SLE and Immunodeficiency

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Focus on

- Primary antibody immunodeficiency disorders associated with SLE.
- Secondary immunodeficiency in SLE – medications and hypogammaglobulinaemia.
Three primary immunodeficiency disorders prone to develop SLE or lupus-like features

- Homozygous deficiency of the early components of the classical pathway of complement activation (C1q, C1r, C1s, C4, and C2) predisposes to the development of SLE.
- IgA deficiency is also strongly associated with SLE.
- Female carriers of the X-linked chronic granulomatous disease allele are prone to develop discoid lupus, lupus-like manifestations and even SLE.
Primary immunodeficiency disorders (PID) reported in SLE patients

- More commonly associated PID are:
  - Selective IgA deficiency (SIgAD)
  - Deficiency of early components of the complement cascade (C1q, C2 and C4)
  - Common variable immunodeficiency disorders (CVID)
  - Selective IgG2 deficiency

- Less commonly associated, mostly case reports and include:
  - Autosomal recessive hyper-IgE syndrome
  - Chronic granulomatous disease
  - CD40 and CD40L deficiency
  - IL-12 receptor β1 deficiency
• Studied *complements and immunoglobulin* levels.
• 72 patients.

**RESULTS**

PID identified in 16(22%).

- Complement deficiencies: 3 with C2, 3 with C4, 2 with C1q deficiency.
- Antibody deficiencies: 4 with IgG2 (<20 mg/dl), 3 with IgA (<7 mg/dl), and 3 with IgM (<35 mg/dl) deficiency.
- One patient had IgA, C2 and C4 deficiencies.
- SLICC/ACR-DI was significantly higher in patients with PID compared with those without (p<0.0033)

**CONCLUSION**

- A high frequency of complement and antibody deficiency observed.
- This suggests that these defects may contribute to lupus development.
Table 2 Distribution of SLE patients and controls according to immunodeficiency-like states

<table>
<thead>
<tr>
<th>Immunodeficiency-like states</th>
<th>Controls, n (%)</th>
<th>SLE, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>5 (1.6)</td>
<td>24 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgA</td>
<td>1 (0.3)</td>
<td>3 (1)</td>
<td>0.372</td>
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<tr>
<td>IgG</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>1.000</td>
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<tr>
<td>IgG subclasses</td>
<td>2 (0.6)</td>
<td>59 (19.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>IgG1</td>
<td>1 (0.3)</td>
<td>5 (1.8)</td>
<td>0.122</td>
</tr>
<tr>
<td>IgG2</td>
<td>1 (0.3)</td>
<td>40 (13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgG3</td>
<td>0</td>
<td>24 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgG4</td>
<td>0</td>
<td>11 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVID</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyper-IgM syndrome</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyper-IgE syndrome</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>CGD</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>CGD gene carrier</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0.499</td>
</tr>
<tr>
<td>C1q</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>C2</td>
<td>0</td>
<td>2 (0.6)</td>
<td>0.248</td>
</tr>
<tr>
<td>C3</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Any immunodeficiency-like state</td>
<td>10 (3.3)</td>
<td>862 (28.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Eighty-six (28.7%) of 300 SLE patients exhibited an immunodeficiency-like state, with no association with immunosuppressant therapy.

Immunodeficiency-like states in SLE were not associated with increased susceptibility to or severity of infections. Low serum immunoglobulin was the most frequent abnormality; IgG3/IgG4 deficiency was associated with lupus nephritis.

Comments on results:
Interesting finding of high frequency of IgG subclass deficiency. Studies from lupus cohorts from other countries and with larger numbers needed.
## Selective IgA deficiency

- Defined as serum IgA levels ≤0.07g/L with normal IgM and IgG levels in individuals ≥4 years old.
- Most common primary immunodeficiency in Western world; prevalence of about 1 : 600 in the general population.
- A polygenic disorder with involvement of genes associated with autoimmunity.
- Most are clinically asymptomatic.
- Recurrent respiratory and gastrointestinal tract infections (especially if concomitant IgG subclass deficiency), allergies and autoimmunity have often been reported.
- Autoimmune diseases often reported: Graves’ disease, SLE, type I DM, Coeliac disease, JRA.
- An increased frequency of IgA deficiency among SLE patients of different ethinical backgrounds.
- Prevalence among SLE patients: 5.2% in juvenile and 2.6% in adult SLE patients.

Prevalence of selective IgA deficiency in SLE

- Serum IgA levels measured in 3,388 SLE patients in Sweden, UK, USA and China.
- IgA deficiency identified in 44 patients; a total frequency of 1:67 in Caucasians and 1:121 in Chinese.
- Interestingly, prevalence of IgA deficiency among Chinese SLE patients was >30-fold higher than in the general Chinese population (1:4,146), indicating a strong association between these two diseases.

