

# An 8 year old boy with recurrent respiratory infections



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## 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

<b>FBC:</b>	
WBC	11.11 x 10 <sup>9</sup> /L – 81.3% Lymphocytes
Hb	12.5 g/L
Platelets	397 x 10 <sup>9</sup> /L
(no other counts available)	

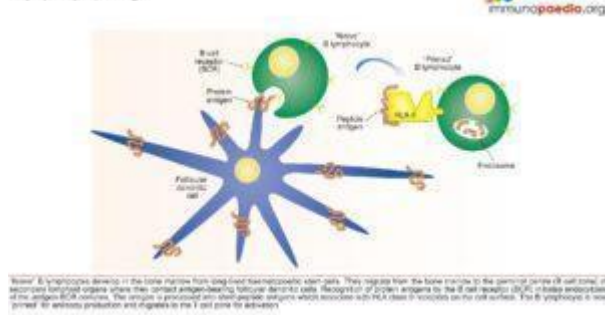
<b>Sputum:</b>	
H. Influenza and	Isolated on culture
S. Pneumoniae	
TB Smear	Negative
TB Culture	Negative
CXR	Suggestive of bronchiectasis with superimposed infection

<b>Serum Immunoglobulins:</b>			
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)

<b>Lymphocyte Subset Analysis:</b>		
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)	

<b>Lymphocyte Subset Analysis:</b>		
		Ratio 0.32:1
Lymphocyte subsets showed low but not entirely absent CD19 (B cells) and elevated C3 and NK cells.		

B lymphocyte priming



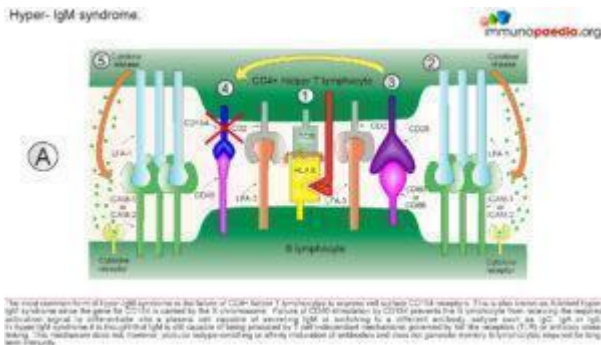
## Discussion

- 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)

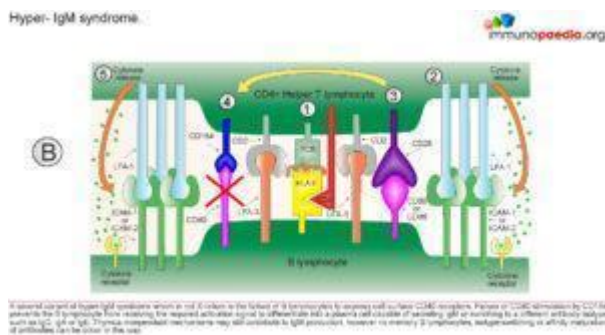


- Germinal centre formation



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

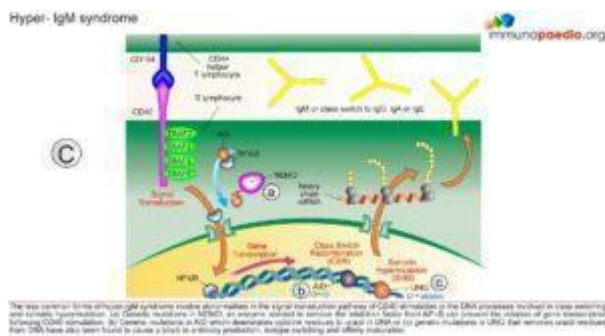


Due to lack of CD154, T cell interaction with protein antigen processing cells such as CD19 is impaired preventing ligand interaction of B cell CD40 with CD154 on T cells with subsequent defective response to T cell dependent antigens i.e. the immunological synapse is not formed.

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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## Hyper-IgM Syndrome

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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

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## References

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