

# Hereditary Angioedema: A Family with Several Affected Members

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## Abstract

Hereditary Angioedema (HAE) is a rare, autosomal dominant genetic disease, characterized clinically by episodic non-pruritic swelling of face, limbs and tissue just beneath the skin. Laryngeal edema is the main cause of death in these patients. Sometimes the disease may affect the family members of the index case. Therefore, early recognition of disease in family members of the patients may prevent potential consequence of mortality.

The report is a family with a large number of patients with this disease. A 33-year-old man was presented with complaints of periodic abdominal pain, episodic swelling of hands and feet, and respiratory distress. Similar symptoms were reported by his siblings and his mother. Laboratory studies illustrated low C4, CH50 and C1q inhibitor levels consistent with HAE. Pedigree analysis indicated a large number of affected people in this family. MLPA was performed to remove or reproduce the SERPING1 gene with probemix P243-A3 of MRC-Holland revealing a heterozygous substitution in exon 3 gene (c.467C>A). Due to the wide variety of disease expression, clinical characteristics and pedigree analysis were appropriate to recognize the HAE.

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## Introduction

HAE is a rare, genetic disease, characterized clinically by episodic non-pruritic swellings in different parts of the body such as face, limbs and tissue just beneath the skin. (1). Bowel edema as the main cause of the gastrointestinal symptoms has been manifested as periodic abdominal pain and vomiting (2). It has been estimated that half of the patients with HAE may experience laryngeal edema as the most life-threatening feature of HAE (3). Autosomal dominant inheritance shows a person with HAE has a 50% chance of passing the mutated gene to each child (4). In 25% of patients with HAE, there is no family history of the disease and are described as *de novo* mutations (5).

Three variants of HAE have been described: Type 1: the most common type is due to reduced production or lack of C1 esterase inhibitor (C1-INH). Type 2: is slightly accounting by 15%, is characterized by normal level but functional impairment of C1-INH (4, 6). Type 3: with normal C1-INH activity levels, the clinical presentations are similar to type 2 except for females, especially when they are exposed to oral contraceptive pills or during pregnancy. Mutations in *SERPING1* gene are responsible for defects in C1 esterase inhibitor in HAE type 1 and 2 (7-10).

This study was done to provide a pedigree of a family with twenty four affected members to demonstrate the importance of family history and pedigree analysis in the early diagnosis of unknown sufferers before life-threatening events.

## Case presentation

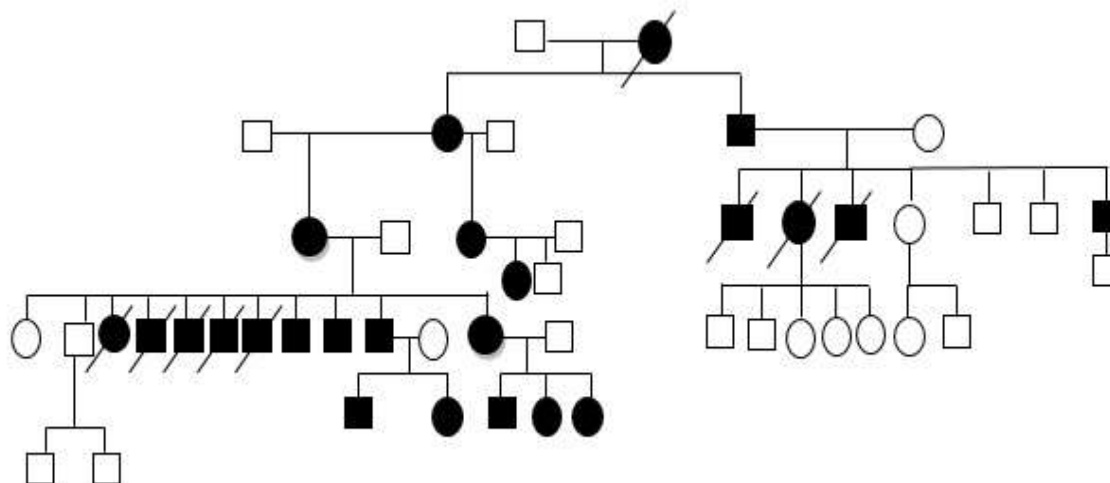
A 33-year-old man hospitalized because of periodic abdominal pain. He usually observed the occasional swellings in his extremities since adolescence with spontaneous resolution. A review on his family medical history revealed that his siblings (two brothers and one sister) and his mother suffered similarly, while four of his brothers and one of his sisters had been died due to severe laryngospasm attacks. After considering the exact date and drawing the family pedigree (**Figure 1**), we identified 15 second-degree affected individuals combined with the index case and his mother and his three siblings who suffered from frequent attacks of angioedema. Severe abdominal pain led to unnecessary abdominal laparotomy in two of his relatives. Laboratory testing revealed the following results: C3:115mg/dl (normal range 90-180 mg/dl), C4<6 mg/dl (normal range 10-40 mg/dl), CH50<50U (normal range 70-150U) and C1q inhibitor 13.2mg/dl (normal range 22-38). The diagnosis of patient's hereditary angioedema was confirmed due to his medical and family history and the laboratory test results. Prophylactic androgen therapy (Danazol 100 mg BD) was prescribed for him, which was effective to reduce severity and the number of his episodes (only three episodes since then).

