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Acute hemorrhagic edema of infancy: 20-year experience from an Italian tertiary referral center

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Abstract

Purpose: Data on acute hemorrhagic edema of infancy (AHEI) are derived from small case series or case reports. We report a 20-year experience at a national referral center.
Methods: We performed a single-center retrospective study including patients who were diagnosed with AHEI from January 1, 2004, to June 30, 2023.
Results: We identified 21 patients (57.1% females) with a median age of 18 months (range 7–33 months). Thirteen (61.9%) patients were admitted to the pediatric ward, the remaining eight (38.1%) presented to the emergency department and were discharged for outpatient management. The median length of hospitalization was 5 days (range 3–9 days). Twenty patients (95.2%) had prodromal symptoms. The most common cutaneous findings were targetoid purpuric plaques. The lesions were most localized on the face (13, 61.9%) and on the upper limbs (18 patients, 85.7%). Sixteen (76%) patients presented with nonpitting and tender edema, localized on the feet (9/16, 56%) and hands (6/16, 37.5%). Systemic involvement was rare, and no patients experienced complications or sequelae. Twelve (57.1%) patients underwent infectious disease investigations, with positive results in only four (33.3%). None of the patients diagnosed after the SARS-CoV-2 outbreak (March 2020) had positive nasopharyngeal swabs for the virus. For the 13 patients who were admitted to the pediatric ward, the median length of hospitalization was five days (3–9 days).
Conclusions: The 21-patient single-center cohort of children affected by AHEI confirmed a generally benign course of AHEI, despite a 62% rate of hospitalization.

KEYWORDS
acute hemorrhagic edema of infancy, Henoch–Schönlein syndrome, purpura, Vasculitis

1 | INTRODUCTION

Acute hemorrhagic edema of infancy (AHEI) is a rare cutaneous leukocytoclastic small-vessel vasculitis presenting with localized purpuric skin plaques frequently associated with edema.[1] Some authors considered AHEI as a milder variant of IgA vasculitis.[2,3] However, more recently, AHEI has been increasingly recognized as a separate entity with distinct clinical and histopathological characteristics.[4] Despite its rarity, incidence data are scarce and probably underestimated, since AHEI is frequently misdiagnosed as IgA vasculitis, purpura fulminans, or urticaria multiforme.[5,6] Most cases are preceded by an infection or vaccination, suggesting the potential role of bacteria or viruses as triggers.[4]

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The classic triad of AHEI is the sudden appearance of purpuric targetoid lesions, non-pitting edema, and fever in an otherwise well-appearing child.[7] AHEI occurs predominantly in young children,[8] although more recently cases have been also reported in older children.[3,9] Cutaneous lesions include targetoid or rosette-shaped and/or ecchymotic plaques on the legs, arms, face, and ears, nonpruritic and not changing within hours. These plaques are frequently associated with edema, especially in the distal extremities. Lesions of the mucous membranes are rare.[2,3] Classification criteria have been proposed for AHEI,[10] but have never been validated in clinical practice. Therefore, the diagnosis is generally based on clinical manifestations in children with overall good condition. Less frequently, a skin biopsy can be used to support the diagnosis.[2]

The clinical course of AHEI is generally benign with spontaneous regression of skin lesions within 3 weeks, and no therapeutic intervention is needed.[11] The prompt recognition of AHEI is essential. It is important to distinguish this benign entity from more serious conditions and avoid unnecessary investigations and treatments. Most of the current knowledge on AHEI arises from case reports, small case series, or systematic reviews. The objective of this study was to report the clinical characteristics and management of patients with AHEI seen at a national referral center over a 20-year period.

2 | MATERIALS AND METHODS

This was a single-center retrospective study of all patients diagnosed with AHEI from January 1, 2004, to June 30, 2023, in an Italian tertiary referral national hospital. Digital and non-electronic records search was performed according to the ICD-9 diagnosis code 287.0 (other specified hemorrhagic conditions). All the patients included in the study received a clinical diagnosis of AHEI following either in-hospital admission or medical evaluation at the emergency department (ED). All the patients were evaluated either by a pediatric rheumatologist or by a pediatric dermatologist, as per protocol in our institution. The protocol was approved by local IRB and informed consent was obtained for every patient in the study.

