

An 8 year old boy with recurrent respiratory infections



- [Patient presentation](#)
- [History](#)
- [Differential Diagnosis](#)
- [Examination](#)
- [Investigations](#)
- [Discussion](#)
- [Treatment](#)
- [Final outcome](#)
- [Evaluation - Questions & answers](#)
- [MCQ](#)
- [References](#)

Patient presentation

An 8 year old boy is referred to a regional hospital for a surgical consultation for a lobectomy following a diagnosis of bronchiectasis due to a chronic history of recurrent respiratory infections.

Acknowledgement

This case study was kindly provided by Dr Monika Esser MMed Paed, Head of Division of Immunology, N.H.L.S Coastal Branch, Tygerberg Hospital.

History

- Bacterial meningitis at age 2 years complicated by deafness – for which he currently attends a school for hearing impaired children.
- Pulmonary TB fully treated, exact age at time of treatment unknown.
- Currently presents with bronchiectasis due to recurrent respiratory infections.
- No significant family history.

Differential Diagnosis

- HIV
- X- linked Agammaglobulinaemia (Bruton's Disease)
- Agammaglobulinaemia
- Hyper IgM Syndrome
- Common variable immunodeficiency
- Severe Combined Immunodeficiency

Examination

On general examination:

- Does not appear acutely ill
- Apyrexial
- Weight on 75th centile, height 90th centile
- Clubbing of fingernails

Respiratory System:

- Persistent productive cough
- Harrison's sulcus
- Bilateral lower lobe crepitations

Other systems:

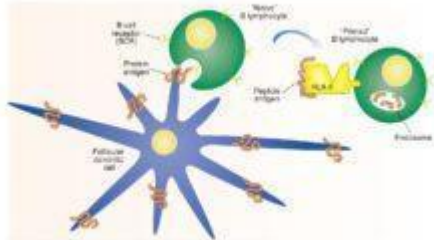
- Nil of note

Investigations

FBC:			
WBC	11.11 x 10 ⁹ /L – 81.3% Lymphocytes		
Hb	12.5 g/L		
Platelets	397 x 10 ⁹ /L		
(no other counts available)			
Sputum:			
H. Influenza and	Isolated on culture		
S. Pneumoniae			
TB Smear	Negative		
TB Culture	Negative		
CXR	Suggestive of bronchiectasis with superimposed infection		
Serum Immunoglobulins:			
Se	IgG	0.393 g/L	(6-20)
	IgA	<0.0563 g/L	(0.8-3)
	IgM	1.09 g/L	(0.4-1.8)
	IgE	4.3 IU/ml	(>60 IU/ml)
Lymphocyte Subset Analysis:			
Percentage		Absolute	
CD19	1% (L)	90	(L)
CD3	97% (H)	8759	(H)
CD4	22% (L)	1987	(H)
CD8	68% (H)	6140	(H)
NK	8% (L)	722	(H)
			Ratio 0.32:1

Lymphocyte Subset Analysis:		
Lymphocyte subsets showed low but not entirely absent CD19 (B cells) and elevated C3 and NK cells.		

B lymphocyte priming

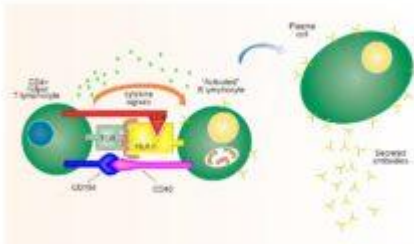


Naive B lymphocytes dwell in the follicle region from long-lived nonreplicative dendritic cells. They migrate from the follicle margin to the germinal center to set course of accurate clonal expansion where they contact antigen-bearing follicular dendritic cells. Recognition of protein antigens by the B cell receptor (BCR) in close association of the antigen-BCR network. The signal is provided by dendritic antigen which associates with MHC class II molecules on the cell surface. The B lymphocyte is then primed for antibody production and migration to the T cell zone for activation.

Discussion

- Upon investigation it was noted that the IgA, IgE and IgG were considerably lower than that of IgM. This was an indication of defective class switching recombination process making Hyper IgM syndrome the evident diagnosis.
- Hyper IgM syndrome is a disease that causes a defective interaction of CD40L(CD154)- CD40 between CD4+ T cells and antigen presenting cells.
- Hyper IgM syndrome patients generally indicate decreased number of isotope memory B cells along with normal numbers of total B cells.
- The majority of patients affected usually presents with a broad spectrum of clinical manifestations which usually develops during infancy and second year of life.

