HAPTENS AND THEIR ROLE IN IMMUNE SYSTEM ORIENTATION

Presenters
Ricardford Connor, Erick Mororo, Steffi Nainan, Iheoma Kwazemem-Opara, Mitty Palangi, Dorjay Pemba, Anietie Umanah

Faculty: Subhajit Dasgupta, Ph.D
Case study and Introduction

Definition of Haptens

Sketch of the pathophysiology of infection

Correlation between pathophysiology and clinical symptoms

Clinical importance of Hapten carrier conjugates

Epidemiology

Treatment and Conclusion
An 18-year-old female college student presents with group A streptococcal pharyngitis and you prescribe penicillin. The patient later informs you that she developed a rash after taking about half a penicillin prescription for a respiratory tract infection 3 months ago. The rash was bright red in color, restricted to the extremities and trunk, and resolved several days after penicillin was discontinued. Prior history indicated patient previously developed pruritic eruptions around the neck and earlobes when wearing costume jewelry. Physical exam reveals erythematous to hyperpigmented periumbilical papules and plaques with sharp demarcation, and hyperpigmented patches on the neckline and ear lobes. You immediately discontinue the penicillin prescription and put her on a different class of antibiotic.
Patient’s Infectious Signs

http://www.danderm-pdv.is.kkh.dk/atlas/pics/2/2-13-3.jpg

Introduction

Haptens are small molecules which alone, are incapable of eliciting an immune response, but when coupled with proteins (carriers), the resultant conjugate induces an immune response that acts against the hapten and the carrier.
Types Of Haptens

Haptens may be of the following types:

**Simple haptens** :- non precipitating and univalent

**Complex haptens** :- Precipitate with specific antibodies and are multivalent/ polyvalent.

**Hapten Carrier Conjugate** :- Chemical coupling of a hapten to a large protein called a carrier yields an immunogenic hapten-carrier conjugate. These conjugates contain multiple copies of the hapten chemically linked to a large protein carrier. They are characterized by having native antigenic determinants of the carrier and hapten as well as new determinants formed by combined parts (adjacent residues of the hapten and the carrier) of both hapten and carrier.
Why Haptens are not Immunogenic?

- Cannot activate Helper T cells
- Failure to activate Helper T cells is due to their inability to bind to MHC proteins
- Haptens are univalent hence cannot activate B cells by themselves
Pathophysiology Sketch of Allergic Contact Dermatitis
The Sensitization Phase

Haptens penetrate the epidermis

Taken up by epidermal and langerhans cells

Present haptenated peptides to CD8 effector T cells and down regulate CD4 T cells in the draining lymph node.

Specific T cell precursors then expand in the lymph node and recirculate in the blood to the skin tissues.
The Elicitation phase

The same hapten penetrates the epidermis and is taken up by epidermal and langerhans cells

Present haptenated peptides to specific T cells

CD8 cells induce apoptosis of keratinocytes + produce cytokines and chemokines by skin residual cells

Recruitment of leukocytes from the blood into the skin.

CD4 cells block activation/expansion of CD8 effector T cells during both sensitization and elicitation phase.
Pathophysiology and Clinical Symptoms

The release of the cytokines and chemokines leads to;

**Inflammation and Pruritis**
- Pruritus is an unpleasant sensation that provokes the desire to scratch. Histamine-stimulated pathway via mechanically insensitive C-fibres

**Erythema**
- Superficial reddening of the skin, usually in patches, as a result of injury or irritation causing dilatation of the blood capillaries

**Bumps or blisters**
- These result from the stress on the surface of the skin, causing formation of fluid-filled pockets
Epidemiology

Industrialized nations:

up to 30% of all occupational diseases involve the skin

Irritant and contact dermatitis account for more than 90% of cases.

Surveillance studies have reported an annual incidence of Allergic Contact Dermatitis (ACD) (including irritant and ACD) of 13 to 34 cases per 100,000 workers.

The prevalence of Allergic Contact Dermatitis in the general U.S. population has been variably estimated between 1.5% and 5.4%.

