Immunodeficiencies

Prof. Md. Akram Hossain

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What is immunodeficiency?

Deficiencies of host defense systems result in an immunologic imbalance that can lead to a susceptibility to infection, an autoimmune disease, or a predisposition to malignancies.
Types of immunodeficiency

May be of two types:

1. **Primary immunodeficiency**
   is usually a genetic defect in the immune responses that one is born with.

2. **Secondary or acquired immunodeficiency**
   one is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses.
Types of immunodeficiency disorders:

1- Primary: Causes in immune system component:

a. According of component:

b. According to the etiology:
   i. Congenital (X-linked disease) ii. Acquired (AIDS)
   iii. Embryogenesis (Digoerage syndrome). iv. Idiopathic

2- Secondary: Non Immunogenic causes:


c. Hodgkin`s and others malignancy. d. Injury, Burns, Splenectomy.

e. Drugs.
Classification:

Primary (congenital).
- Genetic mutations.
- Genetic polymorphism.
  They could be:
  - either Monogenic
    (defect in one gene)
  - or polygenic
    (defect in more than one gene)

Secondary (acquired).
- Most important cause:
  - malnutrition.
  - viral & bacterial infections.
    e.g. AIDS which is caused by HIV
  - Immunosuppressive drugs.
    (corticosteroids).
    For long-time use, it’ll depress the immune system

- excessive protein loss,
  burns, nephrotic syndrome
  (loss of cells like RBC and loss of protein like Ig)
Primary or acquired.
can affect.

Natural immunity
(non-specific body defenses).

Phagocytic cells.

Complement proteins.

Acquired immunity.
(specific body defenses).

T-cells.

B-cells.
B-cell defects.

Gammaglobulinaemias:
B Cell Immunodeficiencies:

- Bruton’s (X-linked) Agammaglobulinemia
- Autosomal Recessive Hyper-IgM Syndrome
- B Cell Receptor Deficiencies
- Common Variable Immunodeficiency (CVID)
- Selective IgA Deficiency
- IgG Subclass Deficiency
Properties of B-cell defects

1. Diverse spectrum of diseases ranging from:

Complete absence of B-cells, Plasma cells and Immunoglobulin's, to selective absence of certain immunoglobulin classes
Properties of B-cell defects..

2. X-linked disease:
   - If heterozygous
   - Female carriers are normal.
   - Males manifest the disease.

3. Severity of the disorder parallels (is Proportional to) the degree of the deficiency.
FEATURES of B-cell defects

- Reduced B-cell counts to 0.1 percent (normally 5-15 percent.)
- Absence of Immunoglobulins.
- Small Lymph nodes, no germinal centers (the home of B-cells in the lymph node)
Lesions can occur at any site in the pathway of B-cell development. B-cell defect could be in any level in the pathway.
Patients with B-cell defects are subject to:

**MCQ**

**Recurrent bacterial infections**

but

Display normal immunity to most viral & fungal infections.

because:

**T-cells are unaffected.**

Because T-cell which stands in the face of viral and fungal infection
<table>
<thead>
<tr>
<th>(The disease)</th>
<th>(the level of defect)</th>
<th>(the result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. X-linked agammaglobulinaemia.</td>
<td>Bruton tyrosine Kinase (Btk)</td>
<td>no mature B-cells.</td>
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</tbody>
</table>

**MCQ**

Is the first I.D. Recognized in (1952)
The most common (80 to 90 percent)

Defect in Bruton tyrosine kinase enzyme (BTK).

**MCQ**

The Defect involve a block in maturation of pre-B-cells to mature B-cells in bone marrow.

Pre B-cell + BTK enzyme ➔ Mature B-cell
Features of XLA:

- Reduced B-cell counts to 0.1 percent (normally 5-15 percent.)

MCQ

- Absence of Immunoglobulins.
- Small L.nodes, no germinal centers.
Affected children suffer from recurrent pyogenic bacterial infections of:

- conjunctiva, throat, skin, ear, bronchi & lung

Infecting microbes include:

- Pneumococci, H. influenzae
- Streptococci

Also the patient is susceptible to certain viruses (polio) and intestinal parasites (giardia).
Most intracellular microbes & fungi are handled normally by (T-cells).
What is XLA?

