Common genodermatoses: ones you do not want to miss

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No conflict of interest
Common genodermatoses: ones you do not want to miss

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Why?
Why?

Diagnosis  Prognosis  Prevention  Management
Why?
Similarity
Case #1

- 2 year-old female patient
- Congenital erythroderma
- Peeling skin
- Palmoplantar keratoderma
- Hypotrichosis
- Food allergies, IgE ↑
- Metabolic wasting, FTT
- Recurrent infections
<table>
<thead>
<tr>
<th>Condition</th>
<th>Case #1</th>
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<tr>
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<tr>
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<td>Genetic defect</td>
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Netherton syndrome

- Autosomal recessive
- Congenital ichthyosis
  - Erythroderma
  - Ichthyosis linearis circumflexa
- Hair abnormalities (trichorrhexis invaginata)
- Atopic diathesis
- Complications: developmental delay, hypernatremic dehydration, infection
- Caused by mutations in \textit{SPINK5} encoding \textit{LEKTI}, a serine protease inhibitor

Chavanas et al, Nat Genet, 2000
Desquamation
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Netherton-like phenotypes

Netherton syndrome

LEKTI
Netherton-like phenotypes

Netherton syndrome

Peeling skin syndrome B

Corneodesmosin

LEKTI

?
Peeling skin syndrome type B

- Autosomal recessive
- Trauma-exacerbated generalized peeling
- Associated with:
  - Pruritus, atopic diathesis, food allergies
  - Failure to thrive and infections
- Caused by mutations in \textit{CDSN} (corneodesmosin)

Oji et al, Am J Hum Genet, 2010
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Case #1

- 2 year-old female patient
- Severe skin dermatitis
- Congenital erythroderma
- Peeling skin
- Palmoplantar keratoderma
- Hypotrichosis
- Food allergies, IgE↑
- Metabolic wasting, FTT
- Recurrent infections
- (SAM) syndrome
SAM syndrome results from $DSG1$ mutations leading to desmoglein 1 deficiency.

Skin biopsy

Family A

Family B

Control

Patient

Netherton-like phenotypes

Netherton syndrome
- Chavanas et al, Nat Genet, 2000
- LEKTI

Peeling skin syndrome B
- Oji et al, AJHG, 2010
- Corneodesmosin

SAM syndrome
- Samuelov et al, Nat Genet, 2013
- Desmoglein 1
LEKTI \rightarrow \text{Proteases} \rightarrow \text{Corneodesmosin Desmoglein 1}

Netherton

Inhibition

Degradation

PSS

Kallikrein inhibitors


Case #2

- Newborn
- Congenital erythroderma
- Skin peeling
- Hypotrichosis
- Recurrent infections
- Acantholysis on histology

### Table: Case #2 vs. SAM Syndrome

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<thead>
<tr>
<th>Condition</th>
<th>Case #2</th>
<th>SAM Syndrome</th>
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<tr>
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<tr>
<td>Genetic defect</td>
<td><strong>KRT1</strong></td>
<td><strong>DSG1</strong></td>
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</table>
Epidermolytic ichthyosis

- Congenital erythroderma
- Near birth: skin blistering
- Later: ichthyosis
- Palmoplantar keratoderma
- Epidermolytic changes on histology
- Mutations in $KRT1$ and $KRT10$
Epidermolytic ichthyosis sine epidermolysis?
Why ?

Diagnosis

Prognosis

Prevention

Management
Why?

Diagnosis

Prognosis

Prevention

Management
Cases #3 and #4

CDH3

Short and sparse scalp hair since birth

KRT86
Cases #3 and #4

CDH3

Hypotrichosis with juvenile macular dystrophy

Sprecher et al, Nat Genet, 2001

KRT86

Autosomal dominant monilethrix

Zhang et al, J Invest Dermatol, 2009
Cases #3 and #4

Blindness

Hypotrichosis with juvenile macular dystrophy

Sprecher et al, Nat Genet, 2001

Follicular papules

Autosomal dominant monilethrix

Zhang et al, J Invest Dermatol, 2009
Genetic heterogeneity
Phenotypic heterogeneity
Cases #5 and #6

X-linked recessive ichthyosis

Why?
Prevention

- Fetal skin biopsy
- CVS/amniocentesis and DNA-based analysis
- Preimplantation diagnosis
- Fetal DNA
Unusual modes of inheritance
Epidermolysis bullosa simplex

