Hereditary Angioedema

Faculty of Medicine
Subject : Immunology
Instructor : Dr. Mohammad Altamimi

Student Name: Balqees Attarakih
Reg. No.: 0140609

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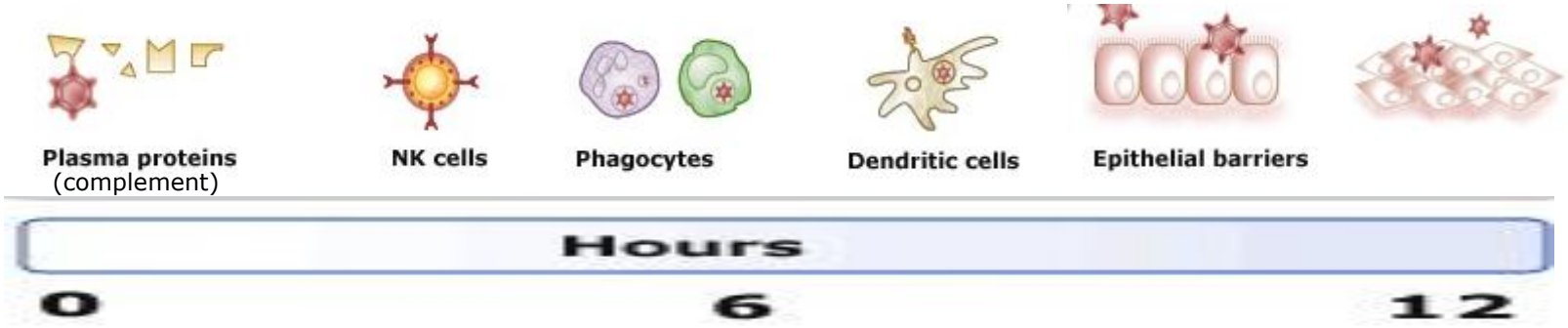
The Innate Immune system (Non-specific or in-born immunity system)

- Nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body.
- These cells are active since birth, and are generally inherited from parents and passed to offspring.
- They recognize all types of pathogens, including viruses, bacteria, fungal organisms, etc. (Non-specific).
- The components of the innate immune system :



Figure(1): The components of the innate immune system.

The complement system

- Consists of small proteins found in the blood, synthesized by the liver, and normally circulating as inactive precursors (pro-proteins).
- When stimulated, they are cleaved by proteases in the system and initiate an cascade producing active components that destroy and eliminate pathogens.
- The complement system is composed of 3 pathways :

1. The Classical pathway
2. The Alternative pathway
3. The Lectin pathway

The three pathways of the complement system:

Classical pathway	• Activated by Antigen-Antibody complex, or antibodies bound on the surface of an pathogen.
Alternative pathway	• Spontaneously activated complement component binds to the surface of a pathogen.
Lectin pathway	• Mannan-binding lectin binds to mannose-containing carbohydrates on bacteria or viruses.

Table(1): The three pathways of the complement system.

- The C3 convertase of the pathways are different but they are functionally the same.
- The early part of each pathway is a series of proteolytic cleavage events generating a convertase (a serine protease).
- This convertase cleaves complement protein C3, initiating the effector action of the complement.

The case of Richard Crafton

Richard Crafton was a 17-year-old high-school senior when he had an attack of severe abdominal pain at the end of a school day. The pain came as frequent sharp spasms and he began to vomit. After 3 hours, the pain became unbearable and he went to the emergency room at the local hospital[1].

At the hospital, the intern who examined him found no abnormalities other than dry mucous membranes of the mouth, and a tender abdomen. There was no point tenderness to indicate appendicitis[1].

Richard continued to vomit every 5 minutes and said the pain was getting worse. A surgeon was summoned. He agreed with the intern that Richard had an acute abdominal condition but was uncertain of the diagnosis. Blood tests showed an elevated red blood cell count, indicating dehydration[1].

