# New proposals for partial antibody deficiencies

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# Criteria - General points:

- Criteria for diagnosis: studies/registers etc
- agreed by ESID & PAGID
- *Definite* = 98% probability that same diagnosis in 20 years;*gene mutation & clinical features*
- *Probable* = 85% probability that same diagnosis in 20 years; *clinical & lab features as no known single gene defect*

# Common Variable Immune Deficiency Disorders [CVIDs]

**Probable**: male/female patient with all of:

- Aged > 4 years
- Serum IgG and IgA more than 2 SD below mean for age
- Poor response to all vaccines
- Causes of secondary antibody deficiencies excluded (eg lymphoma, medications)

# IgA with IgG subclass deficiencies DRAFT

Male or female patient with recurrent/ severe infections and all the following:

- Aged > 7 years
- Marked decrease in IgA [ie <0.05g/l] and at least one of IgG $_{1\text{-}3}$ subclasses less than the 5$^{th}$ centile for age
- Poor responses to some vaccines

# IgG subclass deficiencies

## DRAFT

Male or female patient with recurrent/ severe infections and all the following:

- Aged > 7 years
- Normal levels of IgM & IgA and at least two of IgG $_{1\text{-}3}$ subclasses less than the 5$^{th}$ centile for age
- Poor responses to some vaccines

# Does this patient have an IgG subclass deficiency ?

- Originally investigated in 1983 for boils
  - Staphylococcal phagocytosis & killing defect *? significant*
  - discharged in 1989 without treatment
- 1991 - more boils ?linked to stress
- Family history:
  - Sister (bronchiectatic) had pneumonia
  - Half-brother died - bronchiectasis with CVID
- Serum IgG 5.3 g/l; IgA none, IgM normal
- 1992 -1999 trial of immunoglobulin therapy

  - reduced the boils
- Diagnosis sought
  - normal IgE & CXR -unlikely Job's syndrome
  - low IgG 3 " antibody deficiency"
  - worsening of asthma "APBA" +ve aspergillus precipitins (1 line); mild eosinophilia only
- No more boils after 1995

# IgG subclass deficiency (contd 3)

Transferred in 2000:

- Normal numbers of B cells
- Specific antibodies - present, even to encapsulated pathogens
- Stopped IVIg & no infections (not even boils) for 5 years
- Reviewed every 3 months; IgG and esp. IgG 3 reached stable, normal levels within 6 months
- Aspergillus precipitins now negative (moved to new house)

*Diagnosis: ? transient IgG3 defect*

# We need more data…….

*Mininum data set for ESID online registry:*

- Demographs - age, gender, family Hx
- Serum Ig levels - IgM, IgA, IgG
- B cell numbers including B memory markers
- T cell numbers including CD4, CD8 etc for inter-current complications
- Clinical complications - granuloma, autoimmunity, lymphoproliferation, none
- Antibody responses to test Imx.
  - ? Which and to be done where ?
- IgG subclass levels - ? in a single laboratory