AHEI was diagnosed if children presented with purpuric targetoid lesions, localized on the face/ears, arms/forearms, and thighs/legs with associated edema of the extremities, without pruritus and mucous membrane involvement, and with otherwise good overall condition. Spontaneous resolution of symptoms within a few days or weeks was a required follow-up criterion,[2] Indeed, all the patients admitted to the ward had a follow-up visit at our pediatric rheumatology clinic. All the patients who presented to our ED and were subsequently discharged home had a follow-up consultation either in our pediatric rheumatology or our pediatric dermatology clinic, at the discretion of the attending physician.

In 1996, Krause and colleagues proposed clinical criteria for the diagnosis of AHEI,[10] which have not been validated. Krause's criteria include: (i) age of less than 2 years; (ii) purpuric or ecchymotic target-like skin lesion with edema on the face, auricles and extremities, with or without mucosal involvement; (iii) lack of systemic disease or visceral involvement; (iv) spontaneous recovery within few days or weeks.

In this study, the inclusion criteria relied on clinical diagnosis rather than on the abovementioned criteria, considering studies that have reported cases of AHEI in children older than 2 years of age, and a low but non-negligible rate of visceral involvement in AHEI.[2,3,11,12] Patients were excluded if they presented clinical or laboratory features suggesting other types of vasculitis, according to established diagnostic criteria for other primary and secondary vasculitides.[13] Demographic, clinical, laboratory and outcomes data were extracted from the medical record at the time of presentation to the hospital.

The primary outcome was the phenotypic characterization of patients diagnosed with AHEI in a 20-year time range. Secondary outcomes included duration of hospitalization, rate of cutaneous biopsy and/or other invasive procedures performance, rate of possible etiological examinations performed, rates and types of drugs prescribed (e.g., antibiotics).

Data were managed and analyzed using SPSS v.30 (IBM, Armonk, NY) Descriptive statistics were carried out. Quantitative variables were presented as medians and interquartile range (IQR). Categorical variables were described as numbers and percentages. Comparison among quantitative variables were performed using the Mann–Whitney U test. Analyses of statistical differences among categorical variables were carried out using either the chi-square test or the Fisher exact test, as appropriate.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th version, 2008).

3 | RESULTS

Five-hundred-thirty-seven patients were identified by the retrospective chart review. Of these, 21 (12 females, 57.1%) were included (Figure 1). Thirteen (61.9%) patients were admitted to the pediatric ward, whereas 8 (38.1%) presented to the ED and were discharged home.

The median age at disease onset was 18 months (range 7–33 months). Twenty patients (95.2%) had prodromal symptoms. The clinical characteristics of patients included in our cohort are summarized in Table 1. Only 8 (38.1%) had a fever at admission. None of the other patients had vital sign abnormalities at their first medical evaluation. There were no statistically significant differences in clinical presentation between hospitalized patients and those who were discharged home (Table 1).

Table 2, summarizes the characteristics of cutaneous lesions, which were most frequently localized to the upper limbs (85.7%), followed by the face (61.9%) (Figure 2A–C). No patient presented with purpuric lesions localized on the trunk.

For the 13 patients who were admitted to the pediatric ward, the median length of hospitalization was 5 days (range 3–9 days). During hospitalization, 7 (54%) patients received empiric antibiotic therapy. None of the patients in our cohort underwent cutaneous biopsy.