✓ Described by the IUUIS committee as the ‘prototypical antibody deficiency’.
✓ First immunodeficiency described.
✓ Defect on the X chromosome affecting the $Btk$ gene.
✓ Results in an absence or severe reduction in B lymphocytes and hence immunoglobulin of all types.
Little boys with big infections

6 to 9 months old

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X linked Agammaglobulinemia
Clinical Findings

✓ LITTLE BOYS WITH BIG INFECTIONS!
✓ Symptoms appear at 6-9 months of age (after loss of maternal Ig).
✓ Sites of infection: mucous membranes, ear (otitis media), lungs (bronchitis/pneumonia), blood (sepsis), gut (Giardia, or enterovirus), skin, eyes, meningitis.

Also seen: joint problems, kidney problems, neutropenia, malignancy in older patients.

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Patients with XLA repeatedly acquire infections with extracellular pyogenic organisms such as:

- Pneumococcus
- Hemophilus
- Streptococcus
Susceptibility to encapsulated Bacteria

- *H Influenzae*
- *S pneumoniae*
Sinusitis

Pneumonia

Otitis Media
XLA

✓ BTK, the XLA gene, maps at Xq21.2-22.2
✓ BTK is expressed in all stages of B cell lineage except plasma cell.
✓ BTK is also in mono, mega., platelet mast.....but not in T and NK cells.
✓ Mutational analysis: more than 600.
✓ Clinical feature
✓ Laboratory feature.
The *Btk* gene

- Located on the X chromosome.
- Gene consists of 19 exons over a length of DNA of 37 kilobases.
- Function of the *Btk* gene product is related to BCR signalling.
- Without Btk pre-B cells fail to develop into mature B cells.
Intravenous Immunoglobulin (IVIG)
1. IgA deficiency (1:700)

2. Selective immunoglobulin deficiency.

Most are asymptomatic, but have increased rate of (respiratory tract infection R.T.I)

Some have recurrent R.T.I. and G.I.T. Symptoms

Because of lack of secretion of IgA on the mucous membrane of GIT and respiratory tract.

[Increased incidence of allergic manifestations]

anti-convulsant drugs (phenytoin) may cause secondary deficiency (these drugs are used to treat epilepsy, they destroy IgA)
Selective IgA Deficiency

Selective IgA deficiency is the most common ID disorder. The prevalence is about 1:700.

Pathogenesis: block in B cell differentiation is due to intrinsic B cell defect or abnormal T cell help such as production of cytokine (TGF-B, IL-5) or in B cell responses to these cytokines.
IgA Deficiency

- Clinical feature: Recurrent sinopulmonary infection, Gastrointestinal disorders, Allergy, Cancer and Autoimmune disease.
- IgA Deficiency and genetic factors: association with HLA-A2, B8 and DW3 or A1 and B8.
- IgA Deficiency and drug.
- Serum IgA<5mg/dl but normal IgM and IgG
- Immunopathogenesis: arrest in the B cell differentiation.
Overview of B-Cell Development

Bone Marrow

Lymphoid Stem Cell → Pro-B Cell → Pre-B Cell → Immature B Cell → Mature B Cell → Activated B Cell

Periphery

Activated B Cell → Plasma Cell

Antigen Independent

Primary Lymphoid Organ

Antigen Dependent

Secondary Lymphoid Organs

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X-linked hyper-IgM Syndrome.

Characterized by:

- Low IgG, IgA & IgE
- Markedly elevated IgM
- High levels of autoantibodies (against neutrophils, platelets, red cells)

Recurent infections especially Pneumocystis carinii

[ Pneumocystis carinii usually found in people who have AIDS ]
Defect in the CD 40L in T-cells lead to:
(CD 40L is the hand that Th cell use it to shake other cells hands)

* No co-stimulatory signal for B-cells.

* No response to T-dependent antigens.

* No class-switching.
(The change of one class of Ig to another one)

* No memory cells.

