Clinical Faces of Antibody Deficiency

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Declaration of interest

- No speaker fees from any pharmacological company
- Adult clinical immunologist perspective

Objective

Recognize commonest causes of antibody deficiencies, and have an approach to their management
3 Important clinical rules

• Recurrent regional infections mandates exclusion of anatomical defects.

• Primary immune deficiency can present for the first time in Adults.

• Secondary causes of Immune deficiency are commonest.
Table 1. Acquired, secondary causes of immunodeficiency

- HIV infection
- Post-splenectomy
- Diabetes
- Chronic renal disease – especially nephrotic syndrome
- Chronic liver cirrhosis
- Haematological disorders: chronic lymphocytic leukaemia, myeloma
- Immune suppression due to radiation, cytotoxic and/or steroid therapy
- Malnutrition, vitamin and mineral deficiency (e.g. zinc deficiency)
- Autoimmune disorders, e.g. systemic lupus erythematosus
- Intestinal lymphangiectasia resulting in immunoglobulin and lymphocyte loss
- Malignancy, including thymoma with hypogammaglobulinaemia – Good’s syndrome
Diagnostic Challenge - PID

• May present for 1st time as adults - common underlying problems - sinusitis and associated bronchial hyper-reactivity & Allergy

• Early diagnosis important, to prevent permanent sequelae such as bronchiectasis, yet diagnostic delay common
Approach to patient with Recurrent Infections:

? IMMUNE DEFICIENCY
### Patient with Recurrent Infections: Immune deficiency

<table>
<thead>
<tr>
<th>IMMUNE</th>
<th>CLINICAL</th>
</tr>
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<tbody>
<tr>
<td>1. B-cell</td>
<td>Recurrent URTI/Pneumonia</td>
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<tr>
<td>2. T-cell</td>
<td>Recurrent viral</td>
</tr>
<tr>
<td>2. T-cell</td>
<td>Viral/Protozoa/fungus/mycobact</td>
</tr>
<tr>
<td>3. NK cell</td>
<td>Sup. skin or systemic infections: low grade organisms</td>
</tr>
<tr>
<td>4. Phagocytosis</td>
<td>Infections/autoimmunity</td>
</tr>
<tr>
<td>5. Complement</td>
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III. Predominantly antibody deficiencies
Recurrent bacterial infections eg: Otitis, pneumonia, sinusitis, diarrhea, sepsis

Serum Immunoglobulin Assays: IgG, IgA, IgM

IgG, IgA and/or IgM ↓ ↓
Exclude 2nd causes: drugs [Hx], myeloma [bone marrow], Lymphoma. Ig loss (not hypo-IgM) in urine, GI or skin

B Lymphocyte (CD19+) enumeration (CMF)

B absent

X-Linked Agammaglobulinemia (BTK)
AR Agammaglobulinemias
μ heavy chain Def (IGHM)
Igα (CD79A)
Igβ (CD79B)
BLNK (BLNK)
I5 (IGLL1)
P13K1 def (PIK3R1)
AD E47 transcription factor def (TCF3)

Congenital sideroblastic anemia, deafness, developmental delay: TRNT1 def (TRNT1)
Trichorhexis nodosa TTC37 def (TTC37)
Dysorphic facial features, hypotonia, neurologic disorder; severe hypogammaglobulinemia CDG-IIb (MOGS)

B > 1 %

Common Variable Immunodeficiency Disorders (CVID)
Very rare AR disorders: TACI, BAF-FR, CD19, CD21, CD22, TWEAK, NFκB2

Thymoma with immunodeficiency
Bacterial/opportunistic infections, autoimmunity

Myelodyplasia with hypogammaglobulinemia (Monosomy 7, trisomy 8 or DKC, GATA2)

ILNO80 def (ILN80)
MHS6 def (MHS6) (cancer)

Growth retardation. EBV. CMV viremia.
PIK3R1 loss-of-function (PIK3R1)

Selective IgA def

Low IgG Sub classes

IgA with

Low Specific antibody responses

IgA with Specific Ab deficiency

IgA↓

1 IgG subclasses 1,2,3 levels (measure at least two)
2 Specific antibody responses (anti-PPS antibodies and Tet/dip/hib)?