The surgeon decided to proceed with exploratory abdominal surgery. A large midline incision revealed a moderately swollen and pale jejunum but no other abnormalities were noted. The surgeon removed Richard's appendix, which was normal, and Richard recovered and returned to school 5 days later[1].

The case of Richard Crafton

What Richard had not mentioned to the intern or to the surgeon was that, although he had never had such severe pains as those he was experiencing when he went to the emergency room, he had had episodes of abdominal pain since he was 14 years old[1].

No one in the emergency room asked him if he was taking any medication, or took a family history or a history of prior illness. If they had, they would have learned that Richard's mother, his maternal grandmother, and a maternal uncle, also had recurrent episodes of severe abdominal pain, as did his only sibling, a 1 9-year-old sister[1].

As a newborn, Richard was prone to severe colic. When he was 4 years old, a bump on his head led to abnormal swelling. When he was 7, a blow with a baseball bat caused his entire left forearm to swell to twice its normal size. In both cases, the swelling was not painful, nor was it red or itchy, and it disappeared after 2 days[1].

At age 14 years, he began to complain of abdominal pain every few months, sometimes accompanied by vomiting and, more rarely, by clear, watery diarrhea[1].

The case of Richard Crafton

Richard's mother had taken him at age 4 years to an immunologist, who listened to the family history and immediately suspected hereditary angioedema. The diagnosis was confirmed on measuring key complement components C11NH levels were 16% of the normal mean and C4 levels were markedly decreased, while C3 levels were normal[1].

When Richard turned up for a routine visit to his immunologist a few weeks after his surgical misadventure, the immunologist, noticing Richard's large abdominal scar, asked what had happened. When Richard explained, he prescribed daily doses of Winstrol {stanozolol)[1].

This caused a marked diminution in the frequency and severity of Richard's symptoms. When Richard was 20 years old, purified C11NH became available; he has since been infused intravenously on several occasions to alleviate severe abdominal pain, and once for swelling of his uvula, pharynx, and larynx[1].

The infusion relieved his symptoms within 25 minutes. Richard subsequently married and had two children. The C11NH level was found to be normal in both newborns[1].

The complement proteins of the classical pathway

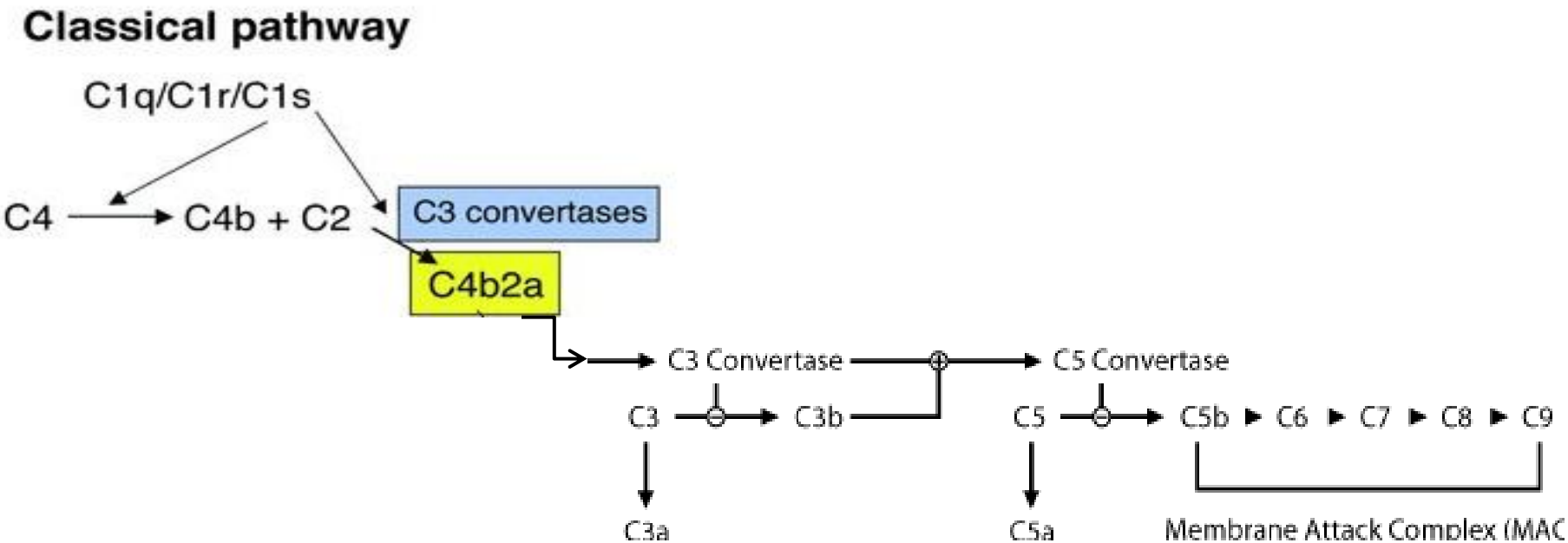
C1	C1 inhibitor	C3 convertase	C5 convertase
•A complex of C1q ,C1r & C1s with six globular heads and a tail. •Binds to IgG or IgM; due to their ability to fixate and activate complements. •Binding occurs on the Fc portion.One IgM is enough for activation, because IgM is a pentamer. •Multiple molecules of IgG , because more than one globular head is needed for activation.	•Is the only inhibtor of this pathway , it also reglulates the serine proteases of the clotting and kinin system.	•Produces C3a and C3b • C3a mediates inflammation and phagocytic recruitment. •C3b mediates opsonization and removal of immune complexes.	•Produces C5a and C5b. •C5a mediates inflammation and phagocytic recruitment.
C2 and C4			