* Marked lymphadenopathy.
3. X-linked hyper-IgM Syndrome.

- The disease: X-linked hyper-IgM Syndrome.
- The level of defect: Defective CD40 Ligand.
- The result: Markedly elevated IgM.
Management of immunoglobulin deficiencies:

MCQ

repeated intravenous immunoglobulin (IV Ig) reduces infectious complications.

--- GIVE Ig ---
Common Variable Immunodeficiency

CVID
CVID has an almost equal sex distribution
• CVID is characterized by hypogammaglobulinemia

• CVID has a tendency to autoantibody formation
CVID

Normal lymphoid follicle

Normal number of circulating B cell

Hypogammaglobulinemia

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CVID abnormalities

- CVID is a heterogeneous group of disorders with intrinsic B-cell defect or a B-cell dysfunction related to abnormal T-cell B-cell interaction.
- Lack of inducible costimulator (ICOS) expression by activated T cell which associated with lack of T cell help for B cell differentiation, class switching and memory B-cell generation.
- In 10-20% of families another member may have selective IgA def.
CVID cont.

✓ Pathogenesis: defect in differentiation into Ig secreting plasma cells.
✓ Reduction class switching
✓ Defect in somatic hypermutation.
✓ Reduction production of cytokines
✓ Increased apoptosis in B and T cells.
✓ Defect in CD27 and CD134 ligand, important in promoting into plasma cells.
Hyper IgM syndrome
Serum levels of immunoglobulin in Hyper IgM syndrome

- IgG↓
- IgA↓
- IgE↓
- IgM↑↑
Hyper IgM syndrome

• Defect in CD40 ligand

T cell → CD40 ligand

CD40

B cell

Ig Class switch
Bruton’s (X-linked) Agammaglobulinemia

- Very low levels of all immunoglobulins (IgG, IgM, IgD, and IgE)
- B cells are virtually absent (Pre B cells present but they fail to mature into B cells due to mutation of tyrosine kinase gene)
- T cells (CMI) normal
- Cl/F
  - Recurrent pyogenic bacterial infections e.g. otitis media, Sinusitis, pneumonia caused by Strep. Pneumoniae, H. influenzae (at 6 months of age)
- Treatment: Pooled gamma globulin
Selective Immunoglobulin Deficiencies

- IgA deficiency is the most common: IgG and IgM deficiency are rarer.
- IgA deficiency may be due to failure of class switching.

CI/F

- Recurrent pyogenic bacterial infections e.g. otitis media, Sinusitis, pneumonia caused by Strep. Pneumoniae, H. influenzae (at 6 months of age)
- Treatment: Should not be with Pooled gamma globulin because they may form antibodies against foreign IgA and by cross-reaction deplete already low levels of IgA.
IgG Subclass and IgA Deficiencies
Patterns of Illness

- Chronic/recurrent upper respiratory infections, especially sinusitis
- Tendency to develop respiratory and gastrointestinal allergies and autoimmunity
IgG Subclass – IgA-D – CVID
Polar Ends of a Common Disease?

- IgA deficiency frequently coexists with IgG subclass deficiency, especially IgG2 and IgG4
- Linkage to Class III region of HLA
- 50% incidence of IgA-D in children of patients with CVID
- Occasionally IgA deficient patients have been noted to progress to CVID
Common Variable Immunodeficiency

- Panhypogammaglobulinemia, usually with lymphadenopathy and splenomegaly
- Absence of clear abnormalities in T and B cell subsets
- Chronic/recurrent respiratory infections, & diarrhea, especially due to *Giardia*
- Tendency to develop autoimmunity and lymphoid malignancies
- Linkage to HLA Class III Region in 2/3 of patients
- One gene identified: ICOS (B7h) (activation antigen on T cells)
Figure 12-4. Congenital immunodeficiencies associated with defects in lymphocyte activation and effector functions. Congenital immunodeficiencies may be caused by genetic defects in the expression of molecules required for antigen presentation in T cells, T or B lymphocyte antigen receptor signaling, helper T cell activation of B cells and macrophages, and differentiation of antibody producing B cells. Examples showing the sites where immune responses may be blocked are illustrated in A, and the features of some of these disorders are summarized in B.
T cell deficiency
Evaluation of cell-mediated immunity

