Hyper IgM Immunodeficiency

Case Study

- A five year old child came to the hospital having an infection symptoms. Upon examination he was diagnosed to be ethmoditis
- Upon taking history:

1. His Mother reported recurrent sinus infections since he was one year old
2. He had pneumonia from an infection with *pneumocystis carinii* when he was three years old

Blood test

- WBC Count :4200 → Low
- Neutrophils ratio : 26% → Low
- Lymphocytes: 56% →Normal
- Monocytes :28% → High

After treatment with AB's his Immunoglobulins levels where calculated :

-IgG:25 mg per dL,(normally it should be between 600-1500).

-IgA was undetectable(normally it should be 150-220)

-IgM was elevated at 210,(normally 75 to 150)

Thus we conclude that IgM was High , and Others Ig's were Low

A biopsy was taken from Lymph Nodes. No germinal centers where found.

→ No B-cell Proliferation !

He had Blood type O and shows reaction against blood group A and B however activated B-cells had ONLY IgM and IgD on their surface .

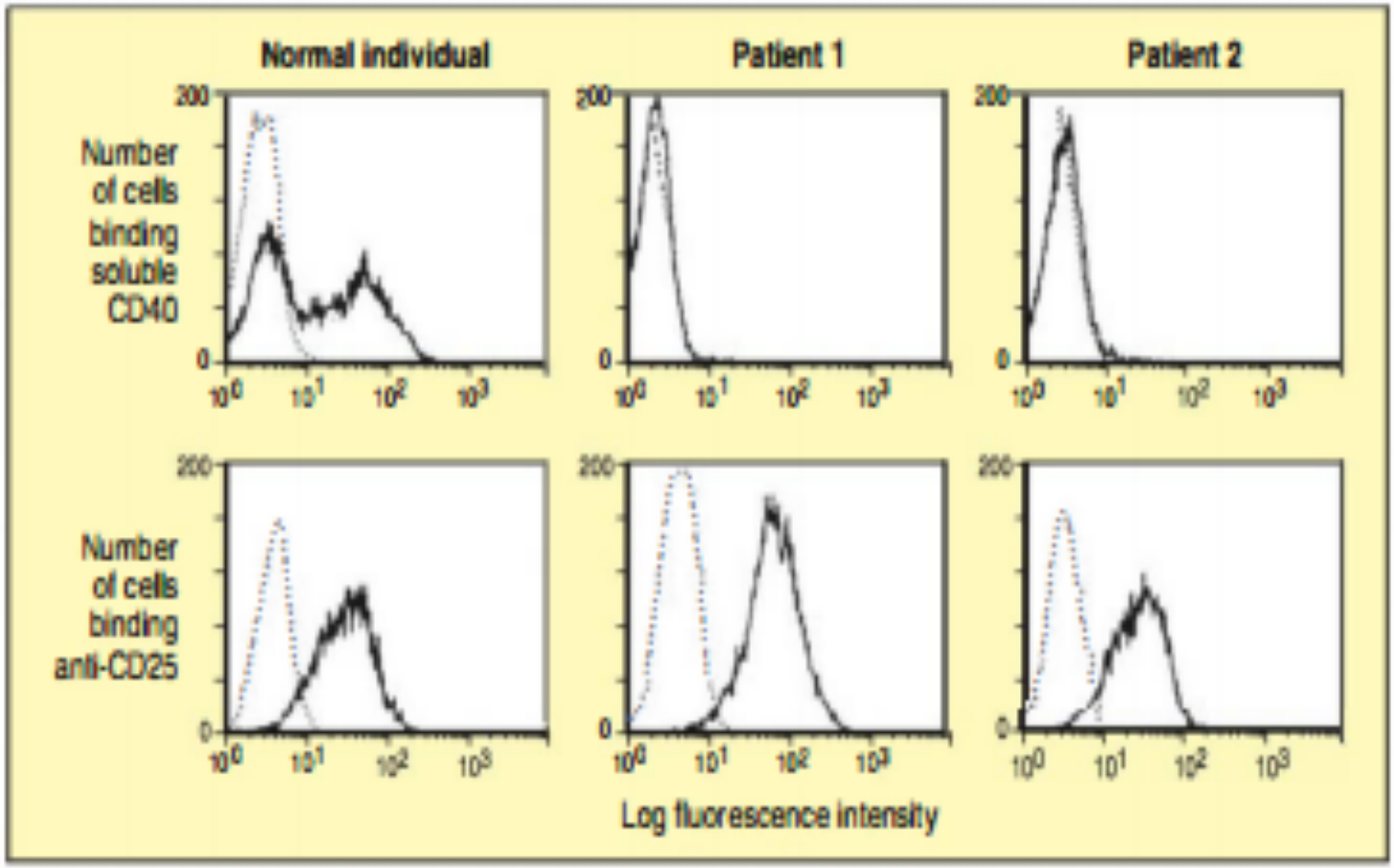
Further studies showed that he had :