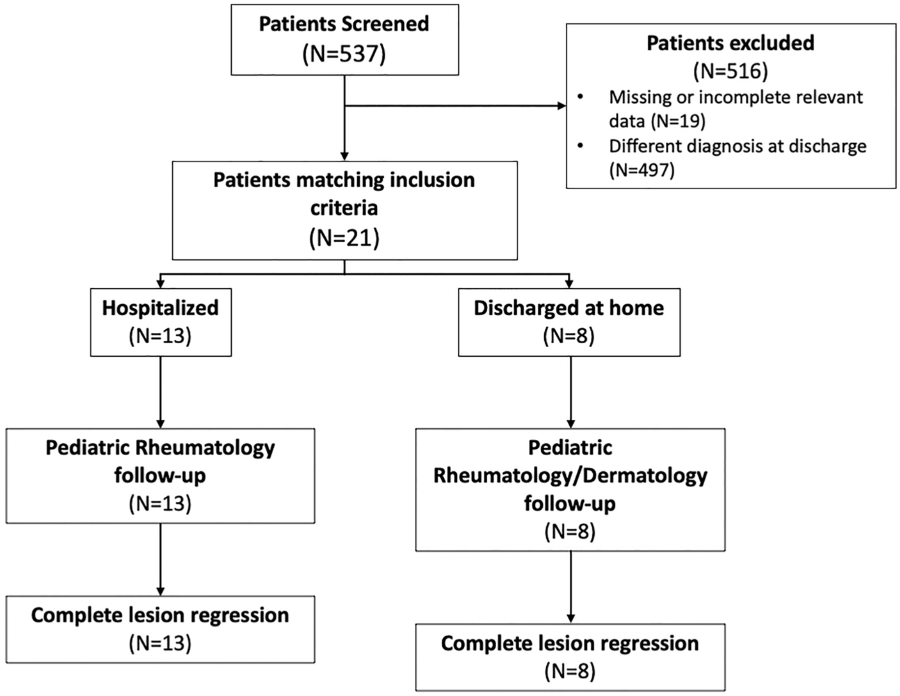

FIGURE 1 Flow diagram of patients included in the study.

TABLE 1 Clinical and demographic characteristics at disease presentation.

Characteristic	Overall ($n = 21$)	ED ($n = 8$)	Hospitalized ($n = 13$)	p
Females, n (%)	12 (57.1)	7 (87.5)	5 (38.4)	.067
Age in months, median (IQR)	18 (13.5)	22 (15)	16 (10)	.293
Time from prodromal symptoms to lesions, days, median (IQR)	6 (7)	5 (4)	6 (2)	.442
Prodromal symptom				
Fever, n (%)	11 (52.4)	3 (37.5)	8 (61.5)	.387
Cough, n (%)	14 (66.7)	8 (100)	6 (46.1)	**.018**
Rhinitis, n (%)	14 (66.7)	7 (87.5)	7 (53.8)	.174
Diarrhea, n (%)	2 (9.5)	0 (0)	2 (15.3)	.505
Pharyngitis, n (%)	2 (9.5)	1 (12.5)	1 (7.7)	1.000
Fever at admission, n (%)	8 (38.1)	2 (25)	6 (46.1)	.399
Laboratory test ($n = 19$)				
CRP (mg/dL) median (IQR)	2.2 (6.1)	0.74 (1.2)	4.9 (9.8)	**.001**
ESR (mm/h), median (IQR)	46 (58)	24 (43)	47 (78)	.142
WBC (/mm^3), median (IQR)	12,980 (6000)	10,830 (4230)	15,085 (2990)	.067
Platelets (10^9/L), median (IQR)	453 (200)	437 (234)	475 (180)	.539
ALT (UI/L), median (IQR)	25 (16)	25 (5)	23 (17)	.569
Fibrinogen (mg/dL), median (IQR)	452 (62)	462 (24)	434 (155)	.955

Abbreviations: CRP, C-reactive protein; ED, Presented to emergency department and not admitted; ESR, Erythrocyte sedimentation rate; IQR, interquartile range.

Eleven patients (52.4%) received at least one medication before AHEI onset. Six (28.5%) received acetaminophen (paracetamol), five (23.8%) a non-steroidal anti-inflammatory drug, and three (14.2%) an antibiotic. In one patient (4.8%) the lesions appeared after meningococcal vaccination.

Nineteen patients (90.4%) had blood tests drawn at disease onset. Hospitalized children had higher CRP levels and a trend towards higher WBC levels ($p = .001$ and $p = .067$, respectively). Renal function was in the normal range in all the tested patients (19/21, 90.4%) (Table 1). All the patients underwent dipstick urinalysis, which was normal except for one patient (4.8%) who was subsequently diagnosed with a urinary tract infection. Five (23.8%) patients presented only isolated mild proteinuria.