Table(2): The proteins of the classical complement system.

The classical pathway

- Links the adaptive humoral immune response to the complement system by binding to antibodies.
- It is activated by:
  - The binding of the complement protein C1q to Antigen:Antibody complex , antibodies bound on the surface of an pathogen.
  - It can occur spontaneously at low levels.
  - It can also be trigged further by plasmin (a protease of the clotting system).

The classical pathway activation steps:



Nomenclature:

C1 = C1q+(Cr)2+(Cr)2

C3 convertase = C4b+C2a (C4b2a)

C5 convertase = C4b+C2a+C3b (C4b2a3b)

Figure(2): The activation steps of the classical pathway.

The classical pathway activation steps:

1. More than one of **C1q** globular heads binds to the Fc pieces of the antibodies activating C1r .

2. **C1r** cleaves the proenzyme C1s.

3. **C1s** is a serine protease , it is going to act on two complement proteins C2 and C4 .

4. Producing **C4b** and **C2b** The C4b,2b is the C3 convertase of the classical pathway.

5. The **C3 convertase** cleaves C3 into C3a and C3b.

6. **C3b** binds to C3 convertase forming C5 convertase

7. **C5 convertase** cleaves C5 into **C5a** and **C5b** .

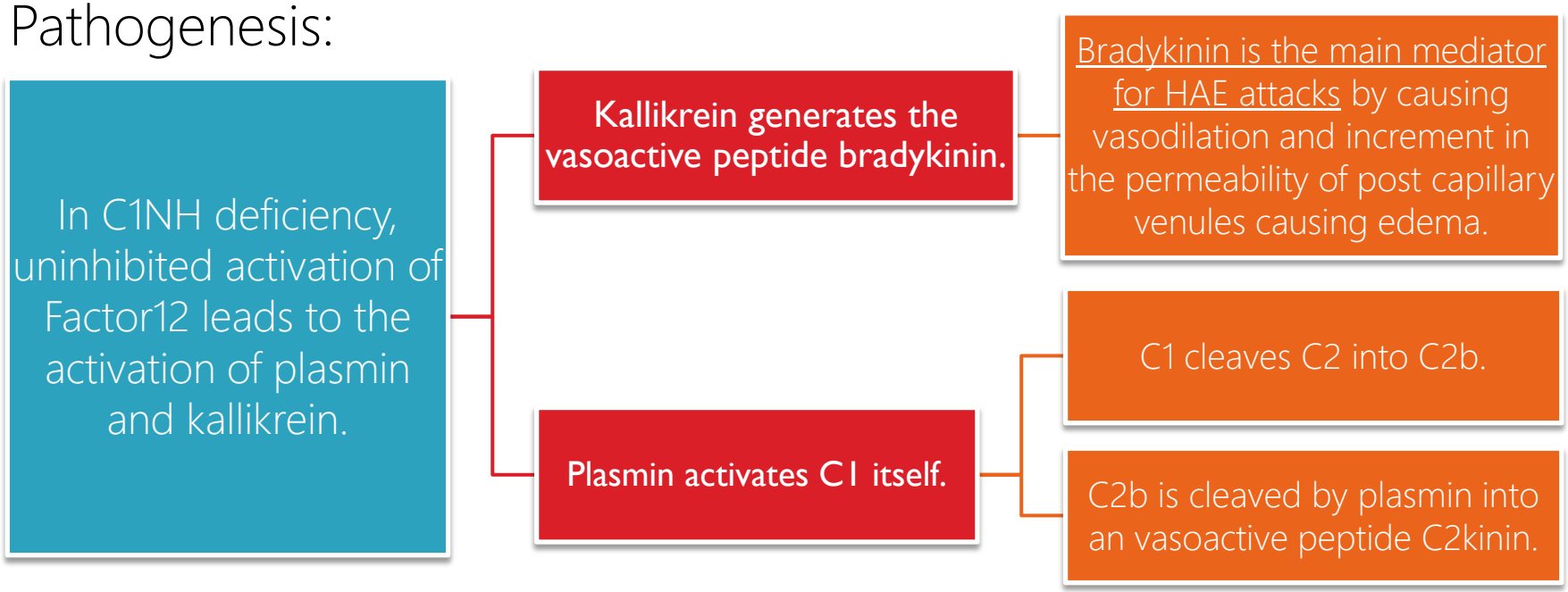
8. C5 triggers the terminal components to assemble into a membrane-attack complex (MAC) that damages the membrane of the pathogen.

