Immunodeficiency and failure to thrive

Patient presentation

A 5 and half year old female, having recently moved provinces, is seen by a new paediatrician and diagnosed with pneumonia. It is also noted that she is failing to grow consistently and has experienced frequent arrests in weight gain.

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

- Conceived through in vitro fertilisation
- Full term gestation, normal birth weight
- Breastfed until age 2 yrs and 8 month
- She received all recommended infant vaccinations, according to the South African expanded program of immunization (EPI) schedule
- She is the only joint child of her parents, she has 3 adult half-siblings
- All family members are healthy
- According to her mother she has had little contact with other sick children

History Relevant To Infections

- Recurrent otitis media, sinusitis and 3 documented episodes of pneumonia starting from 2 years of age
- At age 2 yrs, due to recurrent infections a low Serum Ig was documented – but no intervention was undertaken

Differential Diagnosis

Primary Immunodeficiency

B cell disorder

- X-linked Agammaglobulinaemia (Bruton Disease)
- IgA Deficiency
- Transient hypogammaglobulinaemia of infancy
- Hypogammaglobulinaemia (Common Variable Immunodeficiency)
- Ataxia Telangiectasia
- Ataxia Telangiectasia like disorder (ATLD)
- Nijmegen breakage syndrome (NBS)

T cell disorder

- Severe combined immunodeficiency

- Hyper-IgM syndrome

Cystic Fibrosis – common genetic disorder in SA white population, leading to respiratory infections and failure to thrive

- *Cerebral Palsy*
- *Atopy* – common undiagnosed cause of recurrent URT symptoms
- *Poverty* – early exposure to overcrowding or viruses resulting in perinatal respiratory problems
- *HIV*

Examination

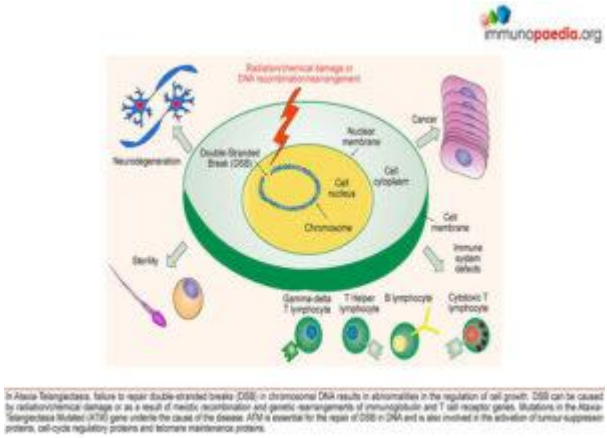
- Age 5 years, 5 months – slender build – weight: 16.6kg, height 105 cm, both on 10th centile for age.
- Moderate generalised lymphadenopathy.
- Nasal speech and slurring of words noted – mother claims onset related to adenoidectomy and tonsillectomy at age 3 and has been receiving speech therapy.
- Crepitations heard in left lung base – was hospitalised 5 days previously for pneumonia.
- Grommets in situ (3rd set).

Investigations

	Value	**Normal Limits**
FBC		
WBC	22.4 x 109/l	
Relative Lymphopaenia		
Hb	12.8/l	
MCV	81	
Platelets	Normal	
Sweat test	Normal	

	Value	Normal Limits
Serum Ig’s		
IgG	0.33g/l	6 - 16g/l
IgA	0.07g/l	0.6 - 3g/l
IgM	1.63g/l	0.5 - 2.6g/l
Results prior to first intravenous immunoglobulin (IVIg)		
CD3	1371 (83%)	1800 - 3000
CD4	558 (33%)	1000 – 1800
Ratio	0.67	
CD8	817 (49%)	800 – 1500
CD19	133 (8%)	700 – 1300
NK	163 (10%)	200 – 600
Immunoglobulin Studies		
IgA	0.49	(0.70 – 4.0g/l
IgM	2.3199999999999998	0.40 – 2.3g/l
IgG	7.54	7.0 – 16.0g/l
Specific Antibodies		
Tetanus antibodies (protein ag)	3.27IU/ml (N)	
Antibodies to Streptococcus pneumoniae IgG (polysaccharide Ag)	48.19mg/L (low N)	

