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Medi Quest BRS Hospital

A monthly News letter from BRS Hospital

Primary Immunodeficiency Disorders - PART II

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Excerpted from Primary Immune Deficiencies Made Simple by Dr Sagar Bhattad

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In this issue, commonly occuring Primary Immune Deficiency disorders (PIDs) are discussed. They can be classified as follows

1.B cell disorders
2.Combined defects
3.Phagocytic defects
4.Complement defects

1. B Cell Disorders:

a) X-Linked Agammaglobulinemia
b) IgA deficiency
c) Common variable immune deficiency
d) IgG2 sub class deficiency
e) Hyper IgM Syndrome

a) X linked Agammaglobulinemia

Also known as Bruton`s Agammaglobulinemia

Clinical features: It is a X linked illness ,affects boys

Common infections : Sinusitis, otitis media, pneumonia

Other infection : Meningitis, Arthritis, enteroviral encephalitis

Diagnosis : Low S.Immunoglobulins IgG, IgA and IgM. Absent B cells on flow cytometry

Treatment : IVIG 400mg/kg/month for life

b) IgA deficiency:

IgA deficiency – Serum IgA < -2SD for age

selective IgA <7mg/dl

Clinical presentation:

It is a mild immune deficiency and patients present with recurrent sino pulmonary infection, otitis media and chronic diarrhoea

Note : Children with severe infections and low IgA must be investigated for IgG2 subclass deficiency.

Some of children with IgA deficiency evolve into Common variable immune deficiency

c) Common variable Immune Deficiency:

Most common symptomatic immune deficiency in adults

Characterised by low serum immunoglobulins and normal B cell numbers

Pathogenesis : Though B cells are present in normal numbers, they fail to differentiate into antibody producing plasma cells

Clinical presentation:

On set in Adolescence and adult hood, present with sinusitis, otitis media, chronic diarrhoea, pneumonia

Prone for auto immune disorders like auto immune hemolytic anemia, auto immune thrombocytopenia and arthritis.

Increased risk of malignancies like

Hodgkin's lymphoma, gastric carcinoma.

Treatment :

IVIG 400mg /kg/month for life

d) IgG2 sub class deficiency

There are 4 IgG sub classes – IgG1, IgG2, IgG3 and IgG IgG2 Protects against encapsulated bacteria

Clinical presentation:

Recurrent infection with encapsulated bacteria

Diagnosis :

IgG levels are normal or elevated – compensatory increase for low IgG2 levels for age, additionally tests to measure vaccine response can be done.

Treatment:

Antibiotic prophylaxis with Co Trimoxazole, vaccination with pneumococcal conjugate vaccine followed by PPSV 23.

If these measures do not give adequate results IVIG 400mg/kg/month is needed

e)Hyper IgM Syndrome :

It is a class switch disorder:

Class switch is the process by which an activated B cells changes its antibody production from IgM to either IgA, IgG or IgE depending on the functional requirements.

Class Switching:

B Cells initially produce IgM in response to an infection later activated T and B cells interact which needs T cell expressed CD40 ligand and B cells expressed CD40

Interaction between C40 Ligand and CD40 from T and B cell leads to Class switching of B cell to switch from producing IgM to producing IgG, IgA and IgE

Deficiency of CD40 Ligand or CD40 would result in class switch defect.

Patients with deficiency of CD40 L or CD40 have B cells that can produce only IgM and with every infection IgM levels keep rising: there by causing Hyper IgM syndrome.

Note : 50% of patients have with hyper IgM Syndrome have normal IgM levels, hence the term hyper IgM levels is misnomer – However all patients have low IgG , IgA and IgE

Clinical presentation of Hyper IgM Syndrome:

Rec infections – Sinusitis, otitis media, pneumonia organisms. Pneumocystis jiroveci pneumonia, cryptosporidiosis. Predisposition to biliary cirrhosis and biliary tumours in 2nd and 3rd decade of life.

Diagnosis :

Normal or high IgM, Low IgG, IgA and IgE. Normal B cell counts. Reduced memory B cells.

Treatment:

Monthly IVIG + Cotrimoxazole + Itraconazole prophylaxis. BMT for Type 1 and Type 3

Combined Defects:

T cell help is crucial for B cell function, T cell defects often result in B cell dysfunction.

These disorder are called combined defects.

Two of the commonest combined defects are

A : SCID severe combined immune deficiency

B : Combined immune deficiency

A : SCID

The most severe form of immune deficiency characterised by absent T cells

Clinical presentation : Present in early infancy with pneumonia, diarrhoea and oral thrush

Diagnosis : The presence of Lymphopenia (ALC < 3000/mm3) in infants

and absent thymic shadow on X-ray chest is a clue to underlying SCID.Lymphocyte subset analysis shows absent T cells

Absolute CD3 < 3000 cells/mm3 is diagnostic

Treatment: SCID is a medical emergency and an urgent BMT is warranted.

B: Combined Immune deficiency

A group of disorders with defect in T cell number or function. These are not as severe as SCID and hence these

children survive beyond 2years of age.

When do you suspect CID ?

Children presenting with opportunistic infections (viral / fungal) and surviving beyond age 2.
Many of them have auto immunity and granulomatous manifestations (granulomas in gut, liver, lymph nodes lungs)
Persistent lymphopenia must raise a suspicion of CID in a patient with recurrent unusual infections.

Diagnosis :
Presence of lymphopenia may be the clue
Reduced T cell counts may be noted
Hypogammaglobulinemia

Syndromes with Immune deficiency

DiGeorge Syndrome:

Etiology : 22q 11.2 micro deletion
Pathogenesis : Defective development of third and fourth pharyngeal pouch
Clinical Features:
Congenital heart defect, hypoparathyroidism resulting in hypocalcemia, abnormal facies and immune deficiency prone to auto immune diseases.