IgG (♀), IgA(♀)
and IgM(N / ↑):
HIGM

Healthy infant, no increased bacterial infections. Normalisation at 36-60 months
Transitomy hypogammaglobulinemia of infancy

AR hyper-lgM disorders, with lymphoid hyperplasia:
AID def (AICDA)
UNG def (UNG)
Others

Inactivated PI3K-δ (PI3KCD, p110)

IgG subclasses Low +/− poor Specific Ab response: Isolated IgG subclass

IgG subclasses Low + impaired response to PPS and hib:
Bronchiectasis, autoimmunity, chronic EBV, CMV infection

Activated PI3K-δ

IgG subclasses +/- IgA, absent IgE, asymptomatic: Ig heavy chain mutations or deletion (mutation or chromosomal deletion 14q32)

All have lambda chain, asymptomatic
K chain def (IGKC)

Normal IgA, IgG, IgM

Congenital B cell lymphocytosis

AD, SPM, Adp.
Bacterial and viral infections, EBV chronic infection, Autoimmune cytopenia
CARD11 gain of function mutations (CARD11)
Outline of Topics

- Transient hypogammaglobulinaemia of Infancy (THI)
- X-Linked Agammaglobulinaemia (XLA)
- Common Variable Immune Deficiency (CVID)
- Good’s Syndrome
- Selective IgA deficiency
- IgG subclass deficiency
- Specific Antibody Deficiency (SAD)
- SAD & MAD
Transient hypogammaglobulinaemia of Infancy (THI)

- 9 month infant – incidental low serum IgG (2.78) and IgA (<0.07)
- No family history of PID & no infections at all
- IVIG therapy considered – yet IgG subclasses & baseline vaccinations were normal

THI - Basics

- Def: Low serum IgG (± low IgA & IgM) on 2 occasions
- Upper & Lower respiratory infections & allergy common
- Most have normal B-cells and AB responses to infection/vaccinations (cf CVID)
  Some have gaps in vaccine-specific protein and polysach. antibodies & require prophylactic antibiotics or rarely Ig replacement
- Retrospective diagnosis: must normalize in childhood or adolescence
Pneumonia & Severe Hypogammaglobulinaemia

• 16 year-old male failed empirical TB RX for chronic cough & night sweats

• Hospitalized with H. Influenza pneumonia, bronchiectasis & clubbing.

• Meningitis age of 5 yrs & prior pneumonia aged 8 yrs.

• No family history of any immune deficiency

• Serum IgA, IgM & IgG all markedly reduced, absent CD19+ cells on flow.
Absent B-cells = XLA
X-Linked Agammaglobulinaemia - Basics

- Severe hypogammaglobulinaemia, recurrent sinopulmonary infections. Typically encapsulated pyogenic bacteria.
- Usually presents between 3 and 18 months.
- Due to mutations in Bruton tyrosine kinase (BTK) gene.
- Severe reduction in serum Ig levels, reduced specific AB responses to immunization and infections & near absence of B-cells.
- Can show defects in BTK gene or BTK protein expression.
- Rx with Ig replacement reduces infections and lowers morbidity & mortality.
- Also important in management is aggressive antibiotic therapy of infections & avoidance of live viral vaccines.
CVID

T-sup  →  T-h  →  B-cell  →  Antibodies

present

XLA

B-cell  →  PRE B-cell

BTK mutation  →  absent
Common Variable Immune Deficiency - CVID

- Commonest primary, intrinsic disorder of anti-body production in both children & adults.
- Markedly reduced serum IgG with low level IgA and/or IgM - exclusion of other B-cell defects & haematological conditions such as myeloma.
- Exclude cystic fibrosis, immotile cilia syndrome, PLE
- Recurrent sinusitis & URTI’s → bronchiectasis.
- Autoimmunity, enteropathy, lymphoid malignancy.
- Heterogeneous, clinically diverse disorder.
Individual complications – 334 Pats

