Outline of training module for medical-science liaisons

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS (2015)

I. Welcome

a. This module focuses on the pathophysiology of atopic dermatitis, also known as atopic eczema or eczema
b. We will review the clinical features of atopic dermatitis, and how disruption of the skin's normal barrier and immune functions cause these signs and symptoms
c. You should spend about 2 hours completing this module
d. Understanding the pathophysiology of atopic dermatitis is essential for understanding the mechanism of action of [DRUG NAME]

II. Introduction

a. Brief description of atopic dermatitis [Eichenfield 2014 – these are the current AAD guidelines]
b. Most common chronic inflammatory skin disease
c. 1-2 sentences on epidemiology (estimated number of patients affected)
d. AD has a complex etiology that involves both disruption of normal barrier function of skin and immune dysregulation (AAD guidelines pt 1)
e. Significant effects on overall health and quality of life (1-2 sentences)
f. **Learning objectives** – after completing this module, you will be able to:
    1. Describe the clinical definition and features of atopic dermatitis
    2. Describe the role of genetics and environmental factors in the pathophysiology of atopic dermatitis
    3. Describe the pathophysiology of skin barrier dysfunction in AD
    4. Describe the pathophysiology of immune dysregulation in AD
    5. Understand the effects of AD on overall health and quality of life

d. **Please Note:** Glossary terms are indicated in **bold text** throughout the module and are defined in the Glossary at the end of this module.

III. Clinical Definition and Features of Atopic Dermatitis

a. AD (atopic eczema, "eczema") is a chronic, relapsing, inflammatory skin disease that affects millions of children and adults, and has potentially severe consequences for quality of life (AAD guidelines pt 1)
b. Itch (pruritus) is a central feature od AD and adversely affects quality of life
c. Affected patients often have elevated levels of IgE antibodies and a personal or family history of atopy (allergies, asthma, allergic rhinitis)
g. AD is a clinical diagnosis based on history, appearance and distribution of skin lesions, and clinical signs. In some cases, the dermatologist may take skin biopsies or perform tests such as measurement of serum IgE levels, KOH preparation, patch testing, or genetic testing to rule out other skin diseases
h. To be diagnosed, patients must have pruritus, AND acute, subacute, or

chronic eczema based on typical appearance of skin lesions for their age group, AND and a chronic or relapsing history of eczema

i. Description (brief) of skin lesions
j. Most patients have early onset, a personal or family history of atopy (allergy), IgE reactivity, and xerosis (abnormally dry skin)
k. Graphic – Box 1 of part 1 of the AAD AD guidelines – "Features to be considered in the diagnosis of patients with atopic dermatitis"
l. Progress check: Identify key clinical features of AD

IV. Genetic Mutations in AD

a. Studies of identical twins indicate that genetic factors play a major role in the development of AD
b. There is good evidence that numerous genetic mutations contribute to skin barrier defects and immune dysregulation in AD
    i. At least 19 gene loci (specific sites or positions on genes) have been implicated (Peng 2014)
        1. Studies of patients with AD have identified heritable mutations in or near genes that help regulate skin barrier function, innate (inborn, immediate) immunity, and inflammatory response
        2. Genetic mutations can adversely affect **barrier function** by impairing adhesion between keratinocytes. As a result, the skin cannot maintain normal hydration or resistance against pathogens and environmental insults
            a. A particularly important mutation involves the FLG gene, which encodes the protein filaggrin, which binds keratin filaments in the stratum corneum of the epidermis, and organizes them into the tightly packed, cross-linked arrays of the insoluble keratin matrix (Sandilands 2009)
            b. Functional mutations of FLG can triple the risk of AD. Even smaller differences in filaggrin expression can significantly increase the risk of AD (Brown 2012)
        3. Mutations can adversely affect **immune function and inflammation** atopic skin by causing abnormal expression of T-helper cells and cytokines (proteins that mediate inflammation) (Bieber 2014)
    c. Progress check: Identify importance and role of genetics and heritable mutations in pathophysiology of AD

