CASE REPORT

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A Potentially Fatal Outcome of Oral Contraceptive Therapy: Estrogen-Triggered Hereditary Angioedema in an Adolescent

Uğur Berkay Balkancı[1], Demet Demirkol[2], Gül Yeşiltepe Mutlu[3], Esra Birben[4], Özge Soyer[4], Özlem Yılmaz[5], Cansın Saçkesen[5]

[1]Koç University Faculty of Medicine, İstanbul, Turkey
[2]Koç University Faculty of Medicine, Department of Pediatric Intensive Care; İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Intensive Care, İstanbul, Turkey
[3]Koç University Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Turkey
[4]Hacettepe University Faculty of Medicine, Department of Pediatric Allergy, Ankara, Turkey
[5]Koç University Faculty of Medicine, Department of Pediatric Allergy, İstanbul, Turkey

What is already known on this topic?

Factor 12-related hereditary angioedema is an autosomal dominant disease with incomplete penetrance. Angioedema attacks in this syndrome are known to occur more frequently with higher estrogen levels. Polycystic ovary syndrome (PCOS) is a relatively common disorder and combined oral contraceptives (OCs) which contain estrogen and progesterone are considered first-line drugs in adolescents with PCOS, for control of symptoms due to hyperandrogenism.

What this study adds?

To the best of our knowledge, this case is the first pediatric case of hereditary angioedema due to factor 12 mutation that is induced by estradiol-containing OC in the literature.

Abstract

Hereditary angioedema (HAE) is characterized by recurrent angioedema attacks with no urticaria. This disease has a high mortality due to asphyxia. Level of complement component 4 (C4), C1 esterase inhibitor (C1-INH) level and function, and genetic mutations determine different endotypes of HAE. Clinical presentation and the triggers of vasogenic edema may change according to the endotypes. An adolescent girl with oligomenorrhea, obesity, hirsutism, and acanthosis nigricans was diagnosed with polycystic ovary syndrome and prescribed ethinyl estradiol and cyproterone acetate containing oral contraceptive (OC). On the sixteenth day of treatment, she developed angioedema of the face, neck, and chest leading to dyspnea. Adrenaline, antihistamine, and corticosteroid treatments were ineffective. In the family history, the patient's mother and two cousins had a history of angioedema. C1-INH concentrate was administered with a diagnosis of HAE. C4 and C1-INH level and activity were normal. Genetic analysis identified a mutation in the factor 12 (*F12*) gene, and the diagnosis of F12-related HAE was made. OC treatment was discontinued. She has had no additional angioedema attacks in the follow-up period of two years. OC containing estrogen may induce the life-threatening first attack of F12-related HAE even in children. Recurring angioedema attacks in the family should be asked before prescribing estrogen-containing OC pills.

Keywords: Hereditary angioedema type 3, hereditary angioedema, angioedema, factor 12, polycystic ovary syndrome

Address for Correspondence: Cansın Saçkesen MD, Koç University Faculty of Medicine, Department of Pediatric Allergy, İstanbul, Turkey
Phone: +90 533 212 87 87 **E-mail:** csackesen@ku.edu.tr; csackesen@yahoo.com
ORCID: orcid.org/0000-0002-1115-9805

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Introduction

Hereditary angioedema (HAE) is a genetic disorder that presents with an abrupt swelling caused by bradykinin-related vasogenic edema. The mechanism of HAE is non-inflammatory and non-allergic but involves increased production of bradykinin. Until now, five different genes have been identified to cause HAE which are serine protease inhibitor G1 (*SERPING1*), factor 12 (*F12*), plasminogen (*PLG*), angiopoietin (*ANGPT1*), and kininogen (*KNG1*) (1,2,3). Different types of HAE consist of low C1 inhibitor (C1-INH) activity caused by low production or loss of function of C1-INH due to *SERPING1* gene mutations, or normal level and activity of C1-INH (HAEnCI) due to mutations of *F12, PLG, ANGPT1*, and *KNG1* genes. HAEnCI presentation is similar to the other forms of HAE and characterized by recurring attacks of angioedema without urticaria that can be fatal due to laryngeal swellings. In this form of the disease, the most common defective plasma protein is FXII (3,4). Factor 12 is a critical molecule where pathways of coagulation, complement activation, contact reaction, and fibrinolysis meet. The promoter region of the *F12* gene carries an estrogen-responsive element and there are multiple case reports that associate high levels of estrogen and HAE attacks (5,6,7). This manuscript describes a patient presenting with her first angioedema attack after initiation of oral contraceptive (OC) treatment for polycystic ovary syndrome (PCOS) who was subsequently diagnosed with HAEnCI with *F12* mutation.