Figure(3): The activation steps of the classical pathway.

Hereditary Angioedema (HAE)

- It is a disease caused by genetic deficiency of C1INH.
- It is not an allergic disease so it doesn't involve itching.
- C1INH inhibits serine proteases in normal conditions, when it is deficient these proteases are going to be activated .

Pathogenesis:



Figure(4): The pathogenesis of Hereditary angioedema (HAE).

Symptoms of Hereditary Angioedema (HAE)

Recurrent episodes of circumscribed swelling of the skin , intestines and airways occur , not painfull nor red or itchy.

If the swelling did occur in the intestines it causes severe abdominal pain and obstructions resulting in vomiting.

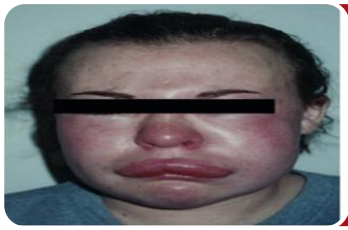
If the colon gets affected it will cause watery diarrhea.

If the larynx gets swollen, it's the most dangerous symptom, the patient might choke to death.

As a result of the edema , which is the movement of the fluid from the vascular spaces to other regions ,it causes the symptoms of dehydration.

Table (3): The symptoms of Hereditary angioedema (HAE)

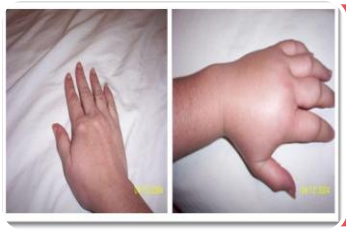
Symptoms of Hereditary Angioedema (HAE)



Figure(5): Lip swelling caused by HAE.

Figure(6): abdominal swelling caused by HAE.

Figure(7): Face swelling cause by HAE.



Figure(8): Hand swelling cause by HAE.