-11% reacted to CD19 → B-Cells however they only have IgM or IgD on their surfce

-87%reacted To CD3 → T-cells

-2% reacted to CD25 → NK cells

However His Activated T-cells did NOT bind to CD40


Normal individual
Patient 1
Patient 2
Number of cells binding soluble CD40
Number of cells binding anti-CD25
200
0
10^0
10^1
10^2
10^3
Log fluorescence intensity

- He was given DPT toxoid as well as typhoid vaccine however after 14 days no antibodies were detected

So there is No action towards specific Ag's

This Patient had an Older brother and sister both are normal and there was no family history of unusual susceptibility to infections.

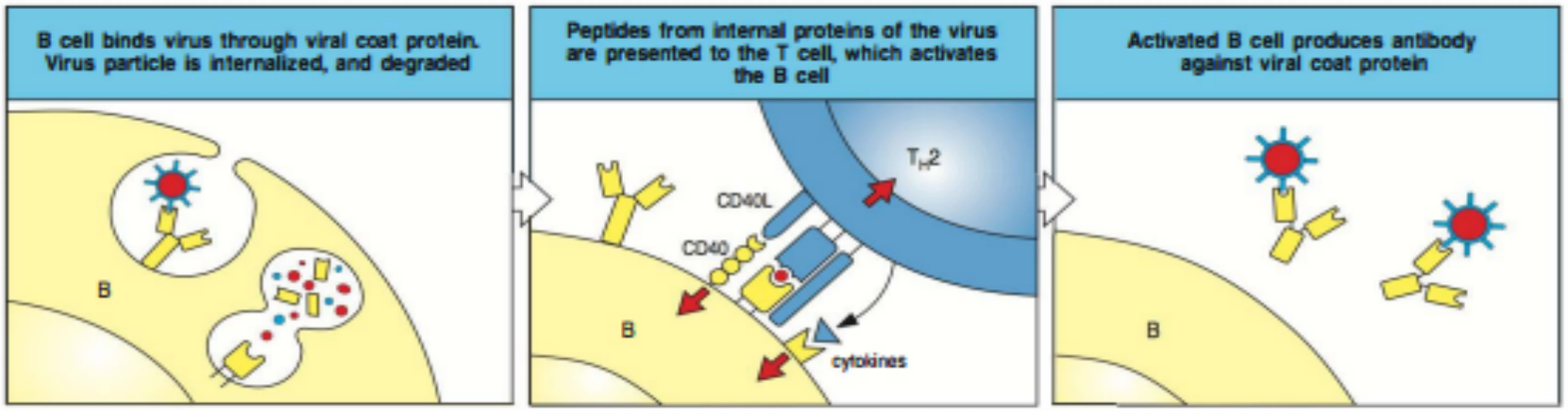
That was the Case of Dennis Fawcett, and he was diagnosed By Hyper IgM immunodeficiency And his Treatment was by giving him IV Gammaglobulins each month , he remained free of infections

- In order to understand this case ,Lets recall some Points.
- For B-cell activation we need two signals :