Case Report

A thirteen-year-old girl presented to the emergency department with dyspnea and swelling in her upper body. Her medical history was notable for PCOS which was diagnosed two weeks earlier in another pediatric endocrinology clinic. She was reported to have irregular menstruation and hirsutism and diagnosed with PCOS with high androgen levels (Table 1) and polycystic ovary morphology on pelvic ultrasound. Ethinyl estradiol and cyproterone acetate-containing OC pill was initiated. On the sixteenth day of treatment, she developed periorbital swelling which spread over the face, the neck, and the upper body in a matter of hours (Figure 1). With the initial diagnosis of anaphylaxis, epinephrine, antihistamines, and steroids were administered but her swellings were unresponsive. Her family history was positive for recurring angioedema attacks in her mother and two cousins. Therefore, she was given 500 IU of C1 esterase inhibitor concentrate with a pre-diagnosis of HAE. She was hospitalized in the Koç University, Pediatric Intensive Care Unit due to the possible risk of laryngeal edema. During her stay in pediatric intensive care, two more doses of 500 IU of C1 esterase inhibitor concentrate were given. The swellings began to recede after 12 hours and they had completely waned within 48 hours. The physical examination was also remarkable for obesity with a body mass index of 29.7 kg/m^2 (> 99th percentile, +2.51 standard deviation score), acanthosis nigricans on the neck, and severe hirsutism with a Ferriman-Gallwey score of 25.

Her laboratory workup showed complement 4 levels of 31 mg/dL (normal range: 10-40 mg/dL) and normal plasma levels (0.31 g/L, normal range: 0.21-0.39 g/L) and activity of C1 esterase inhibitor (107.7%, normal range: 70-130%) which indicated a diagnosis of HAEnCI. Genetic analysis of *F12* gene revealed a heterozygous mutation in the ninth exon, C>A variant which resulted in p.Thr328Lys variation.

Table 1. Laboratory tests showing serum hormone levels

	Value	Normal range
1.4-androstenedion (ng/mL)	2.38	0.24-1.73
Testosterone (ng/mL)	0.24	0.24-1.67
Sex hormone binding globulin (nmol/L)	10.6	11-120
17-alpha hydroxyprogesterone (ng/dL)	107.0	13-185
Fasting blood glucose (mg/dL)	91.0	60-100
Fasting insulin (µU/mL)	66.8	2.6-25

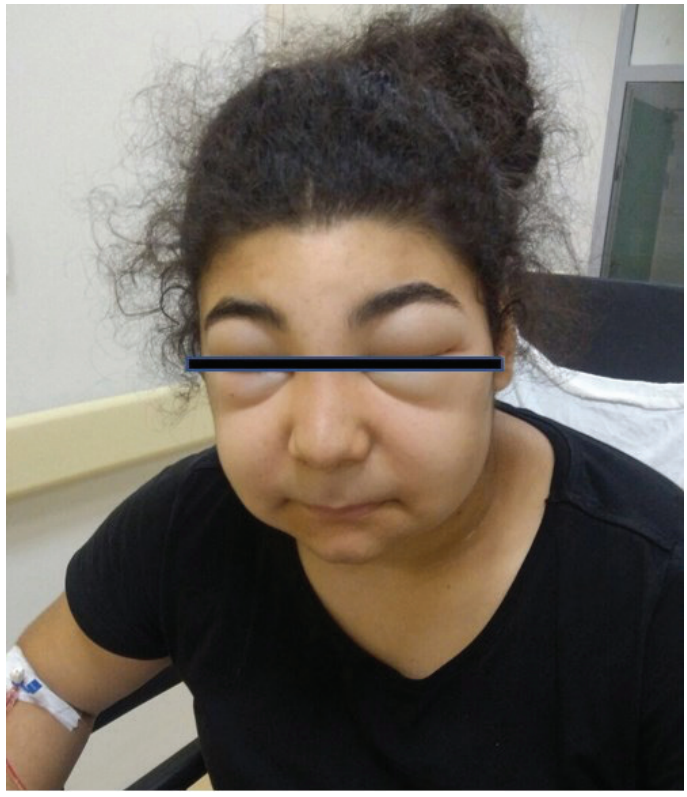

Figure 1. The face of the patient at admission

The OC pill was discontinued and life-style interventions were recommended. No attack occurred during her follow-up over 20 months.