- Autoimmunity
- Lymphoproliferation
- Viral Infection
- Structural
- Cancers

Conditions:
- Atrophic gastritis
- Diabetes
- Haemolytic anaemia
- Hypothyroidism
- Neutropenia
- Pemphigus
- Psoriasis
- Thrombocytopenia
- Thyrotoxicosis
- Ulcerative colitis
- Vitiligo
- Crohn disease
- Granulomatosis
- Hepatomegaly
- Lymphadenopathy
- Hepatitis B
- Hepatitis C
- Bronchiectasis
- Lymphoma/CLL
- Other tumours
- Enteropathy
- Splenomegaly
- Iron deficiency
- Arthropathy
- No complications

Percentage of total cohort [n=334]
Common Variable Immune Deficiency - CVID

34 year-old lady on treatment with monthly IVIG replacement for severe recurrent sinusitis & URTI since 2008, developed massive splenomegaly & severe pancytopenia

Three main indications for splenectomy in CVID:

1. Severe Pancytopenia

2. Autoimmune cytopenias unresponsive to Rituximab

3. Concern for lymphoid malignancy.
Hypersplenism with Pancytopenia

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<tr>
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<th>PRE-OP</th>
<th>POST-OP</th>
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<tbody>
<tr>
<td>HB</td>
<td>9.7</td>
<td>11</td>
</tr>
<tr>
<td>WCC</td>
<td>1.3</td>
<td>8</td>
</tr>
<tr>
<td>Plat</td>
<td>57</td>
<td>250</td>
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14 Years after Discovery: Clinical Follow-up on 15 Patients with Inducible Co-Stimulator Deficiency

Johanna Schepp, Janet Chou, Andrea Skrabi-Baumgartner, Peter D. Arkwright, Karin R. Engelhardt, Sophie Hambleton, Tomohiro Morio, Ekkehard Röther, Klaus Warnatz, Raif Geha and Bodo Grimbacher

Aug 2017, Vol 8, 964
Patient with Recurrent Infections:?

**Immune deficiency**

The case of recurrent lung infection & rapid onset bronchiectasis in a 28 year old man
• March 04: mediastinal biopsy → Thymoma
• May 04: Radiotherapy
June 04 – Ig levels requested

IgG  4.61 g/l  (7 -16)
IgA  0.32 g/l  (0.7 - 4)
IgM <0.25 g/l  (0.4 – 2.3)

Thymoma and hypogammaglobulinaemia = Good syndrome (Robert Good –1954)

- Rare, (5-6% thymomas) adult onset (29-75) immune deficiency @:
  hypogammaglobulinemia, variable T-cell defect with OI’s, lymphopenia, eosinopenia, other hematological disorders
Severe IgA deficiency

- 15 year-old girl with Asthma, recurrent respiratory tract & Sinus infections since age of 3, with severely reduced IgA of 0.07 g/L & normal IgM, IgG & IgG subclasses. Mild bronchiectasis, impaired baseline AB memory, but a good response to vaccination:

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<thead>
<tr>
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<th>Post-Vaccination</th>
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<tbody>
<tr>
<td>Strep. Pneumonia</td>
<td>23.78</td>
<td>151</td>
</tr>
<tr>
<td>H. Influenza</td>
<td>0.25</td>
<td>&gt;9</td>
</tr>
<tr>
<td>T. Toxoid</td>
<td>0.01</td>
<td>1</td>
</tr>
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2 Faces of IgA deficiency

