academy of Pediatrics.
- Richard, C., Moss, C., Traupe, H., Pittelkow, M., Lautenschlager, S., Konig, A., Happle, R., & Itin, P. (2003). *Ichthyosis and Disorders of Cornification*. In L.A. Schachner & R.C. Hansen (eds.) *Pediatric Dermatology* (3rd edition). Edinburgh: Mosby.
- Spitz, J.L. (2005). *Genodermatoses* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins.
- Tidman, M.J. & Garzon, M.C. (2003). *Vesiculobullous Disease*. In L.A. Schachner & R.C. Hansen (eds.) *Pediatric Dermatology* (3rd edition). Edinburgh: Mosby.