Virus Infections and Drug Hypersensitivity

New Horizons Session 4 – December 4th, 2011, Cancún, México
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What is known/speculated?
(Coincidence, aggravation of symptoms)
- Infections in children
  (transient intolerance of antibiotics, in particular amoxicillin)
- Herpes virus infections
- HIV infections

Possible mechanism involved?
- Virus infection – cross-reactivity
- Virus infection – co-stimulation/co-activation

Infections in children
- Many children make a maculopapular exanthema after amoxicillin and other drugs
  - Skin tests and provocation test later often negative
  - Coincidence of viral infection and drug exposure
Which viruses are implicated?

- Picorna-, Corona-, Boca-, Influenza-, Parainfluenzavirus, RSV, Human Metapneumovirus (hMPV)
- detectable in ca. 66%* of children with β-lactam and exanthem ("rash", delayed urticaria)

*Caubet et al. JACI (2011) 127:218

“It is not a hypersensitivity reaction, but a consequence of virus infection”

- Virus infection and immune stimulation (cytokines) enhances T-cell reactivity to amoxicillin
- Sensitization to amoxicillin without co-infection is in most instances too mild to cause symptoms (no skin or provocation test)
- Only a few of amoxicillin reactors (5-12%) show sufficient sensitization to keep reactivity in skin test

Herpesvirus infections

- Cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus-6 and -7 (HHV-6/HHV-7), Herpes simplex virus (HSV)...
- active: e.g. in infectious mononucleosis
- persistent: >10% of T-cells involved in control of endogenous herpesviruses
- reactivating: e.g. in DRESS or MDH (Multiple Drug Hypersensitivity)
Herpesvirus infections - IM

**Infectious Mononucleosis (IM)**


Herpesvirus infections - Diagnostic criteria for DIHS/DRESS

1. Maculo-papular rash 3 weeks after therapy
2. Lymphadenopathy
3. Fever (>38°C)
4. Leucocytosis (>10x10⁹/l)
5. Hepatitis (ALT>100U/l)
6. HHV-6 reactivation

Herpesvirus infections - Sequential reactivation of herpesviruses in DIHS/DRESS (adapted from Bruderer & Kano, (2007) Clin Exp Immunol.)

Clinical symptoms might be triggered by sequential virus reactivation.
"...cutaneous and visceral symptoms of DRESS are mediated by activated CD8+ T lymphocytes, which are largely directed against herpes viruses such as EBV.”

EBV-specific CD8+ T cells in blood, skin lesions, liver, and lungs of DRESS patients

Induction of EBV by culprit drugs
**Definition of MDH:**

**Multiple drug hypersensitivity (MDH) patients**

- Typical medical history of drug allergy (starts often with a severe hypersensitivity reaction like a DRESS)
- > 1 non cross-reacting drug
- positive in skin or/and in vitro tests (LTT)

Herpesvirus infections – MDH triggered by viral co-stimulation?

"... A particular feature of DMH is the fact that the drug-reactive T cells are found in an in vivo pre-activated cell fraction."

Drug-reactive T cells in CD4^+CD25^+ subpopulation

- Drug reactive T cells: enhanced CD38 and PD-1 expression
- Endogenous herpes viruses: HHV-6, EBV, CMV...
HIV infections

**HIV infected patients**

- Sulfonamide hypersensitivity reactions (increased incidence from 4% in normal population up to 60%* or higher in HIV+ population)
- Probability to develop SJS/TEN: 1000-fold** higher!
- Other drug allergies?


Possible mechanism involved?

**CO-STIMULATION**

- MDH
- HIV infection...

**CROSS-REACTIVITY**

- DRESS
- (Picard et al.)

Possible mechanism involved?

**Co-stimulation**

- p-i concept

(Pharmacological interaction with immune receptors)

- hapten concept
  - A) Antigenic hapten-carrier complexes induces T-cell responses

- p-i concept
  - Drugs bind directly...
  - B) to the TCR
  - C) to the MHC

Adam J. et al. BJCP (2011) 71(5):701-7
Pre-activation is needed!

**p-i concept**
(pharmacological interaction with immune receptors)

**Co-stimulation**

T cell repertoire ($2.5 \times 10^7$)

A) Herpesvirus reactivation leads to activated virus-specific T cells
B) Drug binds to (pre-)activated virus-specific T cells (trigger!)

**Cross-reactivity**

Trigger a multiorgan immune response directed against herpes viruses
SUMMARY

- Viruses are activating a broad repertoire of T cells; this activation enhances the response to drugs and facilitates T cell mediated drug allergies (exanthems, hepatitis, DRESS,...).
  - This activation occurs in children (probably caused by different viruses); transient exanthema to drugs in childhood
  - It occurs during adulthood: the chronic herpes viruses (EBV, CMV, HHV-6) are activating T cells (exanthema, DRESS)

- Involved mechanism:
  - Activation of virus-specific T cells -> drug binds to this pre-activated T cell (co-stimulation)
  - drug/virus-cross-reactive T cells (cross-reactivity)

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