# *Conclusions re testing*

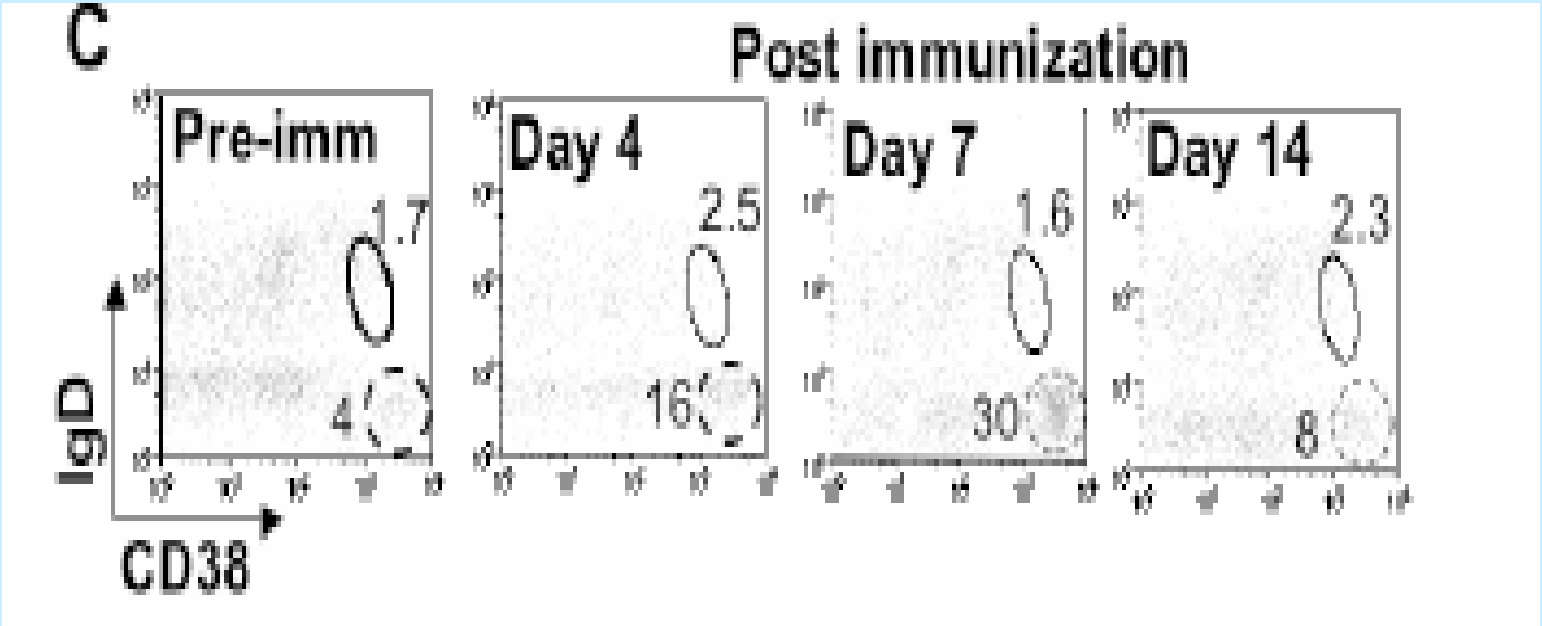
*Currently we need to:*

- Do test Imx responses to standard protein / carbohydrate antigens for all new patients to distinguish CVIDs from partial antibody failures
- Role for new vaccines/assays
- Add neoantigen test Imx for existing/ treated patients in order to categorise them more precisely
- Quality assurance and reference preparations

# Extra essential data

- Antibody [ IgG] responses to which test Imx.
  - Proteins - tetanus, diphtheria, Hib, rabies,
  - Carbohydrates - Pneumovax, Typhim Vi, new vaccine?
  - Neoantigens - Tick-borne encephalitis vaccine
  - Reference preparations from ….. Whom?
  - Reference assays for Consensus to be done……. where ?
- IgG subclass levels
  - ? in a single laboratory ? in Sweden

# Should we add plasmablasts to memory B cell immunophenotyping ?




Plasmablasts on days 0,4,7 and 14 following Imx with influenza vaccine in a normal individual

# IUIS 2006 *(J All. & Clin.Imm.in press)*

| Disease | B cell numbers | Serum Ig | Associated Features | Inheritance | Genetic Defects/presumed pathogenesis |
|---|---|---|---|---|---|
| 2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low numbers of B cells | | | | | |
| a) Common variable immunodeficiency disorders* | Normal or decreased | Decrease in IgG & IgA; IgM may be normal | May have autoimmune, lymphoproliferative and/or granulomatous disease | Variable | Unknown |
| b) ICOS deficiency | Normal or decreased | Decrease in IgG & IgA; IgM may be normal | Recurrent bacterial infections | AR | Mutation in *ICOS* |
| c) CD19 deficiency | Normal | Decrease in IgG & IgA; IgM may be normal | Recurrent bacterial infections | AR | Mutation in *CD19* |
| d) TACI deficiency | Normal | Decrease in IgG & IgA; IgM may be normal | May have autoimmune or lymphoproliferative disease | AD or AR | Mutation in *TACI* |
| e) BAFF receptor deficiency | Normal or decreased | Decrease in IgG & IgA; IgM normal | Recurrent bacterial infections | AR | Mutation in *BAFFR* |

*•This is a diagnosis of exclusion of other known primary antibody deficiencies. There are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogeneses.It is not clear currently whether the mutations associated with some of these patients involve disease causing genes, disease modifying genes or polymorphisms.*

# IUIS 2005

| Disease | B cell numbers | Serum Ig | Associated Features | Inheritance | Genetic Defects/presumed pathogenesis |
|---|---|---|---|---|---|
| 4. Isotype or light chain deficiencies with normal numbers of B cells | | | | | |
| a) Ig heavy chain deletions | Normal | IgG1, IgG2, or IgG4 absent; IgA1 and IgE may be absent | May be asymptomatic | AR | Chromosomal deletion at 14q32 |
| b) K chain deficiency | Normal | Immunoglobulins have only lambda light chains | Asymptomatic | AR | Mutation in Kappa constant gene |
| c) Isolated IgG subclass deficiency | Normal | Reduction in one or more IgG subclass | May be asymptomatic or have recurrent viral / moderate bacterial infections | Variable | Unknown |
| d) IgA with IgG subclass deficiency | Normal | Reduced IgA with decrease in one or more IgG subclass; | Recurrent bacterial infections | Variable | Unknown |
| e) Selective IgA deficiency | Normal | IgA decreased | May be asymptomatic, have allergies or autoimmune disease | Variable | Unknown |