Infectious disease investigations were performed on 12/21 (57.1%) children; 12 (100%) underwent a nasal swab for respiratory pathogens (parainfluenza virus type 1,2,3, human Influenza virus A and B, rhinovirus, bocavirus, metapneumovirus, respiratory syncytial virus, adenovirus). One patient (4.8%) had a positive adenovirus nasal swab test, and another one (4.8%) had a positive rhinovirus nasal swab test. In 4 (19%) cases, a pharyngeal swab for beta-hemolytic group A streptococcus was performed, and none was positive. In 5 patients (24%) a quantitative blood polymerase chain reaction (PCR) assay for the most common etiological agents was performed, and only one (4.8%) patient had a positive PCR for Epstein–Barr virus (EBV) infection. Finally, one patient (4.8%), had a positive urine culture for *Escherichia coli* infection.

Five (24%) patients were diagnosed with AHEI after the COVID-19 outbreak (from March 2020 to April 2023). All of them tested negative for SARS-CoV-2 in a nasal swab (PCR test), without a significant increase in AHEI cases after the SARS-CoV-2 outbreak ($p = .29$). Five (24%) patients had C_3 and C_4 levels drawn and in 2 (9.5%) antinuclear antibodies (ANA) were performed, which were normal.

All the patients had complete resolution of cutaneous lesions at follow-up and findings of repeated urinalysis were normal. The median duration of cutaneous lesions was 9 days (range 5–20 days).

TABLE 2 Characteristics of cutaneous lesions.

Characteristics of skin lesions	Overall ($n = 21$)
Morphology of lesions	
Large, targetoid, purpuric lesions (ribbon-like), *n* (%)	21 (100)
Petechiae, *n* (%)	4 (19.1)
Ecchymoses, *n* (%)	3 (14.3)
Maculopapular, *n* (%)	5 (23.8)
Nonpitting, tender edema, *n* (%)	16 (76.2)
Location of purpuric lesions	
Face and ears, *n* (%)	13 (61.9)
Upper limbs, *n* (%)	18 (85.7)
Lower limbs, *n* (%)	7 (33.3)
Groin, *n* (%)	1 (6.2)
Hands, *n* (%)	16 (76.2)
Feet, *n* (%)	6 (28.6)
Localization of edema	
Face and ears, *n* (%)	3 (18.8)
Hands, *n* (%)	6 (37.5)
Feet, *n* (%)	9 (56)

4 | DISCUSSION

We present a single-center cohort of patients affected by AHEI over a period of almost 20 years, overlapping the SARS-CoV-2 outbreak. We confirmed that AHEI is a rare condition, with an indolent disease course and no sequelae. However, despite its benign nature, almost 2 of 3 patients who presented at our tertiary-level hospital were admitted for inpatient care. The clinical presentation of the admitted patients did not differ significantly from those discharged, suggesting a lack of consensus in the management of AHEI, even within a single national referral center.

Over a 20-year period, we identified only 21 patients with AHEI. The median age at disease onset in our cohort was 18 months, slightly higher than most of the previously published reports. According to previously published literature, approximately 80% of the cases have been described in patients aged 6 to 24 months,[8] although more recently, cases in children up to 60 months of age have been reported, too.[3,9] One possible explanation for this minimal difference could be the fact that Krause's diagnostic criteria previously proposed that the diagnosis of this condition be restricted to patients under age 2 years. This study's inclusion criteria are not limited by Krause's criteria due