- Total or Partial IgA deficiency
- Recurrent sinopulmonary infections
- Autoimmune disorders: cytopenias & SLE
- GIT infections, Celiac disease & IBD
- Allergic disorders: rhinitis & Asthma
- Anaphylactic transfusion reactions - anti-IgA Abs
- Many asymptomatic, severity & complications seen in total IgA or associated IgG subclass deficiency
IgA deficiency - management

- Optimal management of allergic rhinitis & asthma
- Diagnose bacterial RTI’s & Rx antibiotic therapy
- Wean off excessive steroid use & dependency
- Prophylactic ABs in view of recurrent infections & established bronchiectasis

- No Immunoglobulin replacement therapy at this stage - vaccination response demonstrates good functional antibody production
IgG Subclass Deficiency

54 year-old lady with recurrent respiratory tract & sinus infections, & reduced IgG 2 & 3 subclasses, was actually treated with IVIG on this basis. However, antibody response to vaccination was intact.

**Total IgG**  
% Distribution (N) | 7.04 g/L
---|---
IgG1 | 76 (> 60) | 4.69
IgG2 | 20 (> 10-15) | 1.23 (1.69 – 7.86)
IgG3 | 1.6 (> 5) | 0.10 (0.11 – 0.85)
IgG4 | 1.3 | 0.08

Valuable QC - check result validity
3 Criteria to Diagnose Clinically Significant IgG Subclass Deficiency:

1. 1 or more *significantly reduced* IgG subclasses (~10%) with near normal total serum IgG.

2. Inadequate response to vaccination.

3. Recurrent Infections.

Management consists of aggressive treatment of predisposing allergic rhinitis & asthma, appropriate AB Rx, Prophylactic Abs if sinopulmonary infections still persist despite these measures, & IVIG if strict criteria for this are met.
Specific Antibody Deficiency (SAD)

- Recurrent and/or severe sinopulmonary infections
- Seen in both children > 2 years, & adults
- Deficient specific-IgG to polysaccharides with normal response to proteins, normal serum Ig and IgG subclasses
- Occurs in isolation or as part of CVID, asplenia, etc
- Management involves vaccination with 13-valent conjugate pneumococcal vaccine (Prevnar), Mx of atopic conditions, aggressive use of AB’s during infections

R. Sorensen & K. Paris - Uptodate 2017
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SAD & MAD

- 17 year-old girl - Recurrent otitis with grommets aged 5 & 12
- 3 - 4 courses antibiotics annually, bronchitis 2016
- Chicken pox aged 4 years, scarlet fever aged 12
- Past month pharyngitis & otitis – 2 courses of antibiotics
- No vaccinations aside from yellow fever & measles, mother anti-vaccination.

LAB: MBP deficiency & absent diphtheria & T. toxoid specific IgG
Streptococcus Pneumonia low level specific IgG.
High naïve B-cells - 82% but absent class-switch memory B-cells
Kayley Burke
22 hours ago

Vaccinate your kids people... The pictures below show you exactly why...
Our poor baby boy who is too young to be immunised has caught the
cold... It has almost been a week since they showed up... Today he
was admitted to Ipswich Hospital with a secondary infection... Kalliah and
myself also have the chicken pox fortunately since Kalliah hasn't long been
immunised she has a few spots and blisters but is well in herself... Adult
chicken pox is so horrible and painful I would much rather give birth with no
pain relief... They have just given me some medication also to help with my
symptoms...
Bottom line if you don't vaccinate your kids your a bloody idiot... Think about
the risk you are putting on other helpless kids that are too young or who
actually can't be vaccinated!

VACCINATION:
Trading the chance that you may be
protected from a largely benign,
treatable acute illness for the risk
that you will develop a chronic,
lifelong, debilitating and
untreatable condition.

Vaccines have varying degrees of efficacy and carry a real risk of
triggering neurological and autoimmune conditions.
DO YOUR RESEARCH OR YOU MAY REGRET IT FOREVER.
SAD & MAD

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The End

Questions ?