V. Environmental Factors in AD

a. Early exposure to numerous environmental factors (or stressors) have been hypothesized to contributed to AD risk (Wegienka 2015)
b. Genetic and environmental factors are likely to interact in AD pathogenesis
    i. Large study of primary and middle school aged children in Korea – family history of atopy and history of having moved into a newly built house during infancy were independent risk factors for AD (Lee 2012)
c. Rest of this section reviews key environmental factors that have been implicated in AD

d. Atmospheric humidity – AD prevalence in U.S. is lowest in the most humid regions (Silverberg 2013); low humidity accelerates water loss across the stratum corneum (Elias 2014); low humidity exacerbates cytokine signaling in inflammation and are likely also to reduce filaggrin expression in patients with FLG mutations (Elias 2014)
e. UV exposure – eczema prevalence is lowest with highest mean UV index (Silverberg 2013)
f. Psychological stress – a trigger for AD flares. even in healthy individuals, chronic psychological stress has been shown to increase permeability of the epidermis (Elias 2014); this occurs as a result of an increase in production of endogenous glucocorticoids (stress hormones). GCs also inhibit production of the lipids in the stratum corneum of the epidermis that play a key role in the barrier function (Elias 2014)
g. Contact allergens
    i. Recent studies indicate that exposure to indoor and outdoor air pollutants can trigger or worsen AD. Examples – tobacco smoke, VOCs, formaldehyde, toluene, NO2, particulate matter. May induce oxidative stress in the skin, thereby triggering immune dysregulation or barrier disruption, but pathophysiology has not been fully characterized. (Ahn 2014)
    ii. One study found that boys with AD were more likely to have mold in the home compared with boys without AD (Ukawa 2013)
    iii. Patients with AD have similar or higher rates of hypersensitivity (positive patch test) to common contact allergens such as perfume/cologne and metals (Aquino 2014)
h. Microbiota
    i. Emerging evidence indicates that the microbiota (flora, microbiome) of the skin differs between AD patients and healthy individuals: will discuss shifts in microbial diversity and proportions of Staphylococcus aureus (Baviera 2014)
    ii. Gut microbiome (Wegienka 2014, Brosnick 2014)
        1. Positive effects of prebiotics and probiotics in infants indicate a role for gut microbiome in AD pathophysiology
    iii. Delivery mode (C-section, vaginal)
i. Foods
    i. Specific foods have not clearly been implicated in AD, AD is not the same as food allergy, although patients often have both AD and food allergy, and there is evidence that AD is a risk factor for food allergy in infants (Sicherer 2015)
j. Progress check: identify environmental factors for which there is strong evidence for a role in AD

VI. **Barrier Disruption in AD**
    a. Recent evidence indicates that disruption of the normal barrier function of the epidermis is central to the pathophysiology of AD, although immune dysregulation also plays an important role

b. The physical barrier of the epidermis (barrier function) mainly depends on an intact, functional **stratum corneum** and on the tight junctions within the stratum granulosum
c. Based on current evidence, several factors adversely affect skin barrier function in AD (Bieber 2014)
d. Dysfunction in permeability of the SC increases transepidermal water loss, particularly in patients with FGL mutations (Correa 2012)
e. Amount of lipid in SC of AD patients is also lower than in healthy individuals, and the lipids are also organized differently – changes in lipid barrier also increase transepidermal water loss (Correa 2012)
f. Effects of barrier disruption
    i. Disruption of the normal barrier function of the epidermis (as described in section IV) allows molecular allergens and microbes from the environment to penetrate the epidermal barrier and come in contact with antigen-presenting and immune effector cells in the dermis (Correa 2012)
    ii. Excessive activation of immune cells, particularly T-cells and dendritic (antigen-presenting) cells (Mansouri 2015)
    iii. Activation of T-helper cells, particularly Th2 and Th22 activation, with resulting increased expression of inflammatory mediators, including IL-23, IL-12, TNF-alpha, among others (Mansouri 2015, Danso 2014)
    iv. This in turn contributes to inflammation and itching (Correa 2012)
    v. Scratching then exacerbates inflammation (itch-scratch cycle) Yosipovitch 2012)
    vi. Increased susceptibility to pathogens can lead to infections with bacteria such as Staphylococcus aureus (yellowish crusting, pustules, folliculitis – will define terms in plain English)
g. FIGURE: comparison of normal and AD skin (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3449106/figure/fig2/)
h. Progress Check: Multiple choice - pathophysiology of barrier disruption and inflammation in AD