Discussion

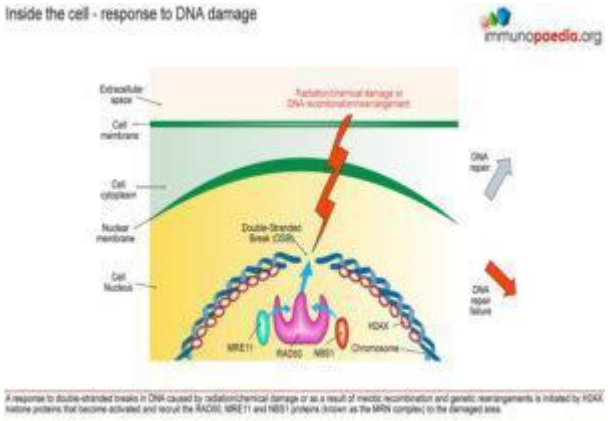


Management and treatment

Bruton like Agammaglobulinaemia was excluded because CD19 (B Cells), IgM and IgA are all present.

Due to the preservation of IgM – CD40 ligand assay was requested which was normal as demonstrated with normal binding of CD154. CD40 is expressed on B cells, macrophages, dendritic cells, and endothelial cells essential for activation. In B cells the interaction with CD40 cell ligand is needed for CLASS SWITCHING for Ig production other than IgM or IgD, ie co – stimulatory binding leads to T cell dependent antibody production (IgG, IgA or IgE).

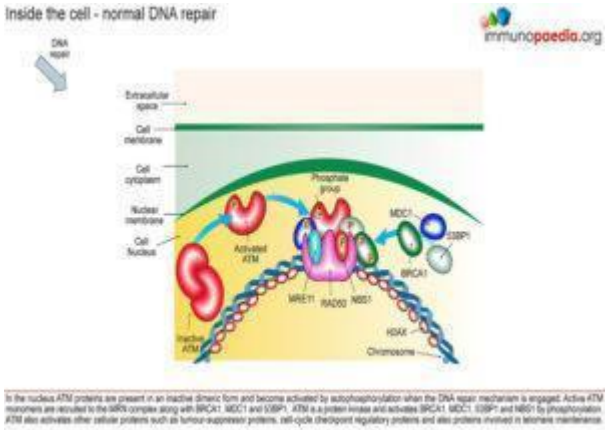
A diagnosis of Hypogammaglobulinemia was made with low but adequate B cells (greater than 2%) and serum IgG (Se IgG) and IgA below standard deviations for age. Differentiating between primary (congenital) and secondary Hypogammaglobulinemia is important as this has implications for evaluation and management of the patient. Secondary Hypogammaglobulinemia was ruled out as there was no indication of immunosuppressive drugs in the patient history and no indication of disease that leads to decreased antibody production or increased antibody loss(Otani et al., 2022). Transient Hypogammaglobulinemia was also considered but ruled out because she is more than 2 years old.



A response to double-stranded breaks in DNA caused by radiation/chemical damage or as a result of meiotic recombination and genetic rearrangements is initiated by H2AX histone proteins that become activated and recruit the RAD50, MRE11 and NBS1 proteins (known as the MRN complex) to the damaged area.

Pathophysiology

What is the main vulnerability of patients with low antibody levels? Antibodies are required to clear extracellular bacteria. These bacteria have capsules that are not recognised by phagocytic cells of the immune system. To clear such bacteria, humans rely on antibodies, together with complement, to assist phagocytic cells to recognise and ingest the bacteria. There are also some viruses that require antibodies for control. They have low lymphocyte phenotypes, except CD8. Although the levels are low there are antibody responses present to proteins and polysaccharides.



In the nucleus ATM proteins are present in an inactive dimeric form and become activated by autophosphorylation when the DNA repair mechanism is engaged. Active ATM monomers are recruited to the MRN complex along with BRCA1, MDC1 and 53BP1. ATM is a protein kinase and activates BRCA1, MDC1, 53BP1 and NBS1 by phosphorylation. ATM also activates other cellular proteins such as tumour-suppressor proteins, cell-cycle checkpoint regulatory proteins and also proteins involved in telomere maintenance.

