CASE REPORT

Normal complement C4 values do not exclude hereditary angioedema

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This report describes a patient with hereditary angioedema (HAE) in whom complement C4 values were consistently normal. There was a family history of HAE, for which the patient had previously been screened, but in view of her normal C4 values she was deemed unaffected. However, at 10 years of age she presented with an eight month history of episodes of swelling affecting her hands and recurrent episodes of abdominal pain over the previous few months. In view of the recent clinical history of swellings and the family history of HAE, C4 and C1 inhibitor (C1inh) were measured. The C4 concentration was found to be within the normal range but the C1inh value was low (0.07 g/litre; normal range, 0.18–0.37). The patient was started on tranexamic acid and at an outpatient review three months later her episodes of swelling were occurring less often and were less severe. Although recent papers have suggested that the diagnosis of HAE can be excluded if complement C4 concentrations are normal, this case highlights the fact that C4 concentrations can be normal in this condition, and it is recommended that both C4 and C1inh concentrations should be measured to exclude HAE.

Hereditary angioedema (HAE) is a rare condition in which uncontrolled activation of the classical complement pathway causes recurrent swelling attacks. It is caused by a deficiency of C1 inhibitor (C1inh) protein. Patients may present with severe abdominal pain and diarrhoea if the swelling attacks affect the gut wall, and may go undiagnosed for many years if the diagnosis is not considered. Respiratory tract swelling may cause death by asphyxiation. Fortunately, both effective prophylactic treatment and treatment for the acute episodes of swelling are available. Recent papers[1 2] have suggested that the diagnosis may be excluded if complement C4 concentrations are normal; however, we report a patient in whom C4 values were consistently normal. In view of the high morbidity and mortality associated with the condition, it is essential that cases are not missed. Therefore, it is advisable that both C4 and C1inh concentrations are measured to exclude HAE.

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The patient, a 10 year old girl, was referred by her general practitioner with an eight month history of episodes of swelling affecting her hands, which occurred particularly after she had been carrying heavy shopping. She had also suffered recurrent episodes of abdominal pain over the previous few months.

Her mother had a 25 year history of episodes of tongue and limb swelling, and of acute attacks of severe abdominal pain and diarrhoea, but had only been diagnosed with HAE five years previously, at another hospital, when blood tests showed a C4 concentration of 0.11 g/litre (normal range for this laboratory, 0.25–0.65 g/litre) and a C1inh concentration of 0.09 g/litre (normal range for this laboratory, 0.15–0.35 g/litre). Her mother's symptoms had improved dramatically on tranexamic acid treatment. After her mother was diagnosed with HAE, our patient's maternal aunt (who had no history of angioedema) and her maternal uncle (who had a history of hand swelling) were tested at other hospitals and were both found to have inherited the condition. Our patient's maternal grandmother (who had a history of limb swellings) declined testing. Subsequently, our patient, who at the time had no history of swellings, had been screened at another hospital for HAE. Her C4 was 0.13 g/litre (normal range for this laboratory, 0.1–0.4 g/litre) and, according to protocol for this laboratory, no further testing was performed because it was deemed that the measurement of C1inh ''was not indicated'' because the C4 value was normal.

In view of the recent clinical history of swellings and the family history of HAE, we requested that C4 and C1inh concentrations should be analysed. C4 was measured nephelometrically (reagents from Beckman Coulter using Beckman Array 360; Beckman Coulter UK Ltd, High Wycombe, UK) and C1inh by radial immunodiffusion (reagents from The Binding Site, Birmingham, UK), according to the manufacturers' instructions. The results were as follows:

- C4: 0.15 g/litre (normal range for our laboratory, 0.1–0.4 g/litre).
- C1inh: 0.07 g/litre (normal range for our laboratory, 0.18–0.37 g/litre).

To confirm the diagnosis of HAE, a repeat sample was taken six weeks later. The results were:

- C4: 0.14 g/litre (normal range for our laboratory, 0.1–0.4 g/litre).
- C1inh: 0.07 g/litre (normal range for our laboratory, 0.18–0.37 g/litre).

The patient was started on tranexamic acid and at outpatient review three months later her episodes of swelling were occurring less often and were less severe.

DISCUSSION

In HAE, reduced concentrations of C1inh protein (type I HAE) or the presence of non-functional C1inh protein (type II HAE)[3] lead to persistently increased activation of the

Abbreviations: C1inh, C1 inhibitor; HAE, hereditary angioedema

classical complement pathway, resulting in the use and depletion of C4 and C2. In type I HAE, which accounts for approximately 85% of cases, the mutant C1inh allele produces no detectable protein. Sequence analysis has shown that Alu mediated deletions and duplications account for the most common genotypes. In type II HAE, a dysfunctional protein is produced—this is usually caused by a mutation that replaces the reactive centre arginine residue. Low, normal, or high concentrations of C1inh protein may be found, although the functional activity, which can be measured by functional C1inh assays, is always low. As a result, nearly all patients with HAE have permanently low C4 concentrations.[4] Very rarely, patients have been identified in whom C4 values are normal,[2] but the explanation for this is not known. During episodes of angioedema, the sudden increase in complement consumption means that C4 concentrations fall below the lower limit of detection of standard laboratory assays.[5] C4 concentrations may return to normal in some patients receiving prophylactic treatment, particularly if androgenic steroids or androgenic steroids and tranexamic acid are used.[6 7] C4 concentrations will also temporarily normalise after infusions of C1inh.[8]

> ''Patients may not always have a positive family history to guide the clinician towards the diagnosis''

Our case illustrates that strict adherence to laboratory protocols for the investigation of HAE is not always appropriate. Indeed, our patient had three separate estimations of C4, all of which were normal. On the first occasion, the laboratory performing the assay issued a report stating that C1inh testing ''was not indicated'' because the C4 concentration was normal. It should be noted, however, that at this time the patient had suffered no episodes of angioedema. Subsequently, she did begin to have swelling attacks and episodes of abdominal pain—and this clinical history, along with the family history of HAE, led us to measure her C1inh concentrations, despite the fact that she had normal C4 values.

It has been proposed that the measurement of C4 alone could be used to screen for HAE, and that the finding of a normal serum C4 is sufficient to exclude the diagnosis of HAE.[1 2] Our patient illustrates that this is not always the case. Indeed, in one of these studies,[2] several patients who were subsequently found to have HAE on the basis of C1inh concentrations also had normal C4 values. In addition, patients may not always have a positive family history to guide the clinician towards the diagnosis because, although HAE is dominantly inherited, there is a high new spontaneous mutation rate leading to the reduced production of C1inh or the production of a non-functional C1inh protein.[9 10] It is essential that screening protocols for a rare, but potentially fatal, condition do not miss individuals with the disease and, therefore, we suggest that both C4 and C1inh should be measured to exclude HAE.

Take home messages

- Although recent papers have suggested that the diagnosis of hereditary angioedema (HAE) can be excluded if complement C4 concentrations are normal, we report a patient with HAE in whom C4 values were consistently normal
- This disease is associated with a high morbidity and mortality, making it essential that cases are not missed, so we recommend that both C4 and C1 inhibitor concentrations should be measured to exclude HAE

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