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

Inmaculada Martinez-Saguer, MD[a] Henriette Farkas, MD, PhD, DSc[b]

abstract

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 attack[5–7] 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

[a]*Hemophilia Center Rhine Main GmbH, Germany; and* [b]*Hungarian Angioedema Center, 3rd Department of Internal Medicine, Semmelweis University, Hungary*

Drs Martinez-Saguer and Farkas drafted, critically reviewed, and revised the manuscript and approved the final manuscript submitted. Both supervised or performed the collection of the data presented in the manuscript.

DOI: 10.1542/peds.2015-2411

Accepted for publication Oct 21, 2015

Address correspondence to Inmaculada Martinez-Saguer, MD, Hemophilia Center Rhine Main GmbH, Hessenring 13a, Building G, D-64546 Mörfelden Walldorf, Germany. E-mail: inmaculada.martinez@hzrm.de

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Martinez-Saguer has received honoraria for lectures and funding for travel expenses from CSL Behring. She is a consultant for the following companies: Baxter, Bayer, CSL Behring, Octapharma, Shire, and Sobi. Dr Farkas has received consultancy/speaker fees and honoraria from Shire Human Genetic Therapies Inc., Swedish Orphan Biovitrum, and CSL Behring.

To cite: Martinez-Saguer I and Farkas H. Erythema Marginatum as an Early Symptom of Hereditary Angioedema: Case Report of 2 Newborns. *Pediatrics.* 2016;137(2):e20152411

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 CI-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 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.

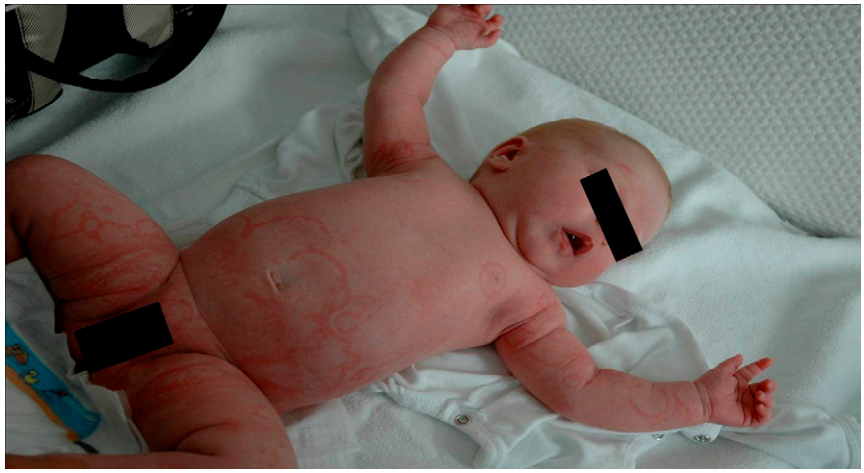

FIGURE 1
A 3-day old girl, born in 2010, developed profound erythema marginatum at the trunk and extremities.

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 CH_{50}/mL, normal: 48–103 CH_{50}/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.

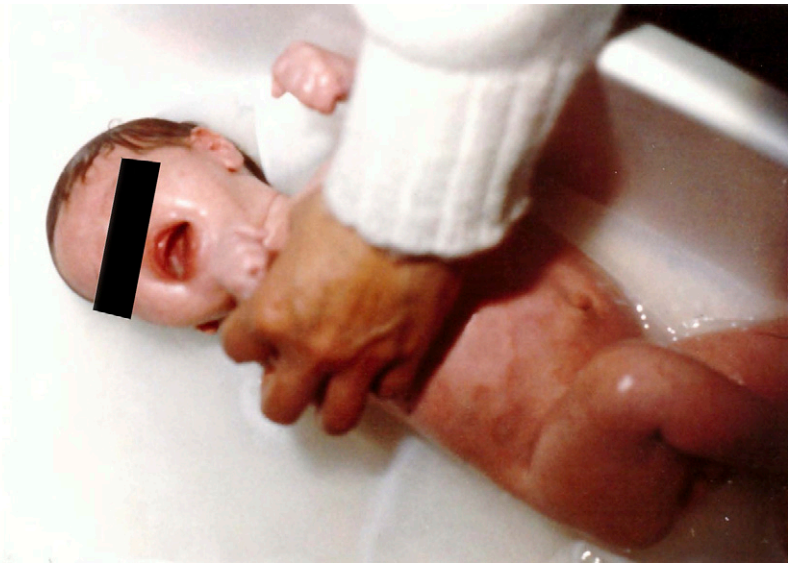

FIGURE 2
A girl who was born in 1988 with erythema marginatum on her belly.