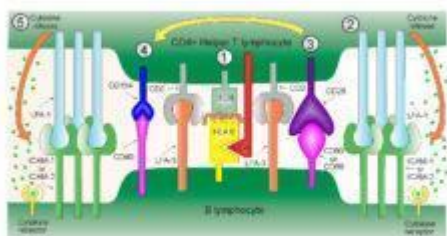
This makes them susceptible to recurrent bacterial (meningitis, pneumonia, and otitis amount other) and opportunistic infections. Patients diagnosed with Hyper IgM syndrome are prone to pulmonary complication, gastrointestinal manifestations, autoimmune disorder, hematologic abnormalities, lymphoproliferation disorders and malignancies (Vaillant & Qurie, 2023; Yazdani et al., 2019)



Primed B lymphocytes migrate from the germinal centers (B cell zone) to the T cell zone of the secondary lymphoid organ where their survival depends on effects of CD40L from T lymphocytes. Recognition of peptide antigens bound to HLA class II molecules on the B lymphocyte by T cell receptors (TCR) on the CD4+ helper T lymphocyte causes the formation of an immunological synapse. The CD40L from T lymphocyte is activated and expressed CD40L and releases cytokines. Stimulation of CD40L and cytokine signals promotes the B lymphocyte to differentiate into a plasma cell.

The Role of CD40 and its ligand (CD154)

- The CD40L gene is located on the X chromosomes which encodes CD40L, is expressed on activated T cells and is a member of the tumour necrosis factor (TNF) family.
- The mutation in this gene usually affects the extra cellular domain, resulting in a defective geometrical fold of the CD40L or preventing the CD40L/CD40 binding.
- CD40, is expressed by a variety of cells including B cells, macrophages, dendritic cells and other nonimmune cell types.
- CD40 activation occurs via binding to its ligand CD154 (CD40L), which is expressed on activated T cells
- However, a mutation in the CD40 or CD154 leads to improper binding and a defective T cell co-stimulation, causing a combined T (cellular) and B (humoral) cell immunodeficiency. which is expressed on activated T cells.

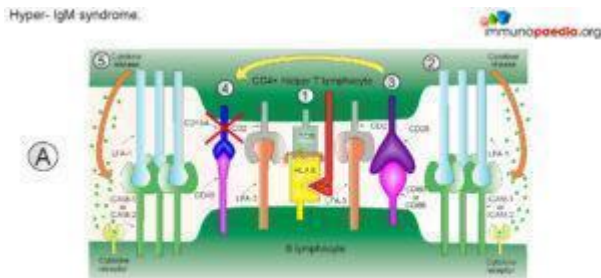


The immunological synapse is initiated by recognition of peptide antigens bound to MHC class II molecules on the primed B lymphocyte by T cell receptors (TCR) on the CD4+ helper T lymphocyte. CD40L also binds to the MHC class II molecule. The receptor is further activated and stabilized by binding of HVEM, GITR and VISTA in the synapse (for a detailed view of CD40L and HVEM in the synapse see [1]). Stimulation of CD40L by CD40 or CD40L activates the CD4+ helper T lymphocyte. The activated CD4+ helper T lymphocyte produces and expresses CD40L which binds to CD40 on the B lymphocyte. CD40L binds to CD40 and stimulates B lymphocyte to differentiate into a plasma cell. CD40L also binds and activates HVEM, GITR and VISTA in the synapse. Cytokines like IL-4 and IL-21 are released from the T cell and act on the B cell to stimulate the differentiation of memory B lymphocytes and plasma cells.

CD40 activation is critical for:

- B cell proliferation
- Ig- Isotype switching

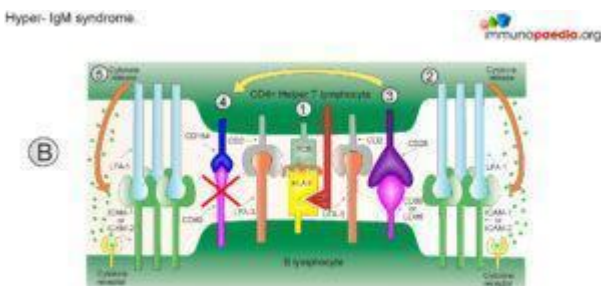
- Germinal centre formation



The most common form of Hyper-IgM syndrome is the lack of CD40 on the T lymphocyte to interact with CD40 receptors. This is also known as X-linked Hyper-IgM syndrome since the gene for CD40 is carried by the X chromosome. Failure of CD40 stimulation by CD40L prevents the B lymphocyte from receiving the required activation signal to differentiate into a plasma cell capable of secreting IgG or switching to a different antibody molecule such as IgG, IgA or IgE. In Hyper-IgM syndrome it is thought that IgM is still produced by B cells because of being provided by T cell independent mechanisms governed by toll like receptors (TLR) or antigen stimulation. This mechanism does not require antigen-antibody complexing or affinity maturation of antibodies and does not generate memory B lymphocytes, observed for long-term memory.