Contact dermatitis is the third most common reason for patients to seek consultation with a dermatologist, accounting for 9.2 million visits. It also accounts for 95% of all reported occupational skin diseases.
Asthma and allergic diseases, such as allergic rhinitis (hay fever), food allergy, and atopic dermatitis (eczema), are common for all age groups in the United States. Asthma affects more than 17 million adults and more than 7 million children.

Allergies are the 6th leading cause of chronic illness in the U.S. with an annual cost in excess of $18 billion. More than 50 million Americans suffer from allergies each year.
1. **Occupation** – include health professionals, chemical industry workers, beauticians and hairdressers, machinists, and construction workers.

2. **Age** – contact sensitization begins in early childhood via exposures such as vaccinations, piercing, topical medications, and cosmetics.
   a. The incidence of ACD increases with age. High rate of ACD in adults due to repetitive and prolonged exposure to potential sensitizers. Medical comorbidities, including stasis dermatitis and venous ulcerations, are contributing factors.

3. **History of atopic dermatitis** – The role of atopy in ACD is controversial, although several studies report a high rate of positive patch tests among atopic individuals.
1. The most common allergen groups associated with positive patch test reaction.
   a. Metals, fragrances;
   b. preservatives, chemicals used in hair care products, topical corticosteroids;
   c. glues, plastics, and rubber.

2. The most common sensitizers:
   a. nickel sulfate, ammonium persulfate;
   b. gold, sodium thiosulfate, thimerosal, and toluene-2,5-diamine (p-toluenediamine)
   c. Penicillin
Type - IV DRUG ALLERGY TO PENICILLIN
- Penicillin is a small molecule and by itself is not immunogenic.

- Once degraded in body it forms very reactive “penicilloyld” group which can react with proteins (albumin) to form a penicilloyl-protein conjugate (hapten-carrier conjugate)

- This is recognized as foreign and provokes an immune response.

- Antibodies (IgE) once generated are bound by IgE receptors on the surface of mast cells and basophils.

- If in such a condition an individual is treated with penicillin it can cause allergic reactions that can be life threatening.

- Drug allergies are thus mainly because of the conjugate acting as an antigen.
Contact Dermatitis:

A form of type IV hypersensitivity in which pre-sensitized lymphocytes led to this inflammatory reaction a couple of days after the patient took the drug.
### Table 2. Classification of Penicillin Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Time of Onset, h</th>
<th>Mediator(s)</th>
<th>Clinical Signs</th>
<th>Skin Testing Useful</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate (type I reaction)</td>
<td>&lt;1 h</td>
<td>Penicillin-specific IgE antibodies</td>
<td>Anaphylaxis and/or hypotension, laryngeal edema, wheezing, angioedema, urticaria</td>
<td>Yes</td>
<td>Much more likely with parenteral administration than oral administration; fatal outcome in 1 per 50,000 to 1 per 100,000 treatment courses; some reactions occurring between 1-72 h of exposure may be IgE mediated (see text for details)</td>
</tr>
<tr>
<td>Late reactions</td>
<td>&gt;72 after exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td></td>
<td>IgG, complement</td>
<td>Increased clearance of red blood cells, platelets by lymphoreticular system</td>
<td>No</td>
<td>IgE not involved</td>
</tr>
<tr>
<td>Type III</td>
<td></td>
<td>IgG, IgM immune complexes</td>
<td>Serum sickness, tissue injury</td>
<td>No</td>
<td>Tissue lodging of immune complexes; drug fever</td>
</tr>
<tr>
<td>Type IV</td>
<td></td>
<td>Contact dermatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (idiopathic)</td>
<td>Usually &gt; 72 after exposure</td>
<td></td>
<td>Maculopapular or morbilliform rashes</td>
<td>No</td>
<td>1% to 4% of all patients receiving penicillin</td>
</tr>
</tbody>
</table>

2500 JAMA, May 16, 2001—Vol 285, No. 19 (Reprinted) ©2001 American Medical Association. All rights reserved.

[http://com-dom-im.sites.medinfo.ufl.edu/files/2012/06/5.16.04-Is-This-Patient-Allergic-to-Penicillin.pdf](http://com-dom-im.sites.medinfo.ufl.edu/files/2012/06/5.16.04-Is-This-Patient-Allergic-to-Penicillin.pdf)
Clinical Manifestations Of an Early Reaction