• Identified a de novo IFIH1(interferon-induced helicase C domain-containing protein 1) mutation in a patient with elevated serum IFNα, severe early onset SLE, selective IgA deficiency(SIgAD), and mild lower limb spasticity.
• Association between SIgAD and SLE, as well as the common IFIH1 polymorphism conferring risk in both diseases, indicates a shared genetic predisposition through IFIH1.
• SIgAD leads to defective host defence against viral infections and abnormal presentation of viral antigens.
• Low or absent IgA may favour autoantibody production and development of autoimmunity.
• SIgAD may be the modifying factor that drove the interferonopathy toward the SLE phenotype in this patient.

Other studies on IFIH1 in SLE and in IgA deficiency:


Common Variable Immunodeficiency Disorders (CVID)

- A group of heterogeneous primary antibody failure syndromes characterized by hypogammaglobulinemia.
- Polygenic inheritance in most cases; monogenic forms described.
- Diagnosis is one of exclusion.
- Onset of the varied clinical manifestations and laboratory abnormalities do not necessarily coincide; may occur from early childhood to old age.
- Phenotype ranges from only bacterial infections, to progression from a CVID-like condition to disease similar to a combined immunodeficiency.
- Some patients may have distinct initial presentations, such as autoimmune disease, granulomatous disease, or enteropathy without recurrent infections.

Autoimmunity in CVID

- Occurs in approximately 25% to 30% of CVID.
- Most common autoimmune disorders: ITP, AIHA, or both.
- Other autoimmune disorders include: seronegative arthritis, Sjogren’s syndrome, SLE, vasculitis, uveitis, inflammatory bowel disease, pernicious anemia, hepatitis, primary biliary cirrhosis, thyroiditis, alopecia, vitiligo.
- In one study, 17% of 224 patients had autoimmunity as one of the presenting manifestations of CVID.
- Autoimmune manifestations may precede the appearance of hypogammaglobulinemia.

CVID and SLE

- CVID is defined by a severe lack of immunoglobulins and variable T-cell dysfunction.
- SLE is characterized by high levels of immunoglobulins and autoreactive antibodies.
- Literature findings suggest CVID in SLE patients may be caused by an intrinsic B-cell defect or by an extrinsic factor with an effect on B-cell maturation.
- SLE-associated CVID is uncommon.
- However, CVID should be considered in SLE when hypogammaglobulinemia is present as it has potentially fatal outcome.
- Recurrent infections in SLE, apart from SLE activity and/or immunosuppressive treatment, must also alert the physician to possible CVID.
Described 2 patients with SLE and CVID and reviewed cases published in English literature.

- Detailed descriptions available for 18 patients; 89% females
- Mean age at onset of SLE of 23.8 years (range 7 to 44 years).
- In 50% of patients, CVID developed within first 5 years after diagnosis of SLE (range: 1 to 22 years).
- All patients had been treated with corticosteroids.
- 72% also had immunosuppressive therapy; 7(38%) azathioprine, 5(28%) cyclophosphamide, and 1 with chorambucil.
- 3(17%) were on carbamazapine, 3(17%) phenytoin, and 2(11%) phenobarbital.
- Sinopulmonary infections were the most frequent symptoms.
- In 67% of patients, SLE disease activity decreased after development of CVID.
- 4(33%) had exacerbations of lupus nephritis and other symptoms of SLE and anti-DNA antibody levels remained high after diagnosis of CVID.
- After diagnosis of CVID, ANAs were present in 11/17(65%) and anti-DNA in 8/17(47%).
Reasons for hypogammaglobulinaemia in SLE patients other than PID

Drugs used to treat SLE:
• Corticosteroids, azathioprine, cyclophosphamide, rituximab

SLE disease manifestations:
• Protein-loosing enteropathy, lupus nephritis with nephrotic state
Corticosteroids and hypogammaglobulinaemia

- Suppressive activity of corticosteroids is predominantly on cell-mediated immunity; marginal inhibitory effect on humoral immunity.
- Studies on suppression of humoral arm were carried out mainly in asthmatic patients:
  • Inhaled corticosteroids have no effect on B-cell function.
  • Oral corticosteroids may suppress humoral immune responses.
  • Low serum immunoglobulin levels, especially IgG and to a lesser extent IgA and IgM noted in patients on oral corticosteroids.
  • Corticosteroids >20 mg daily for 14 days or lower doses over longer periods (months to years) may lead to hypogammaglobulinemia.
  • However, hypogammaglobulinaemia is rarely associated with functional antibody defects.

- Describes an asthmatic patient on low dose corticosteroid for 36 years.
- Developed a clinical and immunologic picture suggestive of CVID.
- Suppression of B-cell percentages and absolute counts, levels of serum IgG1, and specific antibody responses to pneumococcal vaccine during long-term low-dose corticosteroid therapy.
- Gradual normalization over 4 years after corticosteroid was tapered and discontinued.

