The Immune System in Health & Disease

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Overview

- Why do we need an immune system
- Immune mechanisms of defence
- What happens when the immune system goes wrong?
- Case studies
- Appropriate samples/ tests for investigation of immunological disorders
Why do we need an Immune System?

- Immune system defends us against infections caused by microorganisms

- Bacteria
- Viruses
- Parasites
- Fungi
The Immune System

Circulation

Lymphoid tissue

- Cervical
- Supraclavicular
- Axillary
- Mediastinal
- Supratrochlear
- Mesenteric
- Inguinal
- Femoral
- Popliteal

Cells

- White blood cells
  - Monocyte
  - Eosinophil
  - Basophil
  - Lymphocytes
  - Neutrophil

Proteins

- Antibody
- Messengers
- Complement
Immune mechanisms of defence

Neutrophils engulf and kill bacteria
Immune mechanisms of defence

Killer T lymphocytes kill virus infected cells
Immune mechanisms of defence

- B lymphocytes produce antibody
- Marks bacteria for killing
- Neutralises toxins
- Activates complement

1. The B-cell finds an antigen which matches its receptors.
2. It waits until it is activated by a T-helper cell.
3. Then the B-cell divides to produce plasma and memory cells.
4. Plasma cells produce antibodies that attach to the current type of invader.
5. "Eater cells," prefer invaders marked with antibodies and "eat" loads of them.
6. If the same invader invades again, memory cells help to activate the immune system to activate much faster.
Immune mechanisms of defence

- Complement proteins form a hole in bacteria
- Bacterium bursts
Vaccination

Small pox virus
What happens when the Immune system goes wrong?

- Immunodeficiency

- Overactivity
  - Allergy
  - Autoimmunity

Hay fever

Rheumatoid arthritis
Clinical Immunology

- Diagnostic tests – 90,000 tests/year

Patients
- Immunodeficiency
- Autoimmune diseases
- Allergy
Immunodeficiency

Failure of immune system to protect us from infection

Intrinsic defect in immune system

No T lymphocytes

“The boy in the bubble”

Severe combined immunodeficiency disorder
Immunodeficiency

Failure of immune system to protect us from infection
Due to drugs, infection, malnutrition, age
Immunodeficiency

- Age at onset
- Type of infection
- Pattern of infection
- Associated features

Investigation

- *Numbers* of cells or *amounts* of proteins
- *Functional ability* of cells or proteins
Case 1

- 2 year old boy
- Recurrent chest infections & chronic diarrhoea
- Well until age of 6 months, then developed chest & ear infections
- Family history
Sites of infection

Pneumonia - affecting right lower lobe

Otitis media
CT scan of lung - bronchiectasis
Investigations

- Measure Antibody levels
- Immunoglobulin levels (IgG, IgA and IgM)
- Serum sample

Case 1
Absence of antibodies – IgG, IgA, IgM

Turbidimetry
Investigations

- Measure white cells
- Lymphocytes, neutrophils, monocytes
- EDTA sample

Fresh EDTA sample

Measurement of B cells

Flow cytometry

Case 1
No B cells
Role of btk

HSC → Pro-B cell → Pre-B cell → Mature B cell

Bone marrow

X-linked agammaglobulinaemia

Treatment: IVIg & antibiotics
Case 2

- 25 year old male
- History of skin abscesses - staph
- Lung and liver abscesses – *Pseudomonas, Serratia marcescens*
- Lung abscess extending to spinal cord - *Aspergillus*
Flow cytometric measurement: Neutrophil function

- EDTA sample
- Do neutrophils produce superoxide when stimulated?
Chronic granulomatous disease - CGD

Case 2
Defect in superoxide production
Failure to kill engulfed bacteria

- Treatment
  - Prophylaxis (antibiotics)
  - BMT
Immunodeficiency disorders

- **Primary**
  Intrinsic dysfunction of one/more components of the immune system
  *RARE*

- **Secondary**
  Dysfunction of one/more components occurring as result of other process
  *COMMON*

- **Investigations**
  Patient must be well
  Specific samples required
  Functional tests require fresh samples (<24hr)
Atopy/ Allergy

- Predisposition to generate IgE-mediated response to environmental antigens
- Genetic component
- Affects 10% + of population

- Clinical presentation
  - Asthma
  - Hay fever
  - Eczema
  - Foods – especially in children
  - Urticaria
  - Anaphylaxis
Allergy

- Patient history central to making a diagnosis
- Example – food allergy reactions nearly always within 1 hour of food ingestion
- Blood tests – specific IgE to suspected allergen
- Skin prick tests
- Rarely – challenge with food, drug
Case 3

- 16 year old girl
- Brought to ED after severe asthma attack
- Eating in a Thai restaurant

- Severe bronchospasm
- Hypotensive BP 90/50
- Angioedema of lips & oropharynx
- Stridor

**DIAGNOSIS** - Anaphylaxis
Case 3

Treatment

- Intramuscular adrenaline
- IV antihistamines
- Hydrocortisone

- Blood pressure returned to normal
- Stridor still present
- Second dose of adrenaline
Specific IgE to allergen

