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Fever, rash, and arthralgias in a male adolescent

A previously healthy 15-year-old boy presented with a 6-week history of intermittent fever, diffuse erythematous rash, and polyarthralgias. Evaluation in a community hospital revealed no laboratory abnormalities, and a provisional diagnosis of Still's disease was made.

The patient was afebrile at the time of admission. There was an erythematous maculopapular rash distributed over the extremities, including the palms and soles; some lesions had ecchymotic centers. There was no active synovitis. The remainder of the physical examination was unremarkable. He was evaluated for fever of unknown origin. Two blood cultures grew *Neisseria meningitidis*.

1 Which of the following additional studies would most likely be abnormal?

- ☐ Rheumatoid factor
- ☐ Antinuclear antibody
- ☐ Total hemolytic complement
- ☐ IgG
- ☐ IgM

Still's disease was considered unlikely in this patient because of the nature of the rash. (The rash in Still's disease is evanescent and is usually present only during bouts of high fever.)

Even if it were suspected, rheumatoid factor is typically negative in Still's disease and other forms of juvenile arthritis.

Antinuclear antibody, positive in most patients with systemic lupus erythematosus and females with oligoarticular juvenile chronic polyarthritis, would not be expected to be positive in this male without typical signs and symptoms of either of these conditions. One must always keep in mind the high false positive-rate of this test and be prepared to discount a positive result in a patient with an unusual clinical picture and no corroborative laboratory results.

Hypogammaglobulinemia would be unlikely in a 15-year-old patient with no history of infection, and selective IgM and IgG deficiencies generally do not present with chronic meningococcemia, but rather with gram-positive bacterial infections.

DETECTING "LATE" COMPLEMENT DEFICIENCIES

The most likely immune defect in a patient presenting with chronic meningococcemia is deficiency of a "late" complement component (C6, C7, or C8).[1] The simplest screening test for this is a measurement of total hemolytic complement, which tests the integrity of the classical complement pathway.[2] Once this test establishes the existence of a deficiency, one can easily identify the missing component by adding single purified complement components to the patient's serum and determining which one restores hemolytic activity. In this patient, there was a total C7 deficiency.[3]

A recently reported, rarer form of complement deficiency is associated with neisserial infection. Lacking in this condition is properdin (factor P), which stabilizes the C3bBb intermediate complex during activation of the alternative complement pathway.[4] This X-linked defect would not be detected by the total hemolytic complement assay and would

require direct measurement of the serum properdin level for documentation.

2 The patient had two sisters, both clinically well. There was no history of recurrent infections in the family. What is the probability of the occurrence of the same abnormality in each of the sisters?

- ☐ < 1%
- ☐ 25%
- ☐ 30%
- ☐ 50%
- ☐ 100%

THE GENETICS OF COMPONENT DEFICIENCIES

Normal levels of C6, C7, and C8 require genes from both parents. If one parent has only one gene (ie, is heterozygous) for one of the components, the parent has a half-normal level of that component, and the child has a 50% chance of also being heterozygous and having a half-normal level. If both parents are heterozygous, there is a 25% chance that any child will have a total deficiency of the component, a 50% chance of a partial deficiency, and a 25% chance of a fully normal level. In the much less likely event that one parent has a total deficiency and the other a half normal level, there is a 50% chance of total deficiency in the offspring and a 50% chance of a half-normal level.

Thus, expression of each of the late-acting complement components is inherited independently as an autosomal codominant trait, and, in all likelihood, any sibling of a person with a total deficiency (such as our patient) would have a 25% chance of also having a total deficiency. The genes for C6 and C7 are closely linked, and deficiencies of both in the same patient have been reported.[5]

In fact, in this patient's family, both parents were heterozygous with half-normal levels of C7. One sister was totally deficient, and the other had a half normal level. Both, as noted, were perfectly healthy, and this condition would not have been detected if the patient had not developed chronic meningococcemia.

3 The patient responded rapidly to intravenous penicillin G, with which he was treated for 14 days. In addition to that, what else should he have received?

- ☐ Fresh-frozen plasma
- ☐ Plasmapheresis
- ☐ High-dose prednisone
- ☐ IV immunoglobulin
- ☐ None of the above

Deficiency of complement components C3 and C5 markedly increases the likelihood of certain serious infections, and patients with these abnormalities clinically resemble patients with hypogammaglobulinemia in the frequency, though not necessarily the spectrum, of infections.

In these cases, monthly administration of fresh-frozen plasma as a source of complement may be indicated. This is costly and not without risk, however, and for these reasons it is not indicated in patients with late complement component deficiency, who get infected only occasionally and respond well to antibiotics.

Plasmapheresis, prednisone, and intravenous immunoglobulin would be of no help and are not indicated.

Thus, the correct answer is none of the above. Some studies have been done on immunization of late complement component deficiency patients with meningococcal antigens.[6] The limited success of this is not surprising, considering that the highest levels of antibody before vaccination were found in patients with homozygous deficiency of C6, C7, or C8, intermediate levels in heterozygous persons, and lowest levels in normal individuals.[7] Although opinions differ, we believe that vaccination is not helpful.

4 What is the patient's risk of reinfection with *N meningitidis*?

- ☐ Less than normal
- ☐ About the same as anyone else's
- ☐ Greater than normal
- ☐ Inevitable

Although the basis for the specific susceptibility to disseminated neisserial infections in patients with late complement component deficiency is not known, the risk of reinfection is clearly greater than normal.[6] Our patient, in fact, had another bout of chronic meningococcemia 3 years after his original presentation. Because of his history, the diagnosis was easily made, and he was retreated. For the past 15 years, however, he has had no recurrence, and the C7-deficient sister has never had a systemic infection. Thus, reinfection is not inevitable, but the likelihood of reinfection appears to be greater than normal.

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