- Total lymphocyte count
- DTH
- Lymphocyte response
- Total T cell using Anti-CD3
- CD4 and CD8 subset
- Cytokine production
Cell mediated (T cell) Immunodeficiency

1. DiGeorge Syndrome
2. Defect in CD3/TCR
3. Defect in signaling, Defect in ZAP-70
4. Defect in Cytokine production as IL-2 and IFN gamma
5. Defect in Cytokine response
DiGeorge Syndrome

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Immunodeficiency
<table>
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<tr>
<th>Disease</th>
<th>Functional deficiencies</th>
<th>Mechanism of defect</th>
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<tr>
<td>DiGeorge syndrome</td>
<td>Decreased T cells; normal B cells; normal or decreased serum Ig</td>
<td>Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia</td>
</tr>
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DiGeorge Syndrome

- Defective development in thymus and parathyroid that develop from third and fourth Pharyngeal pouch

- Thymic hypoplasia leading to variable immunodeficiency. Other features:
  
  ✓ Characteristic faces
  
  ✓ Deletion in 22q11 in > 80%
  
  ✓ Abnormal calcium homeostasis
Combined Immunodeficiencies:

- Combined immunodeficiency (CID)
- Severe combined immunodeficiency (SCID)
- Omenn syndrome
- ADA (Adenosine Deaminase Deficiency)
- Ataxia-Telangiectasia syndrome (AT)
- Wiskott -Aldrich syndrome (WAS)
Common Features of Severe Combined Immunodeficiency (SCID)

- Failure to thrive
- Onset of infections in the neonatal period
- Opportunistic infections
- Chronic or recurrent thrush
- Chronic rashes
- Chronic or recurrent diarrhea
- Paucity of lymphoid tissue
Fig 2-2.—Progressive varicella in infant with severe combined immunodeficiency.
X-Linked SCID caused by gamma-C Deficiency

- X-linked ID with absent T, NK and Ig synthesis
- Due to mutation in the gene common gamma chain (γc) shared by the receptors for the IL-2,4,7,9,15 which play a role in signal transduction through activation of Jak-3
Combined Immunodeficiency
Autosomal Recessive SCID

✔ Jak-3 deficiency: T⁺B⁺NK⁻-SCID

✔ RAG-1 or RAG-2 deficiency: T⁻B⁻NK⁺
Congenital adenosine deaminase deficiency (ADA deficiency) causes deficiencies of the adenosine deaminase (ADA) and inosine deaminase (INA) enzymes. These deficiencies block purine pathways at several points, leading to accumulation of secondary metabolites and toxic effects on lymphocytes. Secondary metabolites include increased adenosine, deoxyadenosine, S-adenosyl homocysteine, xanthine, uric acid, hypoxanthine, guanine, and guanosine. The accumulation of these metabolites is indicated by the toxic effects on lymphocytes, which include inhibition of ribonucleotide reductase and transmethylation reactions. Prof. Muhammad Akram, Immunodeficiency.
WISKOTT-ALDRICH Syndrome

- X-linked
- Eczema, thrombocytopenia, bacterial infection (polysaccharide antigen)
- Defective gene encode a cytoplasmic protein expressed in BM derived cells interact with adaptor molecule (Grb2) & G proteins regulate actin cytoskeleton.
- Cell surface glycoproteins reduced; CD43
- (or sialophorin) normally on Lymph . neut . Mac and Platelet
- These alterations interfere with migration of Leuk. to inflammation sites.
ATAXIA-TELANGIECTASIA

- Autosomal recessive
- Abnormal gait (ataxia)
- Vascular malformations (telangiectasia), neurologic defects, tumors, and ID
- ID may affect T&B cells
- IgA and IgG2 deficiency
- T cell function is variably depressed
- Gene responsible on chromosome 11
- Gene product may play a role in DNA repair
Defective Class II MHC Expression
Bare lymphocyte syndrome

