IgA: Biology and deficiency

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**Introduction to IgA**

- First described in 1953
- Most abundant and heterogeneous antibody isotype produced in the body
  - 66mg/kg/day - a big energy cost to the body
- Protects the vast surfaces (400m²) of the respiratory, GIT and urinary tract from attack by potential invading organisms.
- Second dominant isotype in the blood (following IgG)
- Functions not clearly understood
- IgA1 monomer is mainly found in blood
- IgA2 dimer is the dominant form in immunosecretions e.g. in tears, saliva, respiratory, GIT and urinary tract
  - Includes a J chain and secretory piece

**Introduction to IgA**

- IgA is highly secreted in breast milk and functions to prevent newborns from enteric and respiratory infections
- Produced by follicular B-cells from Peyer’s patches, mesenteric LN and isolated lymphoid follicles.
- Removal of GALT via tonsils and adenoids results in lower IgA levels compared with patients who had only one type removed or none.

**Introduction to IgA**

- The function of serum IgA is not well understood, Monomeric IgA does not fix complement but may bind Fc receptors and promote phagocytosis in the absence of promoting inflammation.
- Dimeric IgA at luminal surfaces is more resistant to proteolytic cleavage by bacteria.
- Dimeric IgA coat bacterial at the mucosal surface limiting their penetration.
Introduction to IgA

- IgA2 has a shorter hinge region; less vulnerable to cleavage
- The secretory component is the receptor for polymeric immunoglobulin receptor (pIgR)

Transport of IgA across the mucosal epithelium

- Antigens that complex with IgA in the lamina propria may be exported across the epithelium
- pIgA may neutralize newly synthesized viral particles during the exocytosis pathway

Subversion of IgA function by bacteria

- Numerous major pathogens have evolved means to perturb IgA functions e.g.
  - Secretion of proteases that cleave IgA
  - Blockade of IgA function by IgA-binding proteins that compete with Fc receptors
  - Strep Pneumonia co-opt the pIgR transcytosis machinery to facilitate adherence and invasion.
IgA1 proteases
- The bacteria frequently associated with bacterial meningitis all secrete highly specific IgA1-cleaving proteases which correlates to virulence.
- The proteases cleave IgA1 within the hinge region rendering the IgA unable to link functions of antigen recognition with Fc mediated immune mechanisms.

Woof and Kerr J Path 2006

Bacterial IgA-binding proteins
- IgA-binding proteins are expressed by
  - Group A and Group B Streptococcus
- These proteins allow the bacteria to evade IgA-driven eradication processes
- The super antigen SSL7 from Staph. Aureas has also been shown to bind monomeric IgA1 and IgA2 and SIgA

IgA deficiency
- IgA deficiency is the most common primary immunodeficiency
- Defined as decreased serum IgA in the presence of normal IgG and IgM serum levels in a pt >4 years in whom other causes of hypogammaglobulinaemia have been excluded
- A serum IgA of <7mg/dL is considered selective IgA deficiency
- If IgA is less than 2 SD from the mean but >7mg/dL this is partial IgA deficiency
IgA deficiency

- Most pts are clinically well and diagnosed incidentally
- A minority of patients have a clinical course characterised by:
  - Recurrent infections of the respiratory system and GIT
  - Allergy
  - Autoimmunity
- Secretory IgA is not determined in making the diagnosis, therefore it is possible that some patients with asymptomatic IgA deficiency have some retained dimeric IgA function at mucosal surfaces

IgA deficiency: Pathogenesis

- Most IgA deficient patients increase IgM production in an apparent compensatory reaction
- Commonly a maturation defect in B-cells to produce IgA is observed
  - B-cells co-express IgA, IgM and IgD and cannot develop into plasma cells
- The defect appears to involve stem cells as IgA deficiency can be transferred by BMT
- The constant α1 and α2 genes are generally not mutated
- Intrinsic B-cell defects, T-helper cell dysfunction and suppressor cells have all been implicated in the pathogenesis of this disease
- Abnormalities in IL-4, -6, -7, -10, TGFβ and IL-21 have also been implicated
- Mutations in TACI have been observed in a subset of pts with IgA deficiency and CVID

IgA deficiency: Epidemiology and genetics

- Familial clustering with no clear Mendelian inheritance pattern
- AR, AD and sporadic patterns have all been observed
- IgA deficiency (similar to CVID) is likely an umbrella term for a heterogeneous group of conditions
- Incidence ranges from
  - 1:143 (Arabian peninsula)
  - 1:965 (Brazil)
  - 1:300-1:1200 in Caucasians
- Very rare in some Asian populations

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>No. of Patients</th>
<th>No. of Patients with IgA Deficiency</th>
<th>Percentage of IgA Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR7, DQ2 and DR1, DQ5</td>
<td>45%</td>
<td>16%</td>
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<tr>
<td>HLA-DR1</td>
<td>45%</td>
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The most common haplotype found in IgA deficient patients is 8.1 which is the MHC ancestral HLA-A1, B8 DR3, DQ2 haplotype.
- This haplotype is present in 45% of IgA deficient patients and 16% of the general population
- This haplotype is also associated with other autoimmune conditions including autoimmune thyroiditis, SLE, coeliac disease, RA, DM type 1 and myasthenia gravis
- Other implicated haplotypes include:
  - HLA-DR7, DQ2 and DR1, DQ5

