

Erythema Marginatum as an Early Symptom of Hereditary Angioedema: Case Report of 2 Newborns

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Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare genetic disease that causes recurrent swelling attacks that may affect various body tissues. Angioedematous attacks can be fatal in the case of upper airway edema and are often preceded by prodromal symptoms like erythema marginatum. Initial symptoms usually occur in the first decade of life. We report on manifestation of profound and recurrent erythema marginatum in 2 newborns. In both cases, prodromal symptoms could help determine the diagnosis of C1-INH-HAE such that, at a later time, angioedematous attacks could be treated promptly and effectively. Awareness of C1-INH-HAE is low among physicians and even lower among the general public. This report aims at raising the level of awareness and shows that initial symptoms of the potentially life-threatening condition can manifest in newborns and that erythema marginatum can even be present at birth. Recognition of early symptoms and timely diagnosis of the disease along with adequate education of the pediatrician and parents are a prerequisite for prompt and effective treatment of attacks and the successful management of the disease.

Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is a rare genetic disease, usually inherited as an autosomal-dominant trait. Type I C1-INH-HAE (~85% of cases) is caused by a quantitative deficiency of C1 inhibitor (C1-INH) with decreased levels of antigenic and functional C1-INH. In type II C1-INH-HAE (~15% of cases), antigenic C1-INH plasma levels are normal or elevated, but the protein itself is dysfunctional. C1-INH-HAE is characterized by recurrent episodes of nonpitting edema in various body tissues, including swelling of the upper airway. Initial symptoms usually manifest during the first decade of life, whereas perinatal episodes or initial presentation in later adulthood are atypical.¹ Some patients experience symptoms, such as pruritus, nausea,

fatigue, or malaise, that precede the onset of an angioedematous attack^{2,3} and that may enable the patient to predict an impending attack and trigger early intervention. One commonly reported prodromal symptom is erythema marginatum, a nonpitting, nonpruritic, serpiginous rash first described by Osler in 1888,⁴ which can manifest hours to days before the onset of a C1-INH-HAE attack⁵⁻⁷ or may even develop independently of the angioedema. Erythema marginatum occurs in ~42% to 58% of pediatric patients with C1-INH-HAE, but is nevertheless often mistaken for urticaria.^{6,8-10} Misdiagnosis of erythema marginatum can lead to incorrect or insufficient treatment of the symptom and the subsequent edematous attack,⁶ which creates undue and prolonged suffering

abstract

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for patients with C1-INH-HAE and is potentially life-threatening in cases of upper airway edema.¹¹

We report on very early manifestation of erythema marginatum in 2 newborns: a 3-day-old girl with C1-INH-HAE type I and a newborn with C1-INH-HAE type II with erythema marginatum at birth.

CASE REPORT

A 3-day-old girl, born in 2010, developed profound erythema marginatum at the trunk and extremities (Fig 1). Due to a positive family history, the infant was tested for C1-INH deficiency. With a reduced functional C1-INH level of 13% (normal: >68%) and low levels of C1-INH antigen concentration (4.7 mg/dL, normal: 15.4–35.6 mg/dL) and serum C4 complement (7.5 mg/dL, normal: 10 to 40 mg/dL), the diagnosis of C1-INH-HAE type I was confirmed. Additionally, a sonography revealed minor edema around the liver and free abdominal fluid, which subsided slowly. The girl tested negative for viral infection and was asymptomatic; she therefore received no treatment. Four weeks later, a new outbreak of erythema marginatum occurred. The abdomen appeared bulged and strained and a sonography revealed an ovarian cyst and free fluid in the abdomen. The onset of symptom relief occurred within 30 minutes after intravenous treatment with human pasteurized C1-INH concentrate 250 IU (Berinert; CSL Behring, Marburg, Germany) at a body weight of ~4 kg. The treatment was well tolerated and resulted in complete recovery from symptoms within 7 hours. Between the ages of 5 weeks and 18 months, the girl experienced >20 episodes of erythema marginatum without any other angioedematous symptoms, resolving spontaneously with no need for treatment during this period. She was supplied with C1-INH concentrate, which was to be stored



FIGURE 1

A 3-day old girl, born in 2010, developed profound erythema marginatum at the trunk and extremities.

at home and administered to her in case of an attack. Currently (March 2015), the girl is 4.5 years old and has been free of symptoms for almost 2.5 years.

Several members of her family suffer from C1-INH-HAE and some of them experience attacks preceded by erythema marginatum.

The second case describes a girl who was born in 1988 with erythema marginatum on her body (Fig 2). She manifested no angioedematous symptoms, but the erythema marginatum recurred 3 months later. The first C1-INH-HAE attack occurred at an age of 5 years, manifesting as swelling of the face, extremities, and armpit, and resolved spontaneously within 3 days. At the age of 10 years, she experienced recurrent subcutaneous attacks. Subsequent laboratory tests revealed an elevated C1-INH antigenic concentration of 233% (normal: 64%–166%), but low levels of total complement (31 CH₅₀/mL, normal: 48–103 CH₅₀/mL) and serum C4 (15%, normal: 36%–144%) and low C1-INH functional activity (22.5%, normal: >68%). The girl was consequently diagnosed with C1-INH-HAE type II. Between the ages of 10 and 16 years, she experienced up to 10 subcutaneous and submucosal attacks per year, some of which were preceded by erythema marginatum.