Mutations in either CD40 or CD154 gene cause Hyper IgM Syndrome , HIGM3 and HIGM1 respectively , which is characterised by:

- Normal or elevated SeIgM
- Markedly decreased IgG, IgA, IgE



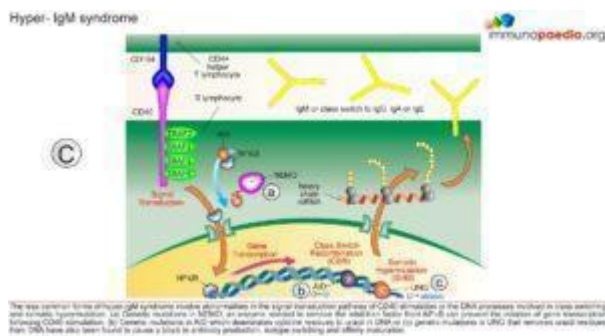
In several variants of Hyper-IgM syndrome which do not affect the lack of B lymphocyte to interact with CD40 receptors. Failure of CD40 stimulation by CD40L prevents the B lymphocyte from receiving the required activation signal to differentiate into a plasma cell capable of secreting IgG or switching to a different antibody molecule such as IgG, IgA or IgE. T cell independent mechanisms may still contribute to IgM production, however no memory B lymphocytes, antigen-antibody complexing or affinity maturation of antibodies can be observed in the case.

Due to lack of CD154, T cell interaction with protein antigen processing cells such as CD19 is impaired preventing ligand interaction of B cell CD40 with CD154 on T cells with subsequent defective response to T cell dependent antigens i.e. the immunological synapse is not formed.

This synapse gives essential costimulatory signals to B cells, necessary for the B cells to switch from low affinity IgM

production primary response to B cell producing high affinity antibodies of different classes such as IgG and IgA. 65-75% of the cases observed, has shown a correlation of Hypo IgM syndrome to an X linked CD40 recessive autosomal mutation, that mostly affect male. However, there are other genetic mutations that also leads to Hypo IgM syndrome:

- AICDA and UNG mutations
- PI3K and PI3KCD mutations
- NEMO and IKBA mutations
- DNA repair gene mutations



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Treatment

- Physiotherapy daily. After 4 weeks of intensive physio a CT chest confirmed bilateral basal bronchiectasis.
- Broad spectrum antibiotics were initiated.
- IVIG at 0,4g/kg – 3 weekly infusions. (Antibody studies to common vaccine antigens were not done prior to IVIG therapy and are therefore not available).

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Final outcome

Long-term Plan:

- IVIG infusions 3 weekly to maintain normal serum levels of IgG and prompt treatment with antibiotics for bacterial infections.
- Prevention or early recognition of protozoal infections of liver and GIT.
- Cotrimoxazole prophylaxis for PCP infections.
- Bone marrow transplant would have been the curative treatment of choice, prior to established bronchiectasis.

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Evaluation – Questions & answers

What is the diagnosis?

The most likely diagnosis of Hyper IgM syndrome was made but screening for CD40 ligand (CD154) was normal.

Give possible reasons for bronchiectasis developing in childhood.

In the absence of known causes for primary or secondary immunodeficiency, possible causes could include measles, pertussis and post infectious complications of pulmonary tuberculosis, especially in a poor socioeconomic setting.

What else on history is essential for evaluating this patient with regards to immunity?

Perinatal history, gestation, birth weight – for example premature infant has an immature immune system and lack of maternal antibodies. Vaccination history with regards to responses to live vaccines such as measles and BCG. Adverse events from vaccinations would point to a T-cell deficiency.

Which other clinical findings would you like information on?

Lymphadenopathy including tonsillar tissue presence, especially where defective B cell development is suspected.

If this child has a primary or secondary Immunodeficiency - which component of the immune response do you expect to be impaired?

T Cell impairment as evidenced by tuberculosis (Intracellular organism) and B Cell impairment which is related to bacterial

meningitis infection.

Comment on the immunoglobulin levels and lymphocyte phenotypes.

There are very low Se IgG, IgA and low IgE, BUT normal Se IgM levels.

How do you explain a normal Se IgM with the other Immunoglobulin isotypes low?

There are high lymphocyte subsets except for very decreased B Cells (CD19).

Could this patient have X-linked Agammaglobulinaemia (XLA) (Bruton's)?

No, XLA cannot produce Se IgM because of absent B cells (BTK deficiency).

What is the possible cause of the T cell subset abnormal distribution?

CMV infection which can result in expansion of CD8 cells while lowering CD4 cells

How would you expect a patient with very low B cells to respond to vaccination?

They cannot respond because of lack of B Cells – hence no Antibody production

Who in the boy's family would possibly be the best match for HLA typing for a bone marrow transplant?

An identical twin or haploidentical sibling

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Multiple Choice Questions

Earn 1 HPCSA or 0.25 SACNASP CPD Points
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1. Vaillant, A. A. J., & Qurie, A. (2023). Immunodeficiency. *StatPearls*. <https://www.ncbi.nlm.nih.gov/books/NBK500027/>
2. Yazdani, R., Fekrvand, S., Shahkarami, S., Azizi, G., Moazzami, B., Abolhassani, H., & Aghamohammadi, A. (2019). The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. *Clinical Immunology*, 198, 19–30. <https://doi.org/10.1016/J.CLIM.2018.11.007>