Discussion

We report a female adolescent with a diagnosis of PCOS in another clinic who presented with an angioedema attack after OC medication was initiated. The final diagnosis of HAEnCI was made after genetic analysis of the *F12* gene showed a heterozygous mutation. *F12*-related HAEnCI is an autosomal dominant condition that shows incomplete penetrance. In most cases, the first symptoms appear before the third decade. Published series of HAE patients report a clear female predominance (8). in addition, women are more likely to be symptomatic than men. Hormonal factors play an important role in the worsening of the condition in women. There are differences in the overall frequency of angioedema symptoms depending on different female life stages (childhood, adolescence, menstruation, pregnancy, and menopause). It has also been reported that administration of estrogen, not progestin, in women with HAE may lead to the emergence or worsening of angioedema symptoms (7). A case series conducted in 61 women with *F12*-related HAEnCI showed that 95% of the women presented with at least one angioedema attack during periods of high estrogen exposure (OC pill, hormone replacement therapy, or pregnancy) (4). Estrogen as a trigger for HAE attacks could not be explained by a single mechanism. However, the limited literature indicates that the main culprit could be the estrogen-responsive element on the 5' flank of the *F12* gene (5,6). Another possible effect of estrogens in the pathogenesis of HAE is that estrogen-containing medications can decrease angiotensin-converting enzyme, which is also a protein responsible for degradation of bradykinin. Once angiotensin-converting enzyme activity decreased, accumulation of bradykinin could occur (7). Although some authors proposed that PCOS might have a protective role regarding HAE attacks due to increased levels of androgen and more stable levels of estradiol in PCOS patients (7), compelling evidence showing the protective effect of hyperandrogenism is lacking. The frequent co-occurrence of PCOS and HAE may suggest a link between the neuroendocrine and immune system, consisting of the presence of a pathology related with hypothalamic-pituitary dysregulation and an immunological disorder (6). However, the relationship between these two disorders needs to be clarified.

The present case also reminds us of the challenges associated with the diagnosis of PCOS in adolescence. Diagnostic criteria for PCOS in adolescence remain controversial because the diagnostic pathological features used in adults, including irregular menses up to two years beyond menarche, cystic acne, and polycystic ovarian morphology, may be normal pubertal physiological events (9). The present case had a history of oligomenorrhea and hirsutismus. She had presented to another pediatric endocrinology clinic with these chief complaints. The pelvic ultrasound which was performed in that center showed PCO morphology and laboratory tests revealed a high level of 1.4 androstenedione but a normal testosterone level. Although serum free testosterone level was unavailable, the low level of sex hormone binding globulin suggested it might be elevated. After being diagnosed with PCOS she was started on OC therapy. No pharmacological treatment has yet been approved by the Food and Drug Administration/European Medicines Agency for use in adolescents with PCOS but some pharmacological interventions, including OC, have been frequently used to manage PCOS symptoms (9). The treatment approach in this patient was discontinuing the estrogen-containing OC pill together with life-style interventions (calorie restricted diet, exercise and behavioral treatment) to provide weight loss. There are some reports showing the efficacy of progestin-only OC in decreasing the attack incidence in HAE (10,11), however the use of these in adolescence is debatable. Another pillar of treatment in HAE is patient education. Patients should be advised to avoid estrogen-containing products and cooperate with their doctors when planning to become pregnant in the future.

Conclusion

To the best of our knowledge this case is the first pediatric case of HAE due to *F12* mutation induced by estradiol containing OC to be reported. Individuals with HAE-related mutations may not have any attack until encountering a trigger, such as estrogen-containing drugs. Thus, we highlight the importance of obtaining a thorough family history regarding any HAE attack before initiation of OC, as this care may be lifesaving.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Uğur Berkay Balkancı, Demet Demirkol, Gül Yeşiltepe Mutlu, Esra Birben, Özge Soyer, Özlem Yılmaz, Cansın Saçkesen, Concept: Uğur Berkay Balkancı, Gül Yeşiltepe Mutlu, Cansın Saçkesen,

Data Collection or Processing: Uğur Berkay Balkancı, Demet Demirkol, Gül Yeşiltepe Mutlu, Esra Birben, Özge Soyer, Özlem Yılmaz, Cansın Saçkesen, Analysis or Interpretation: Uğur Berkay Balkancı, Demet Demirkol, Gül Yeşiltepe Mutlu, Esra Birben, Özge Soyer, Özlem Yılmaz, Cansın Saçkesen, Literature Search: Uğur Berkay Balkancı, Demet Demirkol, Gül Yeşiltepe Mutlu, Esra Birben, Özge Soyer, Özlem Yılmaz, Cansın Saçkesen, Writing: Uğur Berkay Balkancı, Demet Demirkol, Gül Yeşiltepe Mutlu, Esra Birben, Özge Soyer, Özlem Yılmaz, Cansın Saçkesen.

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