Singh et al Autoimm Rev 2014
IgA deficiency: Clinical associations

- Other primary immunodeficiencies

IgA deficiency: Clinical manifestations

- 85-90% are asymptomatic while other develop:
  - Recurrent sinopulmonary infections
    - Particularly with H. influenzae, Strep. Pneumoniae
    - Bronchiectasis may develop as a result
    - Patients with associated subclass deficiency e.g. IgG2 have greater risk of severe infections and complications
  - GIT infections
    - E.g. giardiasis, malabsorption, lactose intolerance, ulcerative colitis, nodular lymphoid hyperplasia
  - Allergy
    - Atopy has been reported in 58% of pts
    - Allergy more common among younger patients
    - IgA-deficient patients may develop anti-IgA antibodies which have the potential to cause anaphylaxis upon RBC or plt transfusion which contain trace amounts of IgA. This occurs with IgE anti-IgA Abs.
    - Testing for Anti-IgA IgE is not readily available in many labs and often Anti-IgA IgG is used as a screening tool
    - Incidence of IgA anaphylactic reactions is estimated to be between 1:20 000 to 1: 47 000 transfusions
IgA deficiency: Clinical manifestations

- Autoimmunity
  - Among the most important manifestations of IgA deficiency. Both systemic and organ-specific autoimmunity are associated with IgA deficiency.
  - The prevalence of autoimmune disorders in IgA deficient patients ranges from 7-36% with approximately 40% having detectable serum auto antibodies.
  - Auto antibodies against sulfatide, Jo-1, cardiolipin, phosphatidylserine and collagen have been reported.

- Malignancies
  - Occurs sporadically, particularly at older ages
  - Lymphoid and GIT malignancies most common

IgA deficiency: Clinical manifestations

- Autoimmunity
  - More common in adults and females
  - Most common autoimmune diseases:
    - ITP
    - Hemolytic anemia
    - Juvenile RA
    - Thyroiditis
    - SLE
  - Auto antibodies
  - Rates of autoimmunity are higher in first degree relatives of patients with IgA deficiency (10%) as compared with the general population (5%)
  - Patients with IgA deficiency have a higher risk of celiac disease despite not developing IgA to gliadin or TTG or endomysium

IgA deficiency and Autoimmunity

Singh et al Autoimm Rev 2014


Singh et al Autoimm Rev 2014
IgA deficiency: Laboratory Evaluation

- FBC and differential
- Quantitative serum immunoglobulin levels
- IgG subclasses
- Specific Ab responses to proteins and antigen
- Lymphocyte subsets
- Celiac screening including IgG
  > Biopsy to confirm

IgA deficiency: Management

- Asymptomatic patients do not require treatment
- Education regarding potential risk of transfusion
- Medical alert bracelet
- Screening for anti-IgA Ab
  > If detected patient required products from IgA deficient donor or saline washed products
- Symptomatic patients require treatment of associated conditions
  > E.g. prophylactic antibiotics
  > Standard treatment of associated allergy and autoimmune diseases

IgA deficiency: Prognosis

- Generally good especially if asymptomatic
- IgA deficiency in children may resolve over time
- IgA deficiency may progress to CVID which is associated with a poorer prognosis
  > Hence even asymptomatic patients should have regular follow-up

IgA deficiency: Future directions

- Delivery of IgA products against common bacterial pathogens?
- Development of mucosal vaccines?
Conclusions

- IgA is the most abundant antibody produced and plays an important role in mucosal immunity limiting pathogenic invasion
- IgA is a weak opsoniser and does not bind Fc therefore relatively "non-inflammatory"
- Several bacteria have derived mechanisms for evading IgA-mediated immunity including cleavage of the hinge region and hijacking the pIgR
- IgA deficiency is the most common primary immunodeficiency
- Defined as decreased serum IgA in the presence of normal IgG and IgM serum levels in a pt >4 years in whom other causes of hypogammaglobulinaemia have been excluded
- The genetic basis remains to be defined

Conclusions

- The majority of IgAD patients are clinically well
  - A minority suffer recurrent infections (sinopulmonary and GIT), allergy (asthma, rhinitis, transfusion anaphylaxis), autoimmunity (thyroid disease, arthropathy, celiac disease)
- Most common in Arabian peninsula
- May cluster with other immunodeficiencies
- Diagnosed by measurement of immunoglobulins and exclusion of other causes
- Asymptomatic patients require monitoring but not treatment
  - Education
    - Particularly around blood/product transfusion
    - Screening for anti-IgA Ab

Conclusions

- Symptomatic patients may require treatment with antibiotics, standard treatments for allergy and autoimmunity
- Prognosis generally good

Thank you

- Questions?