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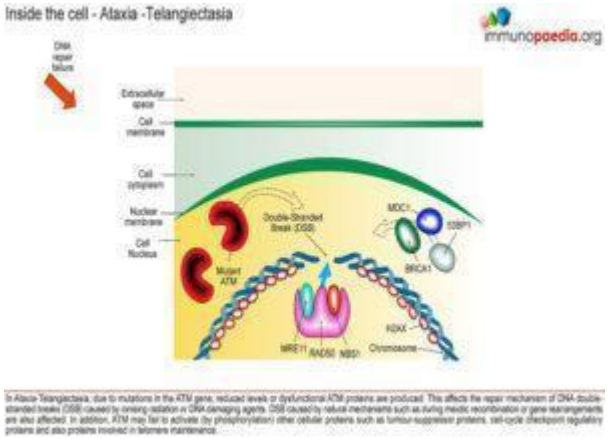

Other Causes of Hypogammaglobulinemia

Secondary to:

- Decreased production
- Malignancy (lymphoma, thymoma, leukaemia, multiple myeloma)
- Medications (carbazepine, oxcarbazepine, immunosuppressive agents)
- Infection (e.g. paediatric HIV)
- Starvation
- Increased catabolism or loss
- Protein-losing enteropathy
- Chylothorax
- Hypercatabolic states

Clinical Course

- Regular intravenous immunoglobulin (IVIG) instituted.
- Follow up with the same paediatrician who monitored the course and Serum IgG (SeIgG) levels.

Follow up visit at 6 years and 7 months

- Patient is receiving 12 grams IVIG every 3 weeks with

trough levels of IgG, 7-8 grams.
- No further significant infections reported.
- CT Scan shows lungs clear.
- Weight 19kg and height 110cm.
- Chest is clear on auscultation.
- Clean perforations in both ears with hearing loss noted on the left side.

Next follow up visit at 7 years and 5 months

- Patient has remained infection free, but balance problems mentioned by mother.
- She has had difficulty with head control and is receiving Occupational therapy.
- Urgent referral to Neurology – Ataxia diagnosed
- Alpha Fetoprotein elevated
- New diagnosis made

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Ataxia-Telangiectasia

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Evaluation – Questions & answers

What is the diagnosis?

Ataxia and Immunodeficiency without Telangiectasia (AT). Ataxia-telangiectasia (AT) is an autosomal recessive genetic disorder. The characteristic features are immune dysfunction, progressive neurodegeneration (cerebellar degeneration),

cutaneous abnormalities (incl. telangiectasia), radiosensitivity, sterility and cancer predisposition. Children with AT have deficiencies in both cellular and

humoral immunity including reduced levels of IgA, IgE and IgG2, absolute lymphopenia and a decreased ratio of CD4+ helper cells to CD8+ suppressor T cells. There is increased susceptibility to recurrent upper and lower respiratory tract infections (particularly those caused by encapsulated bacteria) and an increased risk for the development of malignancies. ATM, the gene associated with AT has been identified as a single mutation on the long arm of chromosome 11 at 11q22-23. This gene controls the production of phosphatidylinositol 3/4 kinase family, an enzyme which is a crucial nexus for the cellular response to DNA double-stranded breaks. So, these kinases are important players in the cellular responses that prevent cancer, control DNA damage and control cellular

responses to stress. The ATM gene is also involved in double strand break repair mechanisms in physiological conditions such as meiotic recombination, the assembly of the T cell receptor and immunoglobulin (Ig) genes by V(D)J recombination and efficient class switch recombination(Amirifar et al., 2019). Accordingly, AT is thus a disease that results from defects in the response to specific types of DNA damage, which is related to pathogenesis including immune dysfunction, lymphoma predisposition and sterility(Amirifar et al., 2019).

Classification

There appears to be three main forms of AT:

- Pure AT where patients present with all/most of the diagnostic symptoms.
- Attenuated AT where sufferers do not possess all of the diagnostic symptoms.
- Carrier AT where individuals with a single ATM mutation

show an increased risk of cancer.

These are sometimes classified into ‘types’ from I to IV:

- Type I: is the classic syndrome with all manifestations.
- Type II: lacks some of the typical findings but shows radiosensitivity.
- Type III: has the classic clinical findings but is not radiosensitive.
- Type IV: shows only some clinical features and is not radiosensitive.

Carrier detection and prenatal diagnosis are possible at specialized centres. In rare instances patients with milder manifestations of the clinical or cellular characteristics of the disease have been reported and have been designated “AT variants.” Variant forms may have a detectable level of functional ATM while exhibiting some of the cellular features of AT.

