

Case Report: Complement and infection susceptibility

## Diagnosis of complete deficiency of C2

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### Case Presentation

The patient was a 14-year-old girl who has healthy parents and a healthy 11-year-old sister. At 10 days of age, this patient had suffered from sepsis and meningitis. Staphylococcus aureus and group B streptococci (GBS) was detected in umbilical secretions and in cerebrospinal fluid grew GBS. The girl recovered after adequate antibiotic therapy.

At age 14, the patient was suffering of meningitis again, this time caused by Neisseria meningitidis serogroup W-135. The clinical course was mild, the patient showed no neurological symptoms and recovered without complications after treatment with antibiotics.

### Evaluation and Diagnosis

Analysis of complement function with the Complement system screen Wieslab® showed no activity for the classical pathway and the lectin pathway but normal activity for the alternative pathway. Further analysis with measurement of individual components in the classical pathway (C1q, C2 and C4) revealed **complete deficiency of C2.**

### Discussion and Conclusion

Increased susceptibility for bacterial infections is seen in several types of complement deficiency. Complete deficiency of C2 as diagnosed here is rare, found in about 1/20 000 individuals. This deficiency is associated with increased susceptibility for infections with encapsulated bacteria such as pneumococci and also increased risk to develop SLE. However, many C2 deficient individuals are believed not to be diagnosed and some appear not to have increased morbidity. Analysis of complement function is the way to detect this deficiency.

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# Diagnosis of common variable immunodeficiency (CVID)

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## Case Presentation

A female 25-year-old student is suffering from recurrent upper respiratory tract infections. She has had pneumonia 3 times during the last 5 years. Six months ago she was diagnosed with autoimmune thyroiditis. Her mother has selective IgA deficiency and two cousins have celiac disease. Now she has problems to keep up with her studies due to frequent infections and she is also chronically fatigued.

## Evaluation and Diagnosis

The thyroid substitution therapy was checked and found to be adequate. Further analysis of the immune system included complement and immunoglobulins. Analysis of complement function with the Complement system screen Wieslab® showed normal activity for all the three activation pathways (classical, alternative and lectin). Measurement of immunoglobulin revealed low levels of two IgG subclasses, IgG1 and IgG2. Also IgA level was very low, below the level for IgA deficiency (0.07 g/L) but IgM was present in normal concentration. The final diagnose became **common variable immunodeficiency (CVID)**.

## Discussion and Conclusion

The symptoms of increased susceptibility for infections may have many different causes and among these are complement deficiencies. To analyze complement function is an elegant way to check for this possibility. When all pathways show normal activity as in this case, the suspicion of complement deficiency can be ruled out and the diagnostic could focus on other explanations.

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## Diagnosis of complete deficiency of C2

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### Case Presentation

A girl of 8 years of age had a sudden onset of febrile illness with headache and was taken to hospital. There she was treated with antibiotics for suspected meningitis or sepsis. Culture of cerebrospinal fluid showed growth of meningococci. Once previously when she was 2 years old, she suffered from pneumonia and sepsis caused by pneumococci. There was no family history of infection susceptibility.

### Evaluation and Diagnosis

Analysis of the immune system was performed including immunoglobulins and complement. The IgG concentration including IgG subclasses and IgM were all normal. The IgA concentration was subnormal but not as low as in selective IgA deficiency.

Analysis of complement function with the Complement system screen Wieslab® showed no activity for the classical pathway and for the lectin pathway but normal activity for the alternative pathway. Further analysis with measurement of individual components in the classical pathway (C1q, C2 and C4) revealed **complete deficiency of C2**.

### Discussion and Conclusion

Complete deficiency of C2 is associated with increased susceptibility for infections with encapsulated bacteria such as pneumococci and also increased risk to develop SLE. From the results of the functional analysis it is not possible to know if there also is an MBL deficiency since C2 is common to the classical and the lectin pathway. Measurement of MBL is then needed. There is some evidence for that a combination of a deficiency like C2 deficiency when in combination with deficiency of MBL gives increased infection susceptibility.

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## Case Report: Complement and infection susceptibility

# Diagnosis of C1q deficiency

Adapted from: Genel et al., *J Investig Allergol Clin Immunol.*, 2010

### Case Presentation

This case was an 11-year-old girl who was admitted with fever and loss of consciousness. Her medical history included bacterial meningitis at the age of 8 and pneumonia at the age of 10. The parents were first-degree cousins.

### Evaluation and Diagnosis

Meningitis caused by *Streptococcus pneumoniae* was diagnosed and antibiotics were administered. The patient was then vaccinated against meningococci, pneumococci, and *Haemophilus influenzae* type B, and penicillin prophylaxis was administered. Her antinuclear antibody and rheumatoid factor titers were negative after repeated investigations. During a 5-year follow-up, she was asymptomatic for autoimmune diseases and infections.

Immunologic studies performed when the patient had recovered revealed normal immunoglobulin levels. Alternative pathway complement activity was normal, but no classical pathway activity was detected. Levels of complement proteins C2, C3, and C4 were within normal ranges. The serum concentration of C1q was below the detection limit and further analysis led to the diagnosis of C1q deficiency. The parents and 5 siblings, who were well and had no history to suggest increased susceptibility to infection, all had normal classical and alternative pathway function, as well as normal C3 and C4 concentrations. However, in 4 of the siblings the serum concentrations of C1q were below the normal range.

Subsequent genetic analysis revealed a homozygous missense mutation in the C1q C gene causing a substitution affecting the collagen-like region of C1q and thus explaining the deficiency.