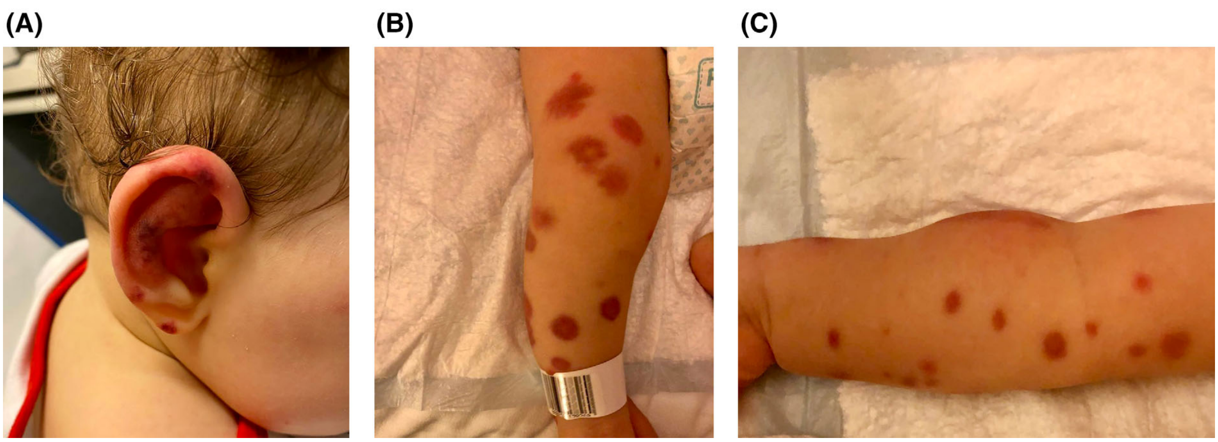

FIGURE 2 Pictures of cutaneous lesions of patients with AHEI. (A) a 12-month-old toddler presenting with acute-onset cutaneous lesions localized at the extremities and at the ears; (B,C) an 8-month-old toddler presenting with purpuric targetoid lesions localized at lower limbs.

to reports of AHEI in children older than 2 years.[2,3,11,12] This difference in the inclusion criteria could partly explain the discrepancy between ours and some of the earliest published reports.

Almost all the patients in this cohort had a history of prodromal infectious symptoms (fever, cough, rhinitis, etc.) as described in other series.[12] Moreover, in this cohort, one patient had disease onset following a vaccination, which has also been reported as a possible trigger for AHEI.[14] This cohort reported data from March 2020 onward, after the SARS-CoV-2 outbreak, at which time all patients were systematically screened for SARS-CoV-2 infection per institutional protocol. Interestingly, despite SARS-CoV-2 having been reported as a possible trigger for AHEI,[15] none of the 5 patients from our cohort after March 2020 had a positive nasal swab for SARS-CoV-2.

In this cohort, the median time from prodromal symptom onset and the appearance of the evocative cutaneous lesions was 6 days. However, despite prodromal symptoms, all the patients were in good clinical condition at the time of presentation without persistence of the prodromal symptoms. Our findings reinforce one of the main differences in terms of clinical presentation between AHEI and Henoch-Schönlein purpura (HSP). AHEI is often heralded by a simple infection, and it is mainly skin-limited, in contrast with HSP.[1,16,17] In our cohort, cutaneous involvement predominantly affected the face and extremities, with complete truncal sparing.[2,3] This pattern appears to differ from the distribution of HSP, where cutaneous lesions (petechiae or purpura) tend to have a lower limb predominance.[18] Moreover, non-pitting tender edema was frequently reported in our cohort (76% of cases), another clinical feature that distinguishes AHEI from HSP.

Systemic manifestations have been reported in AHEI, even if only in a minority of patients. In fact, in a systematic review of 458 cases of AHEI, abdominal features (such as pain, diarrhea, intestinal bleeding, and intussusception) have been reported in 26/458 (5.7%), whereas kidney involvement (proteinuria or hematuria) was observed in only 13/458 (2.8%).[11] Herein, only two patients presented with abdominal pain and diarrhea, who underwent a bowel ultrasound scan with the exclusion of intussusception; therefore, considering the symptoms either as clinical features of a prodromal trigger or as extracutaneous manifestations is challenging. Overall, our results seem to reinforce the excellent prognosis of AHEI as a skin-limited, self-limiting condition, with regression of cutaneous lesions within 3 weeks.

The present study is limited by its retrospective nature and the relatively small number of patients. Given the study's retrospective design, it is possible to have underestimated the true incidence of AHEI, likely also because screening of cases was performed through ICD. Moreover, intrinsically related to the retrospective nature of the study, since clinical diagnosis was made upon clinical judgment and pictures were available only for some of the patients, this may have led to misdiagnoses.

More than 100 years after its first description, there is still debate on AHEI. Its pathogenesis is still unclear, but the clinical observations of symptoms suggesting an infection in the prodromal period have led to hypothesizing a possible role of such a trigger in AHEI development. What is becoming clearer with recent advances is that AHEI should be recognized as a separate entity and that the time has come to include it in the classification of skin vasculitides.

More widespread recognition of AHEI might reduce unnecessary investigations and treatments and ultimately avoid hospitalization. To help the clinician, further multicenter, and, ideally, prospective studies may improve the phenotypic characterization of AHEI and meet the need for validated diagnostic criteria.

CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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