Pathology and Outcome

Primary Immunodeficiency is variable with variable humoral deficiency and thymic hypoplasia. Increased susceptibility to recurrent upper and lower

respiratory tract infections, particularly those caused by encapsulated bacteria. Historically bacterial pneumonia and chronic pulmonary disease have been the major cause of death with the second most common cause being cancer (10-30% lifetime prevalence)(Amirifar et al., 2019). Diffuse Cortical Degeneration of cerebellum – reflecting progressive loss of Purkinje and granular cells is most striking. Furthermore, patients with class switching recombinant disorder (CSRD) have a more serve course of disease leading to a lower quality of life and shorter survival in early ages than other AT patients(Amirifar et al., 2019).

How is Ataxia telangiectasia (AT) diagnosed?

AT is diagnosed clinically and with laboratory tests:

- Early-onset progressive cerebellar ataxia (earliest sign)
- Occulo-cutaneous telangiectasia (dilated blood vessels in the eyes and skin) at age 3-6 yrs.
- Immunodeficiency mostly through lowering of IgA, IgG and IgE levels. In AT the humoral immunodeficiency may not be significant enough to require IVIG and the cellular deficiency rarely gives rise to significant infections other than chronic and recurrent warts.
- Chromosomal instability
- Hypersensitivity to ionising radiation
- Increased incidence of malignancies primarily lymphoid (Non-Hodgkin's lymphoma).
- Raised alpha-fetoprotein levels (differential after 8/12 of age – Hepatitis, Hereditary Tyrosinaemia, Hepatoblastoma or asymptomatic hereditary persistence).
- Gene too large for practical screening.

What is the main effect of AT on the immune system?

There are deficiencies in both cellular and humoral immunity so this is a combined T-cell and B-cell immunodeficiency.

Why are IgM isotype levels not affected in AT?

In AT, normal IgM and IgD isotypes are spared because they are generated by isotype switching occurring at the RNA level via RNA splicing. For expression of IgG, IgA and IgE isotypes by B lymphocytes, a DNA recombination of the switch regions is required which is dependent on a functional ATM protein. In AT the ATM gene can contain mutations that produce reduced levels or dysfunctional ATM proteins, therefore resulting in decreased levels of the three DNA dependent isotypes.

What is the main vulnerability of patients with low antibody levels?

Bacteria that have capsules are not recognized by phagocytic cells of the immune system therefore to clear such bacteria humans rely on production of antibodies, together with

complement proteins to recognize the polysaccharides on the surface of the capsule, to assist phagocytic cells to recognise and ingest the bacteria.

What is CD40 ligand?

CD154, also called CD40 ligand is a protein that is primarily expressed on activated T-cells and is a member of the tumour necrosis factor (TNF) family of molecules. It binds to CD40 on antigen presenting cells (APC) which leads to many effects depending on the target cell type. In general, CD40L plays the role of a costimulatory molecule and induces activation in APC in association with T cell receptor stimulation by MHC molecules on the APC, in B cells it CD40L plays a role in T cell dependant antibody class switching.

What is immunoglobulin class switching?

Immunoglobulin class switching is a biological mechanism that changes an antibody from one class to another, for example, from an IgM isotype to IgG isotype. During this process, the constant region portion of the antibody heavy chain is changed, but the variable region of the heavy chain stays the same. Therefore antigen specificity remains the same.

What is IVIg therapy?

Intravenous immunoglobulin (IVIG) is made from pooled IgG immunoglobulins extracted from the plasma of over a thousand blood donors. It is given as a plasma protein replacement therapy (IgG) for immune deficient patients who have decreased or abolished antibody production capabilities. IVIG is administered to maintain adequate antibody levels to prevent infections and confer passive immunity. Treatment is given every 3-4 weeks.

What is hypogammaglobulinaemia?

It is condition that leads to a drop in serum IgG to a level <7g/l. Hypogammaglobulinemia can be classified as primary (congenital) or secondary. Primary is a genetically determined combined immunodeficiency i.e. both the cellular and humoral systems are affected. Secondary hypogammaglobulinemia occrurs due to the use of medication like immunosuppressants or due to a disease that causes and increase in loss of antibody or a decrease in antibody production(Viallard, 2023). The result of

these defects is that the patient does not produce sufficient antibodies resulting in frequent infections especially upper respiratory tract infections. Diagnosis is often made in the second or third decade of life.

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Multiple Choice Questions

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