✓ Autosomal recessive
✓ Fail to express HLA– DP,DQ,DR on APC and in response to IFN-gamma
✓ Mutation in genes encoding proteins regulate class II MHC transcription
✓ Transcription factor RFX5 or CIITA
✓ May result in defective positive selection of T cell in thymus and reduction of T CD4+
✓ Affected individual are deficient in DTH response and in antibody response to T dependent antigens.
DiGeorge Syndrome:

( congenital thymic aplasia )
First described in 1952

- Characterized by:
  - Absence of the Thymus gland.
    (So, no T-cells in the body)
  - Hypoparathyroidism Which lead to tetany
  - Cardiovascular abnormalities and Characteristic facial features

[ Because they appear from the same embryologic origin of the thymus (3-4 pharyngeal pouches) so they are involved ]
DiGeorge syndrome:

Failure of the third & fourth pharyngeal pouches to develop.

*Features:

- Children may present with seizures (tetany)

- Extreme susceptibility to viral, protozoal, and fungal infections. (Because of no T-cell)

So:

**MCQ**

1. Profound depression of T-cell numbers.
In some cases B-cells are normal and produce effective humoral immunity to bacterial infections.

(Partial Di George Syndrome.)
( thymic hypoplasia, Nezelof syndrome ).

There’s a little number of circulating T-cell but B-cells are normal

In some T-cell – dependant antibody production is absent. (no helper T-cells).
DiGeorge syndrome;

- Management:
  Fetal thymus tissue graft (14 week old).

Steps should be taken to prevent G.V.H. (graft versus host) Reactions

G.V.H. Reactions:
The transplanted thymus or bone marrow recognize the host body cells as foreign body’s cells and attack it.
Severe combined immunodeficiency. (SCID).

Both T and B cells are defected
Severe combined I.D.: Features:

1. Increased susceptibility to viral, fungal, bacterial & protozoal infection. (start at 3 month of age)

2. Failure to thrive.

3. Reduced weight gain.

4. Prolonged diarrhea.

5. Moniliasis due to candida.
Severe combined immunodeficiency (SCID) in Autosomal recessive SCID

- ADA deficiency.
- PNP deficiency.

(ADA and PNP are missing enzymes)

Lead to toxic metabolites in T & B-cells.
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Management of recessive (SCID.)

**MCQ**

1. Infusion of purified enzymes.
2. Gene therapy.
DiGeorge Syndrome

- Both thymus and parathyroids fail to develop due to defect in 3rd and 4th pharyngeal pouch.
- Severe viral, fungal and protozoal infections in early infancy
- Hypoparathyroidism – tetany due hypocalcaemia – most common manifestation.

Other congenital abnormalities are common:

- Characteristic facies
- Cardiac abnormalities
- Deletion in 22q11 in > 80%
DiGEORGE SYNDROME
DiGeorge Syndrome:

- **Cardiac Abnormalities**
  - Interrupted aortic arch 27%
  - Truncus arteriosus 25%
  - Tetrology of Fallot 22%

- **Treatment**
  - Transplant of fetal thymus
Immunodeficiency
Chronic mucocutaneous candidiasis

- T-cell deficiency specific for *C. albicans*
- Skin and mucosa are infected with *C. albicans*

- Treatment
  - Antifungal drugs
Hyper IgM syndrome

- CD4 T cells have a defect on surface protein (CD40L) thus it can not interact with B cells.
  - Class switching from IgM to other classes do not occur.
  - High conc of IgM & very little IgG, IgA, IgE
  - normal T & B cells

Treatment
- Pooled gamma globulin
Hyper IgM syndrome

- Defect in CD40 ligand
- Absent IgG, IgA; normal/raised IgM
- Antenatal diagnosis possible
- Features of T cell immunodeficiency
Interleukin-12 Receptor Deficiency

- Absence of IL-12 receptor prevents IL-12 from initiating Th-1 response.
- Suffers from disseminated mycobacterial infections.
Treatment of SCID

- Bone marrow transplantation, preferably from a histocompatible sibling
- Gene therapy
X-Linked SCID: Common Cytokine Receptor Gamma Chain ($\gamma_c$) Deficiency

- Most common form of SCID (40%)
- Very low T cells and NK cells with low to normal numbers of B cells
- Responsible gene: $\gamma_c$ – the common subunit of receptors for IL-2, IL-4, IL-7, IL-9, and IL-15
Fig 2-2.—Progressive varicella in infant with severe combined immunodeficiency.
Wiskott-Aldrich syndrome

- An X-linked disease
- Inability to mount an IgM response to the capsular polysaccharide of bacteria e.g. pneumococci.
- IgG, IgA are normal but CMI is variable
- Defect is inability of T cells to help B cells.

