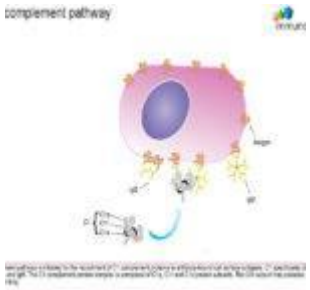
4 year old boy with recurrent bacterial infections



Patient presentation

A four and a half year old boy presents with pyrexia, neck stiffness and a purpuric rash.

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

- At age three years he had his first episode of meningococcal meningitis, from which he made a full recovery. At the time of contracting meningococcal

meningitis he was on antibiotics for an upper respiratory infection he had contracted two weeks previously. Therefore no organisms were isolated from the CSF. There were no known contacts for meningitis at time of infection.

- At age three years and four months he suffered from another episode of bacterial meningitis. No culture was requested.
- At age four years he was diagnosed with meningococcal septicaemia. He made a full recovery with no sequelae.
- The infections were described as relatively ‘mild’ by the referring doctor.
- Other than the above mentioned infections this patient has developed consistently and well and is growing on the 50th centile for weight and height.
- All routine childhood vaccinations were given.
- His family history, including that of his two older female siblings is normal.
- The patient lives at home with his parents and two siblings in a 2 bedroom house with running water and electricity.

Differential Diagnosis

- Meningococcal meningitis
- Meningococcal septicaemia
- Base of Skull (BOS) fracture with cerebral spinal fluid leakage.
- Complement Deficiency
- Selective Antibody Deficiency

Examination

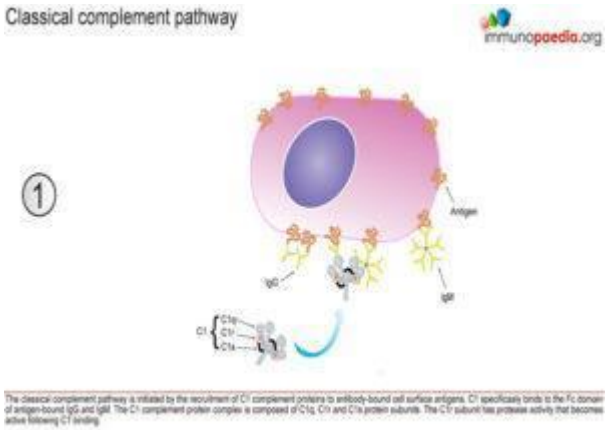
- Axillary temperature, 38.5 ˚C
- Purpuric rash with petechiae noted on the trunk and legs
- Neck stiffness elicited both Kernig and Brudzinski signs
- Generally patient is lethargic

Investigations

rine dipstick	**Normal**
Full blood count	WBC 21 000 with (L) shift
	Hb and platelets – normal
Blood Cultures	MCS – N. meningitides
Lumbar Puncture	Contraindicated
Serum Immunoglobulins	IgG – normal
	IgM – normal
	IgA – normal
Pneumococcal antibody	Present, protective
Peticheal Smear	Gram negative diplococci (see slide)
Total Serum Complement	Less than 25% (Normal 80-100%)
Complement Fraction	Complement levels:
	C1q – present
	C1r – present
	C1s – present
	C2 – present
	C3 – 92mg/dl (N)
	C4 – 25mg/dl (N)

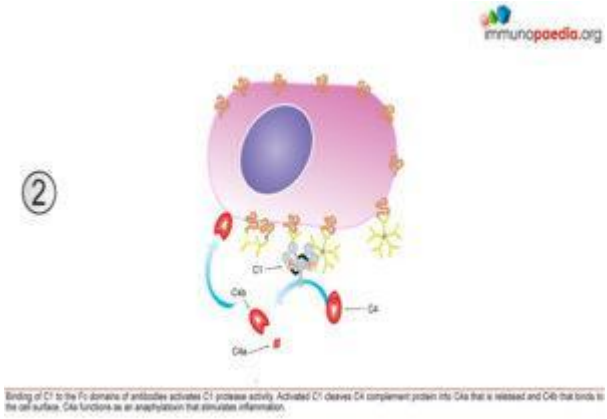
rine dipstick	Normal
	C5 – present
	C6 – absent
	C7 – present
	C8 – present
	C9 – present
	Results show that the total complement activity is abnormally low.
Gel precipitation	Shows an absence of C6 precipitation

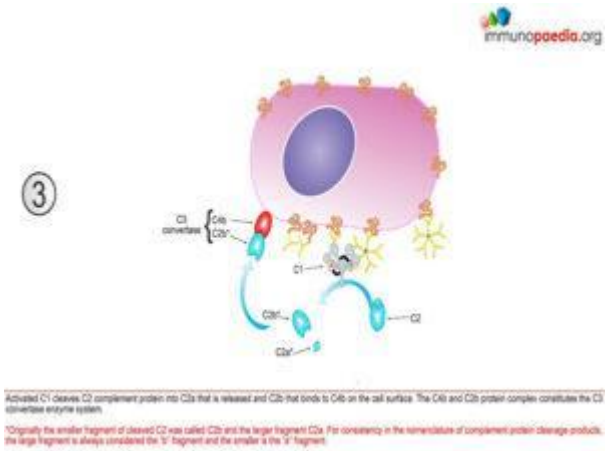
Discussion



Deficiencies in complement predispose patients to infection via two mechanisms:

1. ineffective opsonisation
2. defects in lytic activity (defects in MAC)





The 3 complement pathways (Classical, Alternative and Mannose-Binding Lectin) converge at the component C3. Although each pathway is triggered differently, the common goal is to deposit clusters of C3b on a target.

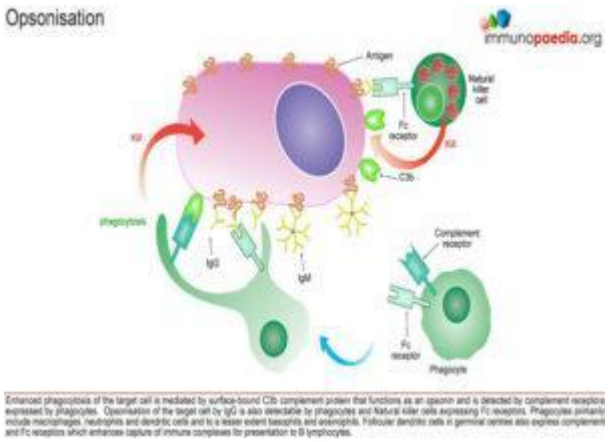
This deposition provides for the assembly of the membrane attack complex (MAC), components C5b-9.

The MAC exerts powerful killing activity by creating perforations in cellular membranes.

Individuals with complement deficiencies that hinder Opsonisation have C3 deficiency and commonly get recurrent infections of *S. pneumoniae*.

Deficiencies of early classical pathway components (C1, C4, C2) do not usually predispose individuals to severe infections but are associated with autoimmune disorders, especially SLE and recurrent upper respiratory tract infections.

Patients with a defect in formation of the MAC (late complement components) are at high risk for recurrent infection with *Neisseria gonorrhoeae* or *Neisseria meningitidis*.



Severe pyogenic infections and sepsis reoccur in children and neonates who have a deficiency of a MAC component.

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Treatment

- Empirically dosed systemic Penicillin for current infection.
- Prophylaxis with oral or IM Penicillin for life.

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Final outcome

Currently he is well and exhibiting a good response to Penicillin treatment.

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Evaluation – Questions & answers

Explain why you would request Complement Function tests in the light of the possible Immunodeficiencies that you are expecting.

Total Serum Complement is a screening test for the Complement Cascade Functional Assay (must be transported on ice).

If low activity is documented this indicates deficiency in complement factors. Specifically deficiency of C6, 7, 8, 9 indicates a susceptibility to neisserial organisms.

What is the role of complement in the normal function of the immune system?

Complement consists of cell surface proteins and a system of serum proteins which interact with one another as well as with other molecules of the immune system. These affect both the innate and adaptive immune responses.

The three pathways of activation depend on the initiating stimulus:

- Classical complement pathway is activated by antigen-antibody complexes
- Alternative pathway by microbial surfaces
- Lectin pathway by plasma lectins that bind to microbes

Each of the pathways consist of a cascade of inflammatory mediators and opsonins and leads to a lytic complex that inserts into the cell membrane

Why is the patient not unusually susceptible to other microorganisms ?

The patient has normal opsonization for bacteria because of intact activation via complement C3. The terminal complement components C5-C9 form the membrane attack complex (MAC). This serum bactericidal activity is crucial in the defense against Neisseria species, but interestingly not to a variety of other gram negative organisms which require bactericidal activity. So with this deficiency it is only Neisseria species that the patient is susceptible to.

What are guidelines to management of this patient to prevent recurrences of these infections?

- Prophylactic Penicillin daily PO (Pen K) or IMI 3 weekly (Bicillin)
- Boosting of immune response with meningococcal vaccine

- Screen for and treat carriers in the house
- Screen family for Complement deficiency
- Medical Alert Badge

Why would you request a Pneumococcal antibody test even though the Serum Immunoglobulins (SeIg) are normal?

Significant Functional Antibody Deficiencies can occur despite normal SeIg levels. These can be selective for specific organisms particularly for the Pneumococcal infections. The first two episodes of recurrent meningitis had no culture isolate and therefore cannot be assumed to have been due to N.Meningitidis.
If the patient had repeated low or absent SeIg of the IgG class, which organ systems would you expect to be involved with recurrent infections?

Upper respiratory tract – sinusitis, otitis media
Lower respiratory tract – pneumonia, empyema
GIT – diarrhea and particular susceptibility to Giardia lamblia infection
General Failure to Thrive

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