Case 3
Specific IgE
Nuts
Skin prick tests

Advantages – inexpensive, rapid information

Case 3
Peanut
Almond
Walnuts
Case 3

Review

- Stopped eating peanuts - tingling mouth sensation
- Past Hx of eczema and asthma since 5 yrs
- Inhaled steroids & daily rescue inhalers
- Nut avoidance
- Self-administered epinephrine pen
- Medic-Alert pendant
Allergy treatment

- Avoid allergen – if possible
- Anti-histamines
- Desensitisation – venoms, pollens
Conclusions - Allergy

- Allergy is common

- Reactions manifest differently depending on tissues affected

- Diagnosis - History history history history
Autoimmunity

- Breakdown in self tolerance
- Immune response to self (cells and organs)

- Autoimmune disease
  - Inflammation
  - Organ dysfunction

- Immune system targets self-tissue /organs leading to dysfunction
  - Organ specific
  - Non-organ specific
Autoimmune diseases

Examples

- Joint disease - rheumatoid arthritis, SLE
- Kidney disease - glomerulonephritis
- CNS disease – multiple sclerosis, myasthenia gravis
- Bowel disease - coeliac disease
- Endocrine disease - diabetes, thyroid disease
Who gets autoimmune disease?

- 3% Western populations
  - Multiple sclerosis, RA and IDDM

- Peak onset – puberty to retirement age

- More common in women x 8

- Clustering within families
Case 4

- 35 year old woman
- Diarrhoea & generalised abdominal pain
- Felt tired for previous 2 yrs
- Lost 8kg in 6 months despite good appetite
- Anaemic
Investigations

Anti-Tissue transglutaminase (tTG)

Case 4
Anti-tTG Positive
EMA Positive

IIF on monkey oesophagus
> 99% specific for coeliac disease

Serum NOT plasma

- Anti-Endomysial antibody (EMA)
Coeliac disease

- Intolerance to gluten
- 1% population
- Screening test
  - Anti-tissue transglutaminase (tTG)

Treatment
- Gluten free diet
Case 5 – 35 year old female

History
- Joint pain, swelling for 6 months, intermittent
- Hands and wrists most affected
- Sharp pain in chest on breathing, intermittent
- No energy x 2 years
- Otherwise generally well
Case 5 – 35 year old female

Examination

- Generally healthy
- Some swelling, tenderness of hand, wrist joints
- Pulse rate 90 beats per min
- Heart and chest exam normal
- Skin rash on face
Investigations

- Rheumatoid factor
- ANA
- Anti-dsDNA

Case 5
RF Negative
ANA Positive
Anti-dsDNA Positive

**DIAGNOSIS** -
Systemic lupus erythematosus
Connective tissue diseases

- Chronic autoimmune conditions
  - inflammation in blood vessels
  - Inflammation in connective tissues

Collagen vascular disorders – “collagen vascular screen”

- SLE
- Mixed connective tissue disease
- Scleroderma
- Sjogren's syndrome
- Polymyositis/Dermatomyositis
SLE : Clinical features

- **Skin**
  - Erythematosus face rash “butterfly”
  - Chronic discoid plaque-like lesions
  - Photosensitivity

- **Arthralgia & arthritis**

- **Haematological abnormalities**
  - Immune thrombocytopenia
  - Haemolytic anaemia
  - Autoimmune neutropaenia
SLE: Clinical features

- Renal abnormalities
  - Proteinuria
  - Haematuria
  - Nephrotic syndrome
  - Acute renal failure

- Cerebral disease
  - Seizures
  - Focal neurological disorders
  - Paranoid, deluded, confused

- Mouth/nasal mucosa ulcers

- Lung
  - Serositis (pleura & pericardium)

Multiple autoantibodies

- Anti-nuclear antibody (ANA)
- Anti-dsDNA antibody
- ENA antibodies
- Anti-RBC antibody
Case 6

- 50 year old male
- Oral ulceration
- Widespread flaccid bullae
Investigations

- Anti-skin antibodies
- Skin biopsy
- Chicken-wire pattern

Case 6
Anti-skin antibody Positive Detachment of cells

Pemphigus vulgaris

Serum *NOT* plasma
Pemphigus vulgaris

- Pemphigus vulgaris DG3
- Intradermal blister formation
- Autoantibodies to desmosome

Treatment
- High dose steroids/Immunosuppression
Conclusions - Autoimmunity

- Breakdown of tolerance
- Organ specific or non-organ specific
- Autoantibodies as markers
Cryoglobulins-Immunoglobulins that precipitate in the cold

**Indications**
- Cutaneous vasculitis
- Renal disease
- Raynaud’s phenomenon

**Investigations**
- Blood taken into prewarmed syringe, prewarmed tube
- Transported 37°C incubator
- Clots at 37°C
- Serum at 37°C, 4°C for 2-3 days
- Cryocrit
- False negative – sample not kept at 37°C

B cell malignancies, chronic infections
Investigations of Immunological Disorders

Immunodeficiency
- Serum samples (measurement of protein levels)
- Fresh samples (function) <24 hrs
  - Sodium citrate samples (C1-Inhibitor function)
  - EDTA samples (cell analysis)
  - Serum samples (complement function)

Allergy
- Serum samples

Autoimmunity
- Serum samples
Summary

- Immune mechanisms of defence

- Immunological disorders
  - Immunodeficiency
  - Allergy
  - Autoimmunity

- Case studies illustrate diseases and tests for investigation of immunological disorders