

New-variant hereditary angioedema in three brothers with normal C1 esterase inhibitor level and function

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Hereditary angioedema (HAE) is secondary to deficiency of C1 esterase inhibitor (C1 INH) (1) or a nonfunctioning protein (2) while acquired angioedema (AAE) is caused by an underlying disease (Table 1) (3). Recently, two types of inherited 'variant' angioedema have been described where the affected patients were women, have a presentation similar to HAE, but have normal qualitative and quantitative C1 INH levels. In 2000, Bork et al. (4) identified 10 females with normal C1

New-variant HAE with normal C1 inhibitor.

INH levels and function and 26 of their female relatives. Binkley and Davis (5) in 2001 identified a family with Italian heritage where angioedema was dependent on high estrogen levels.

This case study was conducted at the Los Angeles Veterans Affairs allergy clinic from December 2001 to March 2002. Consultation with the each brother included history, physical examination and laboratory data. All three brothers had normal C1 INH level and function.

The brothers were African American with ages ranging from 71 to 74 years. Past medical history is significant for hypertension, reflux, hypothyroidism, hypercholesterolemia, dilated cardiomyopathy, and nonmetastatic prostate cancer status, post-prostatectomy in two brothers. Angioedema is limited to the face, extremity, or genitalia with no respiratory or gastrointestinal involvement. Angioedema lasted 24 h in each patient and occurred several times every year for the last 15-20 years. Each brother utilized a unique regimen of antihistamines to abort or suppress the attacks. All three brothers denied any triggers, urticaria, or occupational asso-

ciations. They were the offspring of identical unaffected parents and siblings to one unaffected brother and sister. Offspring from two brothers were also unaffected. A physical examination was performed on each brother, which was unremarkable.

Laboratory data to evaluate the common underlying causes of angioedema were obtained, but were unremarkable except for an elevated prostate-specific antigen level in one brother, but his prostate biopsy was negative for malignancy. In all brothers C4, C1q, and C1 INH levels were normal. In two brothers C1 INH function was normal.

Hereditary angioedema occurs in a variety of forms: HAE, AAE, variant HAE, and these cases were classified as new-variant HAE. The clinical presentation of new-variant HAE is similar to HAE. In our patients, angioedema was limited to cutaneous involvement and without any identifiable triggers. Treatment of angioedema varies between HAE and the other forms. HAE can be treated with attenuated steroids or C1 INH concentrate and is typically unresponsive to antihistamines. In our patients, their

Table 1. Features of hereditary and acquired angioedema with recently described variant hereditary angioedema (6)

Type	Typical onset	Etiology	Inheritance	C1 INH level	C1 INH function	Serum C4 level	Serum C1q level
Hereditary angioedema type 1	Second decade	Quantitative deficiency of C1 INH	Autosomal dominant	5-30% of nl	Low	Low	nl
Hereditary angioedema type 2	Second decade	Qualitative deficiency of C1 INH	Autosomal dominant	nl or inc	5-30% of nl	Low	nl
Acquired angioedema type 1	N/A	Circulating anti-idiotypic Ab against Ig on B-cell surface	N/A	dec	dec	Low	dec
Acquired angioedema type 2	N/A	Autoantibodies against C1 INH	N/A	nl or dec	dec	Low	dec
Variant hereditary angioedema in Bork et al. (4)	Early adulthood	Unknown: Possibly through a vasoactive peptide with estrogen association	Postulated X-linked dominant	nl	nl	nl	nl
Variant hereditary angioedema in Binkley and Davis (5)	Early adulthood	Unknown: But association during pregnancy or exogenous estrogen	Postulated Autosomal dominant	nl	nl	nl	Not reported

nl, normal; dec, decrease; inc, increase; N/A, not available.