### Discussion and Conclusion

C1q deficiency is a rare but in many cases very serious deficiency although this varies between patients. The deficiency is associated with both SLE-like disease which about 90% suffer from and infections as was predominant in this case. Since there is a great variation in the symptoms treatment must be individualized. The C1q molecules are produced in myeloid cells and therefore hematopoietic stem cell transplantation has been tried in a few cases. When symptoms suggesting SLE is present an initial analysis of complement function and not only C3 and C4 is needed to not overlook this deficiency.

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Case Report: Complement and infection susceptibility

## Diagnosis of properdin deficiency

Adapted from: Genel et al., Acta Paediatr., 2007

### Case Presentation

A 5½-year-old boy of non-consanguineous parents was admitted to our hospital with meningococcal septic shock. He had previously been suffering from recurrent respiratory infections. His 13-year-old brother had also been treated for meningococcal meningitis when he was 7 years old. A 19-year old brother was healthy.

### Evaluation and Diagnosis

Immunological studies, done after recovery, on the patient and his two brothers revealed normal immunoglobulins, IgG subclasses, C3, C4 and classical pathway activity while activity of the alternative complement pathway could not be detected. Further analysis revealed a properdin concentration of <0.01 mg/L while factor D was 50% of the normal and factor B 97% of the normal. These findings confirmed the suspected diagnosis of **properdin deficiency**. The concentration of complement proteins were also studied in the family members. The two brothers of the patient were also properdin-deficient and the mother had a reduced properdin level which is seen in most female properdin deficiency carriers.

### Discussion and Conclusion

Properdin deficiency is associated with highly increased risk for Neisserial infections. The gene for properdin is located on the X-chromosome and therefore male individuals are affected. It is important to study family members to find other who also may have the same deficiency. Deficient individuals are given prophylaxis by vaccination against meningococci. Awareness of the increased risk is also important to ensure proper antibiotic therapy when needed. Analysis of complement function with the Complement system screen Wieslab® is an excellent assay for detection of all types of alternative pathway deficiencies.

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Case Report: Complement and infection susceptibility

# Diagnosis of properdin deficiency

Adapted from: Helminen et al., *Scand J Immunol.* 2012

## Case Presentation

The patient was a previously healthy boy, aged 14 years who was suspected to have meningococcal infection based on fever and skin symptoms. Preceding hospital care the patient had vomiting, loose stools and worsening arthralgia on his wrists and ankles.

Laboratory investigations revealed leucocytosis and highly increased CRP level. Since the clinical picture seemed to indicate meningococcal infection i.v. penicillin therapy was started.

## Evaluation and Diagnosis

Serology showed normal immunoglobulin and tetanus antibody levels. The C3 level was normal but C4 level subnormal.

When analyzing with the Complement system screen Wieslab® test, the functional activity of the classical pathway was normal but the functional activities of the alternative and lectin pathways were undetectable. Subsequent analysis showed no properdin protein and sequencing of the properdin gene confirmed properdin deficiency.

A mutation in exon 9 of the properdin gene at codon 388, where tryptophan was changed to a premature stop codon (W388X), was identified.

## Discussion and Conclusion

In cases with meningococcal disease the possibility of complement deficiency has to be considered. Particularly deficiencies affecting the alternative pathway are important and properdin deficiency is associated with highly increased risk for Neisserial infections.

The gene for properdin is located on the X-chromosome, i.e. male individuals are affected and family members should be investigated. Prophylaxis by vaccination using tetravalent meningococcal vaccine may prevent additional life-threatening infections in family members with properdin deficiency. This was the first case in a family in Finland where a mutation in the properdin gene was reported.

The Complement system screen Wieslab® is an useful assay suited for detection of all types of alternative pathway deficiencies.

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Case Report: Complement and infection susceptibility

## Diagnosis of complete factor B deficiency

Adapted from: Slade C et al., *N Engl J Med*, 2013

### Case Presentation

A 32-year-old woman with recurrent pneumococcal and meningococcal infection. Clinically significant infections dating from childhood included primary pneumococcal peritonitis at the age of 2 years. Two years later, she was treated for community-acquired pneumonia.

At 15 years of age, she developed meningitis (N. meningitidis, serogroup Y) and at age 30, she suffered from pneumococcal pneumonia complicated by a unilateral empyema.

### Evaluation and Diagnosis

Screening tests revealed normal immunoglobulins and lymphocyte subsets. Using the Complement system screen Wieslab® normal classical pathway activity was demonstrated but the alternative pathway was inactive.

Studies showed that the activity of the alternative pathway was restored to the patient's serum by properdin-deficient serum but not with factor B-depleted serum. Factor B was undetectable by means of radial immunodiffusion and ELISA indicating **complete factor B deficiency**.

Genome sequencing of the factor B gene revealed compound heterozygous mutations. These mutations were also identified in the mother and father, respectively. The patient received tetravalent meningococcal vaccine, 23-valent pneumococcal polysaccharide vaccine, as well as continuous prophylactic amoxicillin, and she has not had any further severe infections.

### Discussion and Conclusion

In cases with meningococcal disease the possibility of a complement deficiency has to be considered, especially deficiencies affecting the alternative pathway.

Several cases with properdin deficiency and a few with factor D deficiency are previously described, but this is, to our knowledge, the first case report of complete factor B deficiency. The findings confirm the crucial role of the alternative complement pathway in protection against infection by organisms causing meningitis.

This case clearly demonstrates the usefulness of functional assays for screening of complement deficiencies. The use of such tests means that more deficiency cases can be found and thus also that appropriate treatment can be given to the deficient individuals and when needed their family members.

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