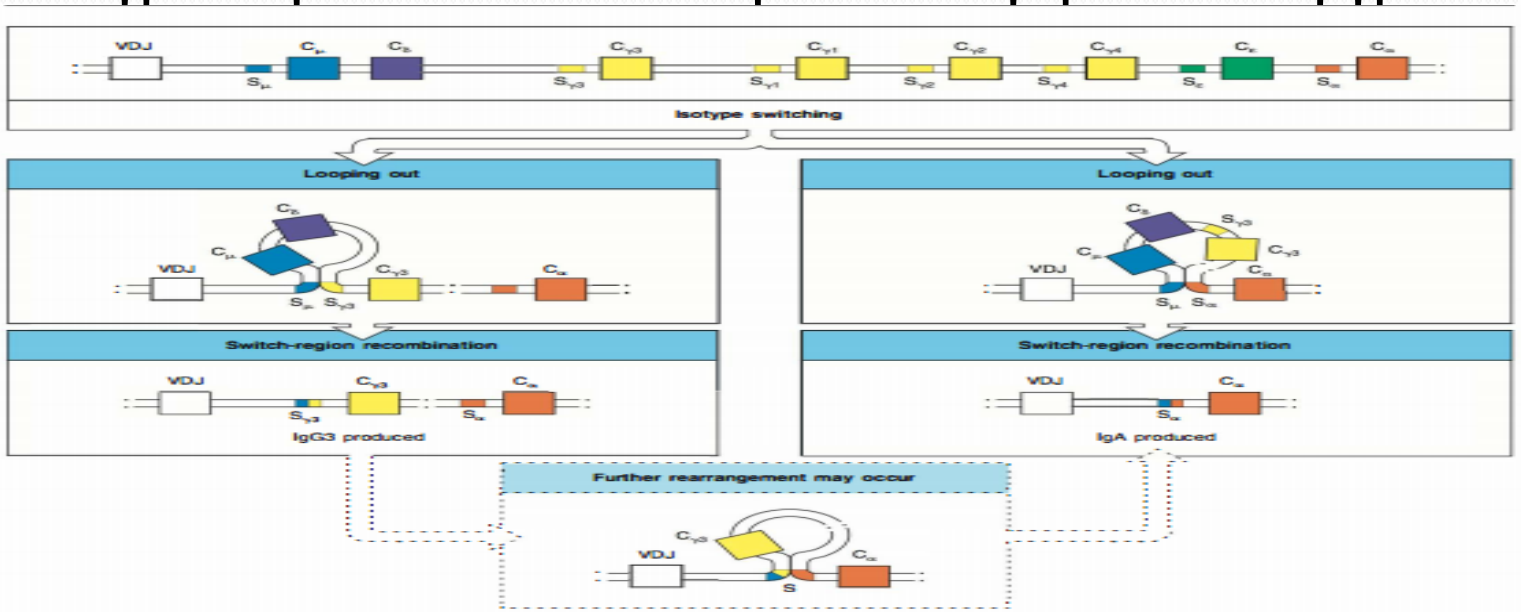
- BCR binding to Ag.
- Co-stimulation by

T-cell dependent that include CD40 and CD40L

T-cell Independent that include **IFNγ** or cytokines



- The first Ig to be produced is IgM or IgD then later on some events will cause class switching to other types, and this doesn't not require any enzymes since there is no switching domain between them , each VDJ have Cd and Cm and then its spliced to yield one of them.



- The CD40L found on T-cell and it was encoded by short arm of chromosome X . Its Important for Co-stimulation after binding with CD40 receptor found on B-cell .
- Now in case of these patients they don’t express the CD40L thus no co-stimulation of B-cell and no Class switching occur !

- To go more in details, Hyper IgM immunodefficieny is hereditary disease caused by mutation of CD40L . Its X-liked so Mainly Males are affected .
- Patient have BOTH the humoral immunity and cell-mediated immunity defects !

Humoral Immunity defects

- First of all its not FULL loss since B-cell have a Loop which is co-stimulation by Independent pathway however its defect since dependent pathway (which include t-cell)is not found so Class switching will Not occur Only IgM produced → leaving these patients susceptible to many bacterial, viral and parasitic infections !

That's why patient rejected the Blood

Cell-mediated Immunity defects

- This mainly depend on the fact that CD40L is Important for Macrophages activation . And aslo activated T-cells and Macrophages tend to produces GM-CSF. In this patient there is no activation → No GM-CSF produced →failure to develop leukocytosis secondary to neutropenia !
- Note that neutropenia is prominent feature of this disease and lead to blisters in their month , throat, and sever sores due to bacterial infections.

- How did we Rule Out SCID or Omenn Syndrome ?

B-cells were detectable

- How did we Rule Out MCH II deficiency?

Neurtopenia and normal leukocytes count , also we can notice that IgM was high.

- Why did he show reaction against A and B blood types, but Not against the DPT toxiod?

Since response against the blood types didn't require specific B cell activation so in that case it was independent activation however we need specific Tcell dependent activation for the DPT .

- He had High IgM however he was still susceptible to infections ,why ?

  Since IgM is a mainly for activation of complement system and some neutralization so at some point the bacteria will be able to overcome the complement system and causes infection, however the one responsible for opsonization and phagocytosis of pyogenic bacteria is IgG

- Will newborn show symptoms early in

  ] No, because he will have IgG and IgA from his mother as passive immunity .

- Why did the patient have high monocytes count ?

  Since the body is trying to compensate and fight infections using the innate immune system .

Thank you!

Questions ??