The girl was treated with tranexamic acid for long-term prophylaxis and received human pasteurized C1-INH concentrate 500 IU (Berinert; CSL Behring) on 3 occasions for acute treatment during this period. Because of recurrent laryngeal edema, she was switched from tranexamic acid to long-term prophylaxis with danazol 50 mg per day at an age of 17 years. With increasing attack frequency, from 15 attacks per year in 2006 to 78 attacks per year in 2009, the daily dose of androgens was increased first to 100, then to 200 mg per day, and C1-INH concentrate was administered more frequently (up to 32 doses per year). When she became pregnant at an age of 25 years, attack frequency increased even further, up to 119 attacks per year. During this period, treatment with attenuated androgens was discontinued and the patient was treated on-demand with human pasteurized C1-INH. In 2014, she had 92 attacks, each of them being preceded by an erythema marginatum, and received 130 doses of pnfC1-INH and 10 doses of icatibant.

The patient has as an Arg444Cys de novo missense mutation and a negative family history of C1-INH-HAE with her parents' and her sister's complement parameters being within the normal range.



FIGURE 2
A girl who was born in 1988 with erythema marginatum on her belly.

DISCUSSION

In the cases presented here, initial manifestation of early C1-INH-HAE symptoms occurred in newborns as profound erythema marginatum, an early sign of increased bradykinin release, in the absence of other symptoms of an attack. A similar case was reported by Farkas et al in 2001⁶: a 6-week-old infant developed erythema marginatum that recurred on several occasions over a 5-year period, never being accompanied by swelling. Subcutaneous attacks started when the patient was 5 years old, but C1-INH-HAE was not diagnosed until another 5 years later. Also, Hubiche et al⁹ described a case of a girl who, since infancy, presented with widespread erythema marginatum every 4 to 6 weeks, followed by abdominal pain or swelling of the extremities 2 or 3 times a year. She was finally diagnosed with type I C1-INH-HAE at an age of 12 years, when she was hospitalized due to facial edema. These 2 cases resemble our second case in that, even though erythema marginatum is a typical prodromal symptom of C1-INH-HAE attacks in the pediatric population, a correct diagnosis could be established only

after years of misdiagnosis and inadequate treatment. Similar cases of delayed diagnosis of C1-INH-HAE have been reported in the literature and often describe a long history of untreated or inadequately treated swelling attacks.^{1,8,12-14} Due to an autosomal-dominant pattern of inheritance of the disease, cases of C1-INH-HAE in the family history may facilitate a prompt and correct diagnosis in other family members, whereas *de novo* mutations, which account for ~25% of HAE cases,^{1,15} and a negative family history can hinder timely diagnosis. In the first case reported here, due to a positive family history, and because the treating physician recognized the erythema marginatum as a potential prodrome of an attack, the newborn was immediately tested for C1-INH deficiency such that, 4 weeks later, symptoms of an abdominal attack could be treated promptly and effectively with human pasteurized C1-INH concentrate. Indeed, international guidelines highly recommend the examination of all family members, including infants and toddlers, in families with a history of C1-INH-HAE.¹⁶ Active screening can thereby establish a

diagnosis in children even before the first manifestation of symptoms such that effective preventive or therapeutic measures can be taken. It has to be kept in mind, however, that complement concentrations, including antigenic and functional C1-INH levels, in newborns are approximately 60% to 70% lower than maternal levels.¹⁷ Thus, testing of children at the age of 6 months or younger might misleadingly indicate a diagnosis of C1-INH deficiency and should be repeated at a later age.^{18,19}

Although the cases presented here involved early symptoms that were mild and almost entirely restricted to erythema marginatum, potentially life-threatening laryngeal attacks have been reported elsewhere as an initial symptom of C1-INH-HAE even in children.^{20,21} Bork et al^{11,22} reported the case of a 9-year-old boy who, despite a known family history of C1-INH-HAE, died of asphyxiation during a laryngeal attack that was his first manifestation of angioedematous symptoms. This potential danger, along with a possible correlation between initial symptom manifestation during early life and high disease severity,^{18,23} highlights the importance of recognition of early symptoms, timely diagnosis, and adequate physician and patient education.

The aim of this report was to raise awareness of C1-INH-HAE among health care professionals, specifically pediatricians. Providing an adequate education to affected families and treating physicians on the recognition of symptoms, including prodromal symptoms, and on the availability of safe and efficacious treatment options for children, is an important step in preventing the misdiagnosis and incorrect treatment of C1-INH-HAE.

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ABBREVIATIONS

C1-INH: C1 inhibitor

C1-INH-HAE: hereditary angioedema due to C1-inhibitor deficiency

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