- Urticaria
- Angioedema
- Laryngeal edema
- Wheezing

http://com-dom-im.sites.medinfo.ufl.edu/files/2012/06/5.16.04-Is-This-Patient-Allergic-to-Penicillin.pdf
<table>
<thead>
<tr>
<th>Antiserum against</th>
<th>Aminobenzene (aniline)</th>
<th>α-Aminobenzoic acid</th>
<th>m-Aminobenzoic acid</th>
<th>p-Aminobenzoic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminobenzene</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>α-Aminobenzoic acid</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>m-Aminobenzoic acid</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>p-Aminobenzoic acid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

KEY: 0 = no reactivity; + = strong reactivity

Uses Of Hapten Carrier Conjugates

❖ To determine the effect of various chemical structures on immune specificity

❖ Diagnosis - use of the anti-hapten antibodies in the home pregnancy test to determine the hcg in the urine

❖ in situ hybridization - Technique that allows the visualization of target mRNA or DNA sequences in cells of a mixed population

❖ Antibody affinity - is used for thermodynamic investigation of the interaction of antigenic site and the antigen

❖ Antigen presentation - B lymphocytes and its role in development of humoral immune response.
The diagnosis of ACD is based upon a combination of:

1. Clinical features (morphology, location, and symptoms) of the eruption
2. History of exposure to a putative allergen during work, hobbies, or home activities
3. Patch testing results
4. Laboratory tests and/or histopathologic examination
5. Lack of recurrence after empirical treatment of the dermatitis and avoidance of the suspected allergen
Diagnosis

Patch testing

Patch testing is an essential investigation in patients with persistent eczematous eruptions when contact allergy is suspected or cannot be ruled out. Patch testing may help to identify allergens that should be avoided.

Laboratory tests and biopsy

The evaluation of the general health status, including complete blood count (CBC), liver, kidney, and thyroid function tests, should be performed in patients presenting with a widespread, recalcitrant dermatitis.

Histologic examination on itself may provide little help in differentiating ACD from other eczematous dermatitides (including irritant contact dermatitis (ICD), atopic, nummular, dyshidrotic, and seborrheic dermatitis), since all present eosinophilic spongiosis as the key feature. However, histologic examination may be helpful when the diagnosis is not clear.
Response to empiric therapy

When the possible offending allergen is identified on the basis of clinical features and history, response to empiric therapy may avoid the need for patch testing. Improvement or resolution of the dermatitis with allergen avoidance and empiric treatment supports the diagnosis of ACD.
A. Two strategies:

   a. Treatment for the present allergy symptoms
      
      i. Withdrawal of the drug (Penicillin G is the most common)
      
      ii. Antihistamines (mild allergic reaction)
      
      iii. Corticosteroids (severe allergic reaction)
      
      iv. Treatment of anaphylaxis (severe allergic reaction)

B. Drug desensitization

   I. This method is recommended with there is not another antibiotic for the treatment;

   II. Mechanism of Drug desensitization: Small doses $\rightarrow$ 15 to 30 min $\rightarrow$ for several hour or days $\rightarrow$ NO REACTION $\leftrightarrow$ Treatment could be continued.

   III. Patient monitoring is required in case an reaction occurs and the treatment should be stopped.

"Sanjib Bhattacharya"
1. Medication that could cross-react after penicillin allergies have been established: **Cephalexin**, **Cefadroxil**, **Cefaclor**, **Cephradine**, **Cefprozil**, **Ceftriaxone**, and **Cefpodoxime**

2. Medication that would be safe: **Cefazolin**, **Cefuroxime**, **Cefdinir**, **Cefixime**, and **Ceftibuten**

Conclusion

❖ Identify the population group that could be affected by ACD

❖ Be aware about the risk factor

❖ Know how the hapten function and mechanism of action;

❖ Know the substances that can act as hapten

❖ Have good foundation of ACD

➢ clinical presentation, pathogenesis and diagnosis

❖ Function of haptens... carriers conjugates clinically
Thank You!
References


Khuntia, A., & Baldwin, J. (2004). Common Triggers and Distribution: Table 1 and Table 2. *Contact Dermatitis.*


Pubmed ,http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3255391/