Immune deficiency in Digeorge Syndrome:

Patients with DiGeorge Syndrome have a
small or absent Thymus reduced or absent naïve T cells
Confirmation of Diagnosis :
By genetic testing Microarray for 22q 11.2 microdeletion (FISH study)
Treatment :
Multi disciplinary approach
Patients with absent thymus need thymic transplant

WISKOTT ALDRICH SYNDROME

Triad of recurrent infections, eczema and low platelets
Clinical presentation:
Recurrent infections from early childhood
-Otitis media, pneumonia, diarrhoea, meningitis and colitis
Persistent thrombocytopenia from birth .

Diagnosis :
In every boy with persistent thrombocytopenia look at mean platelet volume low – MPV is a feature of WAS in boys with thrombocytopenia. WAS protein expression studied by flow cytometry is reduced in WAS. Genetic testing to look for mutations WAS
Treatment : Monthly IVIG and Cotrimoxazole prophylaxis BMT is curative.

Phagocytic Defects

Chronic Granulomatous Disease
Leucocyte Adhesion Deficiency

Chronic granulomatous Disease (CGD)

The inability of neutrophils to kill intracellular organisms
Etiology: Defect in NADPH oxidase. This enzyme is essential for the production of super oxide ions ,free radicals necessary to kill intracellular organisms (bacteria and fungi)
Clinical presentation:
CGD is characterised by recurrent suppurative infections, suppurative lymphadenitis, empyema, lung abscess liver abscess osteomyelitis and non resolving pneumonia
Diagnosis :
Diagnosis of CGD can be established by an abnormal NBT (Nitro blue Tetra Zolium Test) and dihydrorhodamine test.
Genetic Testing by NGS (Next generation sequencing)
Immunological Phenotype:
CGD is characterised by hypergammaglobulinemia lymphocyte subsets are normal. Diagnosis is by NBT and DHR tests.

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Treatment

In the presence of fever, empirical treatment covering S.Aureus warranted
Cotrimoxazole and Itraconazole prophylaxis. HSCT is curative

Leucocyte adhesion deficiency (LAD)

Pathogenesis : Leucocytes fail to extravasate to the site of infection. There is a defect in adhesion of neutrophils to the endothelium, leucocytes fail to extravasate and reach site of infection, this is responsible for high neutrophil counts in blood stream

Clinical Features:

Delayed fall of umbilical cord, recurrent pneumonia, ear infections, non healing ulcers, gingivitis, peri anal lesions are and high Neutrophil counts are features of LAD

Diagnosis :

Absent CD18 and CD15 expression on Neutrophils for type I & type 2 LAD deficiency in flow cytometry.

Treatment :

Severe forms – Bone marrow transplant . Milder forms – antibiotic prophylaxis

Complement Defects

C1q Deficiency

Pathogenesis: C1q is an opsonin, coats encapsulated bacteria and is a pre requisite for phagocytosis

Clinical Features :

Deficiency in C1q results in infection with encapsulated bacteria like pneumococcus and H.Influenzae
Early onset Lupus is noted

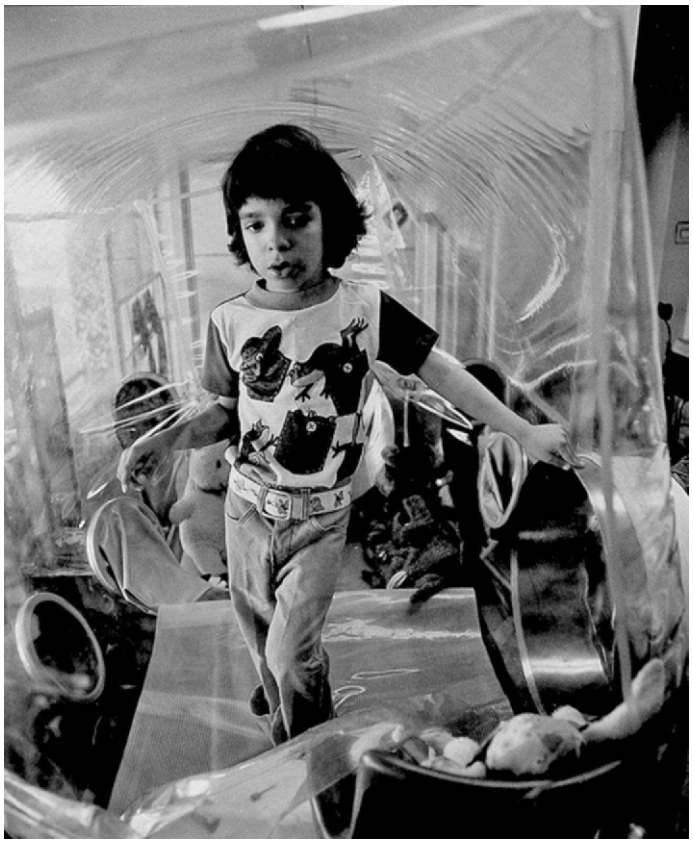
Diagnosis :

C1q levels and genetic testing

Treatment:

FFP infusions can be tried as it provides C1q .Bone marrow transplant is curative.

BUBBLE BOY



David Phillip Vetter (September 21, 1971 – February 22, 1984) was an American who was a prominent sufferer of severe combined immunodeficiency (SCID). Vetter was referred to as "David, the bubble boy" by the media, as a reference to the complex containment system used as part of the management of his SCID.

He died in 1984, at the age of 12 following complications of a bone marrow transplant

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