CONCLUSION
Long-term, low-dose corticosteroid use may reversibly decrease B-cell counts and specific antibody responses.
Hypogammaglobulinaemia and association with Azathioprine and cyclphosphomide

- In SLE, these two drugs have been reported to cause reversible hypogammaglobulinemia.
- Such secondary hypogammaglobulinemic states present as panhypogammaglobulinemia, involving decreased levels of IgG and other immunoglobulin isotypes.

Rituximab (RTX)

- A chimeric anti-CD20 mAb, rapidly depletes circulating CD20+ B cells.
- Spares progenitor cells (allows B cell regeneration) and long-lived plasma cells (prevents excessive reduction of normal immunoglobulin levels, at least with initial therapy).
- Half life of 21 days.
- B cells peripherally can remain depleted for 6-9 months.
- Although RTX does not deplete fully mature plasma cells, repeated courses may lead to hypogammaglobulinemia.
- RTX crosses the placenta, manufacturer (Roche) recommends to avoid pregnancy for ≥ 12 months post last drug administration, BSR consensus is 6 months before planned conception.
- Licensed for RA, GPA, MPA but not for SLE; widely used to treat refractory lupus based on strong open-label experience.
Rituximab associated Hypogammaglobulinaemia

• Can be an important adverse outcome.
• May be transient or persistent.
• Transient hypogammaglobulininemia may not require specific therapy.
• Persistent hypogammaglobulininemia with infection would require immunoglobulin replacement.
• Factors that increase risk of persistent hypogammaglobulininemia in ANCA associated vasculitis and other autoimmune diseases:
  - Higher cumulative dose or repeated cycles of RTX
  - Concomitant or sequential use of immunosuppressants (especially cyclophosphamide)

Hypogammaglobulinaemia during long term maintenance treatment with RTX in granulomatosis with polyangiitis (GPA)

- 29 GPA patients.
- Received a median total cumulative dose of cyclophosphamide (CYC) of 17g and were treated with 2g RTX followed by re-treatment with either 2g once annually, 1g biannually or a combination of both.
- Hypogammaglobulinaemia defined as levels of total Ig <6 g/L.
- During a median follow-up of 4 years, patients received a cumulative dose of 9g RTX.
- While serum Ig levels decreased during RTX maintenance, the largest decrease occurred after the first infusion.
- Baseline Ig levels and CYC cumulative dose predicted Ig levels, whereas the RTX cumulative dose did not.
- At baseline, low Ig levels were present in 30% of patients, perhaps reflecting the effect of high dose cyclophosphamide.

Besada E. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology 2014;53
In registry data, patients with low IgG post-therapy was low, 3.5 %.

In RCTs and LTE studies, 22.4 % of patients developed low IgM, levels lower on 2×1000 mg RTX versus 2×500 mg RTX.

Low IgM prior to and post-RTX has not been associated with SIE.

Registry data show that IgG level (<6 g/L) before a cycle of RTX was associated with SIE, particularly in the 3 months following RTX infusion.

Development of low IgA post-RTX is uncommon (1.1 %) and does not appear to be associated with serious infectious events.

* SIE = serious infectious event


Observational study, measured serum immunoglobulin levels.

57 consecutive patients with SLE treated with RTX and concomitant or sequential immunosuppressants.

Serum total IgG, IgM, and IgA and anti-dsDNA Ab measured over a median of 48 months most recent follow-up.

12(21%) had persistent IgM hypogammaglobulinemia (<0.4 g/L) and 3/55(5%) had low IgG (<7g/L) at most recent follow-up (range 12-144 months); not associated with serious adverse events.

Factors predictive of low serum IgM included: baseline serum IgM ≤0.8g/L and subsequent therapy with mycophenolate mofetil (MMF).
Rituximab and infection and vaccine response

- Anti-microbial antibody responses are generally relatively robust.
- However the degree of response to challenge with influenza, pneumococcal and tetanus vaccines after treatment may be impaired found to relate to the degree and duration of B cell depletion in peripheral blood in patients with RA and SLE.

Prevention of infections - vaccinations

- Administration of inactivated vaccines, particularly inactivated influenza vaccine and 23-valent polysaccharide pneumococcal vaccine, is strongly encouraged in SLE patients on immunosuppression.

- Vaccines should ideally be given 4 weeks before commencing B-cell depleting therapy such as RTX, or at least 6 months after the start of therapy but 4 weeks before the next course.

- Live attenuated vaccines should be avoided in immunosuppressed patients.

Summary

- Homozygous deficiency of the early components of the classical pathway of complement predisposes to the development of SLE.
- SIgAD is the most common primary antibody deficiency found in SLE.
- Besides PID, hypogammaglobulinaemia in SLE may be the result of complications of lupus activity as well as drug therapies.
- Evaluation of hypogammaglobulinaemia and diagnosis of associated PID in SLE can be challenging.