

Hereditary angioedema and pregnancy

A successful outcome using C1 esterase inhibitor concentrate

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Hereditary angioedema is a relatively uncommon condition. It manifests as episodes of abdominal pain and angioedema and can be a painful and even life-threatening disease.¹ With respect to this disease and pregnancy, there is a paucity of information in the literature. The case below, which presents a pregnant patient with hereditary angioedema, illustrates the difficulty in diagnosing and managing the disease and the patient's successful treatment with C1 esterase inhibitor (C1-INH) concentrate given routinely throughout the full term of her pregnancy and before the cesarean section delivery.

Case description

The patient was born in January 1984. Her parents are both of Métis-Cree ancestry. It is presumed the patient's medical problems began in 1994 at the age of 10 when she had an episode of unexplained abdominal pain. In 1997 she presented with edema in her right hand, which was not associated with any noted trauma. In January 1998 she was seen for swelling in her left foot; this was attributed to wearing her friend's shoes. In May 1998 she presented with substantial swelling in her lip, which occurred after she bit her own lip. In August 1998 the diagnosis of angioedema was first entertained when she presented with the spontaneous onset of painful swelling in her right hand.

The patient was referred to a dermatologist in December 1998 and a pediatrician in November 1999; a definitive diagnosis was not established. In September 2000 she was seen in the emergency department with acute facial swelling. A pediatric consultation was obtained and testing of C1-INH levels was ordered. Her C3 level was normal with a dramatically reduced level of C4 (<0.03 g/L; normal 0.16 to 0.47 g/L) and reduced functional C1-INH (0.02; normal 0.7 to 1.30). In December 2000 she suffered an episode of uvular edema that fortunately seemed to respond to subcutaneous adrenalin.

The patient continued to suffer from attacks of abdominal pain and peripheral angioedema until August 2001 when she was admitted to the intensive care unit with oral edema. She was started on danazol 200 mg/d. By September she had experienced headaches and mood volatility, so danazol was reduced to 100 mg/d. When once again she became symptomatic, the dose was increased to 150 mg/d



Swelling in the hand caused by hereditary angioedema

then to 200 mg/d. An endocrine consultation was obtained in May 2002.

In December 2004 the patient suffered from severe abdominal pain in the right upper quadrant, which was associated with elevated liver enzymes. Because of the concern about possible hepatotoxicity from the danazol, it was discontinued. Although the cause of the right upper-quadrant abdominal pain was discovered to be cholelithiasis, the patient elected to remain off the danazol. She was first administered C1-INH concentrate in March 2005 for an episode of facial edema associated with dyspnea. Her symptoms did not progress following the infusion, and the edema lasted about half the duration of a usual attack.

In May 2005 the patient presented with a positive pregnancy test. Her last menstrual period was around April 2. She subsequently started to receive infusions of 500 U of C1-INH concentrate approximately once every 2 weeks. In October she continued to have minor episodes of extremity and facial swelling and the dose was increased to 1000 U every 2 weeks. Following the increase to 1000 U, she remained asymptomatic. Her pregnancy went postdates, and induction was attempted at 41 weeks and 3 days. After several unsuccessful attempts, the patient opted for a cesarean section, which was performed semi-electively on January 22, 2006. She received 1000 U of

C1-INH concentrate immediately before surgery and there were no complications. The baby was healthy, with an Apgar score of 7 at 1 minute and 8 at 5 minutes. The birth weight was 4111 g.


Discussion

Hereditary angioedema is an autosomal-dominant disease produced by a deficiency of functioning C1-INH. The C1-INH is a plasma protease that functions to block the activation of complement and the formation of bradykinin at multiple sites in the sequence.² Lack of this enzyme allows the complement cascade to proceed relatively unimpeded, resulting in clinical angioedema. Typical therapy has involved the prophylactic use of danazol (or other androgenic agents) at doses titrated to prevent attacks. Antifibrinolytic agents, particularly ϵ -aminocaproic acid, are less effective than the androgens but do tend to be used in prepubertal children or if androgens are otherwise not tolerated or are contraindicated. Danazol is pregnancy risk factor X.³ Aminocaproic acid is pregnancy risk factor C but owing to its thrombogenic properties poses a high risk for maternal thrombosis during pregnancy.

This case illustrates a classic presentation of hereditary angioedema and exhibits many of the usual symptoms. Treatment was successful throughout this patient's pregnancy using infusions of C1-INH concentrate. The C1-INH concentrate was required, on average, only once every 2 weeks, differing from some protocols in which the concentrate was administered every 3 days.⁴ The clinical efficacy of the C1-INH infusions would, therefore, seem to outlast the theoretical half-life of the enzyme. This patient's angioedema did not progress once she was given an infusion of C1-INH concentrate, but her edema did persist for up to about 12 hours postinfusion, which is consistent with the findings of Bork and Barnstedt.⁵

A case report that involved using C1-INH concentrate symptomatically in pregnancy and for prophylaxis during delivery was published in 1999.⁶ A case report similar to mine, which also included the use of danazol and C1-INH concentrate, was published in January 2006.⁷ An even more recent case report described symptomatic treatment of hereditary angioedema during pregnancy that required multiple hospital admissions for episodes of angioedema before the patient's admission for delivery.⁸ The patient described in my report only required hospitalization during her pregnancy for the induction of labour and subsequent delivery by cesarean section.

Conclusion

This case is an example of a successful treatment approach. Because of the prophylactic infusions of C1-INH concentrate for this patient, the pregnancy outcome was successful; potentially teratogenic or thrombogenic drugs were not used, and hospitalization for the underlying disease process was avoided. 

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Competing interests

None declared

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Characteristics of hereditary angioedema include the following:

- recurrent angioedema without urticaria,
- swelling of the face, trunk, gastrointestinal tract, and upper airways, and
- abdominal pain, mimicking infantile colic, acute appendicitis, or acute abdomen.

Other important information regarding hereditary angioedema includes the following:

- Symptoms often worsen with estrogen-containing birth control pills or hormone replacement therapy and can either worsen or paradoxically improve during pregnancy.⁹
- Episodes tend to be prolonged, typically becoming worse over the first 24 hours then slowly resolving.
- Trigger factors include minor trauma, stress, menstruation, pregnancy, some drugs, or infections.
- Attacks are usually periodic and are not daily occurrences.
- Symptoms usually do not respond to antihistamines or glucocorticoids, although treatment with epinephrine might be successful.¹⁰