Cl/F:
- Recurrent pyogenic infections, eczema, bleeding

Treatment:
- Bone marrow transplantation
Combined B-cell & T-cell Deficiencies

- Severe Combined Immunodeficiency (SCID)
- Wiskott-Aldrich Syndrome
- Ataxia-Telangiectasia
Severe Combined Immunodeficiency Syndromes (SCID)

- Both B cells and T cells are defective
- In some cases B & T cells are absent and in others no. of cells normal but do not function normally.
- Ig levels very low and lymph nodes are absent
SCID – Genetics & Types

- X-linked SCID ($\gamma_c$ deficiency)
- Jak3 kinase deficiency
- Adenosine deaminase deficiency
- Purine nucleoside phosphorylase deficiency
- Bare lymphocyte syndrome
- RAG1 and RAG2 deficiency
Common Laboratory Features of SCID

- Hypogammaglobulinemia
- Absence of antibody responses to immunizations
- Absent mitogen responses
- Low or absent T cells
- Often low or absent B cells
Common Clinical Features SCID

- Failure to thrive
- Onset of infections in the neonatal period
- Opportunistic infections
  - Infections by *Pneumocystis carinii*, *C. albicans*, V-Z virus, CMV & RSV
- Chronic or recurrent thrush
- Chronic rashes
- Chronic or recurrent diarrhea
- Paucity of lymphoid tissue
Ataxia - Telangiectasia

- An autosomal recessive disease
- Lymphopenia and IgA deficiency occur
- Defect is in DNA repair genes
- Cl/F:
  - Ataxia (Staggering), telangiectasia (enlarged small blood vessels of conjunctiva and skin)
- Treatment:
  - Not successful
Phagocyte Deficiencies:

- Chronic granulomatous disease (CGD)
- Leukocyte adhesion deficiency (LAD I)
- Chediak-Higashi syndrome
- IL-12/IFNγ pathway deficiencies
- Chronic or cyclic neutropenia
Neutrophil Defects

1. Generally have neutrophilia

2. Leukocyte adhesion defect
   - AR, recurrent infection, no pus
   - Defect in adhesion molecules

3. Chronic granulomatous disease
   - Usually X linked, pus++
   - Defect in oxidative burst/regulation
Chronic Granulomatous Disease

- Inability of phagocytes to generate hydrogen peroxide due to mutations in one of four proteins comprising the NADPH oxidase
- Severe tissue infections with catalase positive organisms, esp. *Staph aureus, Serratia marcescens*, mycobacteria, and fungi such as *Aspergillus*
Chronic Granulomatous Disease

- Widespread granulomas seen that may cause obstruction stomach, esophagus or bladder
- X-linked in 60-80% cases and autosomal in remaining
- Due to defect in the intracellular microbicidal activity of neutrophils due to lack of NADPH activity, no H₂O₂ or superoxide produced.
- B cells & T cells functions are normal.
- Severe tissue infections with catalase positive organisms, esp. *Staph aureus*, *Serratia marcescens*, mycobacteria, and fungi such as *Aspergillus*
Chronic Granulomatous Disease: Diagnosis

- Nitroblue tetrazolium (NBT) or test
- or, more recently, flow cytometric tests using fluorescent dyes such as dihydrorhodamine (DHR)
Chronic Granulomatous Disease: Treatment

- Prophylaxis with antibiotics (Cotrimoxazole and itraconazole) and gamma interferon
- Bone marrow transplant with HLA identical sibling
- Gene therapy (?)
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Immunodeficiency
DHR Flow Cytometric Assay