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 2001[6]: 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 al[9] 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.

ACKNOWLEDGMENTS

We thank the parents who gave consent for the publication of

these data. Furthermore, we thank Dorottya Csuka, PhD, for genetic testing; PhD student Kinga Viktoria Kohalmi, MD, for collecting clinical and laboratory data of the second case; nurse Judit Bali (Hungarian Angioedema Center, Semmelweis University, Hungary) for maintaining the Hungarian HAE registry; and Eva Kestner (Trilogy Writing and Consulting GmbH, Germany) for medical writing services on behalf of CSL Behring GmbH.

ABBREVIATIONS

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

REFERENCES

1. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(suppl 3):S51–S131
2. Reshef A, Prematta MJ, Craig TJ. Signs and symptoms preceding acute attacks of hereditary angioedema: results of three recent surveys. *Allergy Asthma Proc*. 2013;34(3):261–266
3. Magerl M, Doumoulakis G, Kalkounou I, et al Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. 2014;39:298–303
4. Osler W. Hereditary angio-neurotic oedema. *Am J Med Sci*. 1888;95(4):362–367
5. Prematta MJ, Kemp JG, Gibbs JG, Mende C, Rhoads C, Craig TJ. Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks. *Allergy Asthma Proc*. 2009;30(5):506–511
6. Farkas H, Harmat G, Fáy A, et al. Erythema marginatum preceding an acute oedematous attack of hereditary angioneurotic oedema. *Acta Derm Venereol*. 2001;81(5):376–377
7. Starr JC, Brasher GW. Erythema marginatum preceding hereditary angioedema. *J Allergy Clin Immunol*. 1974;53(6):352–355
8. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161(5):1153–1158
9. Hubiche T, Boralevi F, Jouvencel P, Taïeb A, Leaute-Labreze C. Reticular erythema signalling the onset of episodes of hereditary angioedema in a child [in French]. *Ann Dermatol Venereol*. 2005;132(3):249–251
10. Kjaer L, Bygum A. Hereditary angioedema in childhood: a challenging diagnosis you cannot afford to miss. *Pediatr Dermatol*. 2013;30(1):94–96
11. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692–697
12. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol*. 2006;101(3):619–627
13. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med*. 2008;359(10):1027–1036
14. Zanichelli A, Magerl M, Longhurst H, Fabien V, Maurer M. Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. *Allergy Asthma Clin Immunol*. 2013;9(1):29
15. Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106(6):1147–1154
16. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents—a consensus on therapeutic strategies. *Eur J Pediatr*. 2012;171(9):1339–1348
17. Nielsen EW, Johansen HT, Holt J, Mollnes TE. C1 inhibitor and diagnosis of hereditary angioedema in newborns. *Pediatr Res*. 1994;35(2):184–187
18. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. *Allergy Asthma Clin Immunol*. 2010;6(1):18
19. Craig T, Aygören-Pürsün E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J*. 2012;5(12):182–199
20. El-Hachem C, Amiour M, Guillot M, Laurent J. Hereditary angioneurotic edema: a case report in a 3-year-old child [in French]. *Arch Pediatr*. 2005;12(8):1232–1236
21. O'Bier A, Muñiz AE, Foster RL. Hereditary angioedema presenting as epiglottitis. *Pediatr Emerg Care*. 2005;21(1):27–30
22. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc*. 2000;75(4):349–354
23. Martinez-Saguer I, Graff J, Rusicke E, et al Does early clinical manifestation of hereditary angioedema (HAE) influence the clinical course of the disease? J Allergy Clin Immunol. 2013;131:SuppIAB30

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

Inmaculada Martinez-Saguer and Henriette Farkas

Pediatrics originally published online January 12, 2016;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Inmaculada Martinez-Saguer and Henriette Farkas

Pediatrics originally published online January 12, 2016;