Stimuli, clinical findings and treatment of HAE

- **Stimuli for HAE attacks:** 1. trauma 2.mental stress 3. excessive exercise 4. extreme temperature 5.menstrual periods 6. some drugs like: (oral contraceptives and angiotensin converting enzyme inhibitor).

- **Clinical findings :**
  - Elevated Red blood cell count ,due to dehydration.
  - C1NH levels are 16% of the normal mean (16 to 33 milligrams per deciliter)[2].
  - C4 levels are decreased while C3 levels are normal.

- **Treatment (for preventing attacks and acute episodes):**
  - Purified or recombination C1NH.
  - Kallikrein inhibitor and bradykinin receptor antagonist.

Questions related to Richard Crafton's case

1) Activation of the complement system results in the release of histamine and chemokines, which normally produce pain, heat, and itching. Why is the edema fluid in HAE free of cellular components, and why does the swelling not itch?[3]

- Because HAE isn't an allergic disease, so it is not mediated by histamine and thus doesn't cause pain, heat, and itching and no recruitment of cells to the site of release.

1) What is stanozolol, and why was it prescribed? [3]

- It is a synthetic anabolic steroid , effective in controlling the frequency and severity of attacks of Angioedema and in increasing serum levels of C1 INH and C4.

Questions related to Richard Crafton's case

3) Richard has a markedly decreased amount of C4 in his blood. This is because it is being rapidly cleaved by activated C1. What other complement component would you expect to find decreased? Would you expect the alternative pathway components to be low, normal, or elevated? What about the terminal components? [3]

- C2 , because it is also cleaved by activated C1.
- Normal , because HAE does only affect complement proteins C4 and C2.

3) Despite the complement deficiency in patients with HAE, they are not unduly susceptible to infection. Why not? [3]

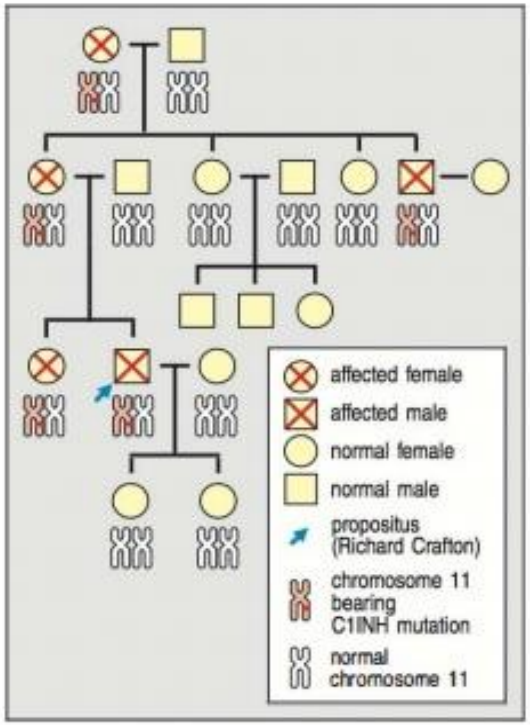
- Because the other complement system pathways are still active and they will therefore compensate.

Questions related to Richard Crafton's case

5) Emergency treatment for HAE cases is sometimes necessary because of airway obstruction. In most cases, however, a patient with obstruction of the upper airways is likely to be suffering from an anaphylactic reaction. The treatment in this case would be epinephrine. How might you decide whether to administer epinephrine or intravenous C1/NH? [3]

- We administer epinephrine ,if the patient improves then it is an anaphylactic shock , if not then it is HAE and we administer intravenous C1NH in this case.

Questions related to Richard Crafton's case



Figure(5): The inheritance of Hereditary Angioedema in Richard's extended family.

6) Figure (5) shows Richard's family tree. What is the mode of inheritance (dominant or recessive, sex-linked or not) of HAE? Can Richard's two children pass the disease onto their offspring? [3]

- Autosomal dominant
- Yes , if his wife is not diseased there is a chance of 50% that his children will be diseased.

References

1. Case Studies in Immunology: A Clinical Companion, 7th Edition ,page 183
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Thank you