Patient

Father

Mother

Red Fluorescence
CGD patient with skin infections due to *Serratia marcescens*
Leukocyte Adhesion Deficiency I

- Autosomal recessive disease
- Neutrophils adhere poorly to endothelial cell surface & phagocytosis is inadequate.
- Absence of adhesion molecules ($\beta$-integrins CD11/CD18) on leukocytes
- Inability to make pus due to entrapment of phagocytes within the vasculature
- Lethal within the first decade of life without bone marrow transplant
Omphalitis in LAD I patient

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Chediak-Higashi Syndrome

- Autosomal recessive disease
- Due to failure of fusion of Lysosomes with phagosome
- Large granular inclusions composed of abnormal Lysosomes seen.
- Chemotaxis is also abnormal.
- CI/F
  - Recurrent pyogenic infections by Staphylococci & Streptococci
- Treatment:
  - Antimicrobial drugs

Recurrent pyogenic infections by Staphylococci & Streptococci
Chediak-Higashi Syndrome

- Abnormal large granules in a variety of cells leading to:
  - hypopigmentation/partial albinism
  - severe immunodeficiency
  - neurologic abnormalities
  - mild bleeding tendencies

- Defective gene: CHS1 located on 1q42-43, protein product involved in granule trafficking
Immunodeficiency
IL-12/IFNγ Pathway Defects

- IL-12 receptor
- IL-12
- IFNγR1 and IFNγR2
- STAT-1

Pattern of infections: overwhelming infection with intracellular pathogens, esp. atypical mycobacteria
Cytokine Defects

- Present as typical or atypical mycobacterial infections
- E.g., BCG, M. avium

Requiring in vitro cytokine assays for diagnosis
- Some respond to gamma interferon
Critical pathways in mycobacterial control

IFN-γR1 → IFN-γR2 → IL-12Rβ1

NK cell

IL-12Rβ2 → IL-12

IFN-γ → IL-12Rβ1

T cell

IL-12Rβ2 → IL-12

TNF-α → Mφ

AFB

NO → TNF-αR
Complement Deficiency

**CLASSICAL PATHWAY**
- C1
- C2
- C4
  - Deficiency leads to immune-complex disease

**MB-LECTIN PATHWAY**
- MBL
- MASP1
- MASP2
- C2
- C4
  - Deficiency of MBL leads to bacterial infections, mainly in childhood

**ALTERNATIVE PATHWAY**
- Factor D
- Factor P
  - Deficiency leads to infection with pyogenic bacteria and Neisseria spp. but no immune-complex disease

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**C3 convertase**

**C3b deposition**
- Deficiency leads to infection with pyogenic bacteria and Neisseria spp. Sometimes immune-complex disease

**Membrane-attack components**

- C5
- C6
- C7
- C8
- C9
  - Deficiency leads to infection with Neisseria spp. only
Complement Defects

SLE

Infection

C4A

C3A

Lytic Complex

C4, C5, C6, C7, C8, C9

Alternative Pathway

C2

C4

C1q, C1r, C1s

MBL

Infection
Hereditary angioedema (C1 Esterase Inhibitor Deficiency)

- Recurrent angio oedema
  - *not urticaria*
- Low C4
- Autosomal dominant
  - Reduced protein 90%
  - Reduced activity 10%
- Acquired defect
- Treat with FFP or rC1inh
1. **Common variable Hypogammaglobulinemia**
   - B cells amount normal but unable to synthesize IgG and other Ig.
   - Due to defective T cell signaling
   - Occurs in 15 -35 yrs of age group
   - CL/F:
     - Recurrent sinusitis, pneumonia by *S. pneumoniae, H. influenzae*
   - Treatment
     - I/V gamma globulin

2. **Malnutrition**
   - Severe malnutrition can reduce synthesis of IgG due to low aminoacids.
Acquired Immune Deficiency syndrome (AIDS)

» HIV attacks CD4 T cells and thus CMI as well as Humoral immunity are depressed.