- Trauma-induced skin blistering
- Occasionally keratoderma
- Most mutations in $KRT5$ and $KRT14$
- Inheritance: autosomal dominant
- Pathomechanism: dominant negative effect
Epidermolysis bullosa simplex

- Dominant inheritance
- De novo mutation
- No need for testing
Case #7

Dominant inheritance

De novo mutation

No need for testing

Wrong diagnosis
Epidermolysis bullosa simplex

99%
1%
US/Europe

Case #8

KRT5

I183T

I183T

I183T
Digenic inheritance

KRT5

KRT14

R388H

I183T

I183T

Epidermolysis bullosa simplex

Modes of inheritance

- Autosomal dominant
- Autosomal recessive
- Autosomal digenic
- Semi-dominant
- Germ line mosaicism
Why?
Why?
Nevoid basal cell syndrome

Treated with corticosteroids

Dystrophic epidermolysis bullosa

Bullous pemphigoid
Congenital erythroderma

- Seborrheic dermatitis?
- Ichthyosis?
- Netherton syndrome?
- Psoriasis?
- Atopic dermatitis
- Immune deficiency?

Bone marrow transplantation

- Omenn syndrome
  - Autosomal recessive
  - Fatal infections
  - Hyperactive oligoclonal T cells
  - High IgE, low B cells

van der Burg and Gennery, Eur J Pediatr, 2011
Congenital erythroderma

- Seborrhеic dermatitis ?
- Ichthyosis ?
- Netherton syndrome ?
- Psoriasis ?
- Atopic dermatitis
- Immune deficiency ?

- Pityriasis rubra pilaris
  - Autosomal dominant
  - Life-long erythroderma
  - \textit{CARD14} mutations
  - NFkB signaling

Ustekinumab

\begin{itemize}
  \item Before
  \item After
\end{itemize}

Case #13

- 49 year old male
- **Medical history**
  - Interstitial lung disease
  - Gluten intolerance
  - Chronic sinusitis
  - Interstitial nephritis
  - Keratitis sicca
  - Past smoker
- **Family history**
  - No skin or systemic diseases
  - No consanguinity
Further investigations
Dyskeratosis congenita

p.Ala202Thr

Yamaguchi et al, N Engl J Med, 2005
Evaluation of telomere length by Terminal Restriction Fragment (TRF) analysis

Sagie et al, Hum Mol Genet, 2014
Dyskeratosis Congenita
Poikiloderma
Bone marrow failure
Leukoplakia
Nail dystrophy
Dyskeratosis Congenita

Diagnosis

Dyskeratosis congenita?
Diagnosis

Dyskeratosis congenita?
Invariable variability in dyskeratosis congenita

<table>
<thead>
<tr>
<th>Clinical feature/abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major/common features</strong></td>
</tr>
<tr>
<td>✔ Abnormal skin pigmentation</td>
</tr>
<tr>
<td>✔ Nail dystrophy</td>
</tr>
<tr>
<td>✗ BM failure</td>
</tr>
<tr>
<td>✗ Leucoplakia</td>
</tr>
<tr>
<td><strong>Other recognized somatic features</strong></td>
</tr>
<tr>
<td>✗ Epiphora</td>
</tr>
<tr>
<td>✗ Learning difficulties/developmental delay/</td>
</tr>
<tr>
<td>mental retardation</td>
</tr>
<tr>
<td>✔ Pulmonary disease</td>
</tr>
<tr>
<td>✗ Short stature</td>
</tr>
<tr>
<td>✗ Extensive dental caries/loss</td>
</tr>
<tr>
<td>✗ Esophageal stricture</td>
</tr>
<tr>
<td>✔ Premature hair loss/greying/sparse eyelashes</td>
</tr>
<tr>
<td>✗ Hyperhidrosis</td>
</tr>
<tr>
<td>✗ Malignancy</td>
</tr>
<tr>
<td>✗ Intrauterine growth retardation</td>
</tr>
<tr>
<td>✗ Liver disease/peptic ulceration/enteropathy</td>
</tr>
<tr>
<td>✗ Ataxia/cerebellar hypoplasia</td>
</tr>
<tr>
<td>✗ Hypogonadism/undescended testes</td>
</tr>
<tr>
<td>✗ Microcephaly</td>
</tr>
<tr>
<td>✗ Urethral stricture/phimosis</td>
</tr>
<tr>
<td>✗ Osteoporosis/aseptic necrosis/scoliosis</td>
</tr>
<tr>
<td>✗ Deafness</td>
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</table>
A diagnosis of consequences...
Not to miss is bliss
Thank you