VII. **Immune Mechanisms in AD (Bieber 2014)**

a. Patients have both local and systemic immune dysregulation (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3122139/)
b. Innate immunity – Decreased expression of AMPs increases susceptibility to bacterial infections in AD patients;
c. Acquired immunity – Overexpression of Th2 cells vs. Th1 cells in acute lesions, increased IgE levels, eosinophils; cytokines and chemokines; dendritic cells
    i. The effect of cytokines on the epidermal barrier in AD is not fully understood, but recent evidence indicates that the pro-inflammatory cytokine TNF-alpha contributes to abnormal changes in the structure of the SC and reduced expression and function of lipids in the SC (Danso 2014)
d. Role of S. aureus – decreased AMP production increases S. aureus colonization in lesional and nonlesional skin; AD inflammation enhances

binding of S. aureus to skin

e. Overexpression of IL-12 and several other cytokines contributes to chronicity of lesions

VIII. **How Pathophysiology Informs Treatment Approaches**

a. Reducing transepidermal water loss (Wollenberg 2014)
b. Reduce shedding of corneocytes
c. New approaches to historical molecular targets: Histamine receptors, interleukins and other T-cell cytokines
d. New molecular targets: toll-like receptors, tight junction proteins

IX. **Summary** (table, similar in format to onychomycosis module 1)

X. **Multiple Choice Self-Assessment** (15 questions, all multiple-choice questions have only one correct answer)

XI. **Answers to progress checks and self-assessments**

XII. **Glossary**

XIII. **References**

Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-51.

Lyons, J., Milner, J., & Stone, K. (n.d.). Atopic dermatitis in children: Clinical features, pathophysiology, and treatment. Immunology and Allergy Clinics of North America, 35(1), 161-183.

Ahn K. http://www.ncbi.nlm.nih.gov/pubmed/25439225
Tamari 2014. http://www.ncbi.nlm.nih.gov/pubmed/24628071
Peng W. http://www.ncbi.nlm.nih.gov/pubmed/25090248
Wollenberg A. http://www.ncbi.nlm.nih.gov/pubmed/24720588
Lee JY. http://www.ncbi.nlm.nih.gov/pubmed/22123373
http://www.ncbi.nlm.nih.gov/pubmed/22955908
Sandilands 2009. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721001/
Baviera 2014. http://www.ncbi.nlm.nih.gov/pubmed/25126558
Wegienka 2015. http://www.ncbi.nlm.nih.gov/pubmed/25459574
Aquino 2014. http://www.ncbi.nlm.nih.gov/pubmed/25017524
Brosnick 2014. http://www.ncbi.nlm.nih.gov/pubmed/25454036
Langan 2013. http://www.nature.com/jid/journal/v133/n7/full/jid2013128a.html
Silverberg 2013 http://www.nature.com/jid/journal/v133/n7/full/jid201319a.html
Brown 2012.
http://www.ncbi.nlm.nih.gov/pubmed/22071473?dopt=Abstract&holding=npg
Elias 2014, http://www.ncbi.nlm.nih.gov/pubmed/25131691
Sicherer 2015. http://www.ncbi.nlm.nih.gov/pubmed/25662305
Mansouri 2015. http://www.mdpi.com/2077-0383/4/5/858
Danso 2014. http://www.nature.com/jid/journal/v134/n7/full/jid201483a.html
Bieber 2014. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2883413/