**Table 1** shows the clinical presentations and laboratory studies for 9 members. Mutation analysis was conducted at the Semmelweis University of Budapest for the pedigree patients. MLPA was performed to reveal deletions or

duplications in the *SERPING1* gene with probemix P243-A3 of MRC-Holland (<http://www.mrc-holland.com/>).

The DNA sequence of *SERPING1* was determined by direct DNA sequence of PCR products amplified from total genomic DNA.

**Figure 1.** Genetic tree of the studied family Black shapes represent the affected patients. Squares represent males and circles represent females



**Table 1.** Summary of main information related to 10 patients

ID	Age (year)	Sex	GI symptoms	Limb swelling	Laryngeal Edema	C3 (mg/dl)	C4 (mg/dl)	CH50 (U)	C1q inhibitor (mg/dl)
1	33	Male	+	+	+	115	<6	<50	13.2
2	43	Male	+	+	+	124	<6	<50	12.7
3	31	Male	+	+	+	122	<6	<50	11.6
4	52	Female	+	+	+	*	*	*	*
5	68	Female	+	+	-	*	*	*	*
6	14	Male	+	+	-	*	*	*	*
7	11	Female	+	+	-	150	<6	<50	12.3
8	29	Female	+	+	+	130	<6	<50	10.9
9	28	Male	-	+	+	*	*	*	*
10	23	Female	+	+	+	*	*	*	*

These Patients were determined to be heterozygous for a substitution in exon 3 of the *SERPING1* gene (c.467C>A) causing an alanine to aspartic acid change at codon 156 of the C1-inhibitor protein (p.A156D). This mutation was known as a pathogenic disease and was not present in healthy people.

## Discussion

Hereditary angioedema is a rare, autosomal dominant genetic disease. It is characterized clinically by episodic non-pruritic swellings to asphyxiation caused by life threatening laryngeal edema (2). HAE attacks are sometimes triggered by trauma, surgical, medical or dental procedures,

emotional stress and certain medications (11-13). Differentiation between the hereditary angioedema and other disorders with characteristics of angioedema is important due to the differences in management of attacks particularly (12). Severe abdominal pain, nausea and vomiting in HAE may be misdiagnosed with acute abdominal conditions, such as appendicitis, consequently may lead to performing unnecessary surgeries (14).

Büyüköztürk et al in their study, on a Turkish family with 3 sisters affected with HAE who had homozygote mutations in the C1INH promoter region (c.-101A>G) reported that all the subjects responded to Danazol treatment(15). In another study, 2 Taiwanese families were also studied with history and laboratory tests compatible with HAE. These patients had mutations in *SERPING1* gene; causing abnormality in C1 esterase inhibitor (16, 17). In the present study, 24 affected members of the same family from 5 different generations with HAE were studied, and the most significant family with the highest number of familial patients in Iranian primary immunodeficiency registry was selected for investigation. Considering the pedigree, the mode of inheritance was found to have an autosomal dominant pattern and the negligence of correct diagnosis during at least 28 years was also highlighted (since 1990 and description of HAE genetic cause). Genetic study on patients suspected for HAE could be beneficial to distinguish this disease from other differential diagnoses. However, as genetic tests are not

always available, detailed medical and familial histories along with drawing pedigree are usually helpful tools in diagnosis of HAE.

The identified mutation was previously reported and published in another study on another patient with HAE caused by C1-inhibitor deficiency reinforced the pathogenicity of the variant (18). A large number of affected patients in this pedigree with an autosomal dominant inheritance were suggested to have gene mutation with high penetrance.

### Conclusion

Hereditary angioedema is a rare life threatening genetic disease with completely different management from other types of conditions with the characteristics of angioedema. Therefore, a detailed medical and family history may play important role in diagnosis and treatment of these patients. In addition, genetic study is considered as another helpful tool in the assessment of the condition of these patients. Because of the autosomal pattern of inheritance, other family members should also be investigated in order to diagnose the disease as early as possible before life threatening events occur.

**Conflicts of interest:** The authors declare that they have no conflicts of interest.

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