» Patients suffers from opportunistic infections e.g.
  – Atypical mycobacteria
  – Pneumocystis carinii
  – Candida albicans
  – CMV etc.

Measles

» Patients with measles have transient suppression of T cell functions but their antibody level is normal.

» During this stage quiescent tuberculosis become active
Complement deficiencies

» Liver failure
  – By alcoholic cirrhosis or chronic hepatitis B or HCV can reduce synthesis of complement proteins by the liver.

» Malnutrition
  – Severe malnutrition can reduce the supply of amino acids and thereby reduce the synthesis of complement proteins by the liver
Phagocyte deficiencies

1. Neutropenia
   - If neutrophil count falls below 500 /ul then it predispose to acute infections by pyogenic bacteria like *S. aureus*, *S. pneumoniae*
   - Cytotoxic drugs, leukaemia etc can cause neutropenia

2. Chronic fatigue syndrome (Chronic fatigue immune dysfunction syndrome)
   » Persistent debilitating fatigue lasts for 6 months and not relived by rests.
   » Cause is not known
Chronic fatigue syndrome (Chronic fatigue immune dysfunction syndrome)

- Persistent debilitating fatigue lasts for 6 months and not relieved by rests.
- Exact Cause is not known.
- Abnormalities in various components of immune system have been reported like:
  - Increased levels of cytotoxic T cells.
  - Loss of DTH.
An eight-month-old boy was presented to a pediatrician with fever, aseptic meningitis, left ocular and facial palsy, and flaccid paralysis of the lower extremities.
Two months earlier, the child had received an oral poliovirus immunization. A presumptive diagnosis of post-infectious polyneuritis was made, but, because of a serum IgG concentration of 9 mg/dl (extremely low), the infant was referred to a pediatric allergist-immunologist. Mature B-cells were absent from the circulation. T-cell immunity was
Based upon the absence of mature B-cells in the circulation and a state of panhypogammaglobulinemia, a diagnosis of Agammaglobulinemia was made.

The child has done well on monthly intravenous immunoglogulin replacement therapy, but is hemiplegic.
Individuals with a primary immunodeficiency should NOT be given live virus vaccines!
A four-month-old infant was noted to have persistent oral thrush due to *Candida albicans*. 
A consulting immunologist ordered a barium swallow x-ray, and ulcer craters due to this same organism were observed throughout the esophagus.
The child’s serum IgG was normal (maternal IgG) but the IgA and IgM were virtually absent. Few mature T-cells could be detected by examination of surface antigen phenotypes by flow cytometry, and there was no response of peripheral blood lymphocytes to stimulation by mitogens.
A diagnosis of **SCID** (Severe Combined Immunodeficiency) was made based on the very low T-cell number and their suppressed function.

- The child survived with a bone marrow transplantation from his HLA-compatible sister.
IVIG in PID

- IVIG (IntraVenousImmunoGlobulin) is purified human IgG prepared from pooled plasma of thousands of donors.

- **Mechanism of action:** It is estimated that an IVIG preparation contains ten million antibody specificities. This mechanism leads to:
  - Neutralization of viruses.
  - Opsonization of bacteria.
IVIG in PID

- **Indications:**
  - Agammaglobulinemia.
  - CVID.
  - CID.

- **Dosage:** It is recommended to maintain a trough IgG level of > 500 mg/dl. This can be achieved in most patients by the administration of about 400-500 mg/kg q 3-4 wks intervals.

- **Monitoring:** IgG trough level and liver enzymes q3-6 months. Clinical evaluation q 6 months.
Adverse Effects: non-specific generalized reactions are usually reported in 1-10% of patients, mostly mild.

- **Mild**: flushing, headache, back pain, chills, myalgia, nausea. Intervention: slow infusion and treat symptoms.
- **Moderate**: urticaria, bronchospasm, vomiting. Intervention: stop infusion and treat symptoms.
- **Severe**: anaphylaxis/anaphylactoid. Intervention: stop infusion and resuscitate. Very rare. ? IgG or IgE anti IgA antibodies.

Organ-Specific and idiosyncratic reactions are rare.

Risk of disease transmission.
Thank you all