Acute hemorrhagic edema of infancy: the experience of a large tertiary pediatric center in Israel

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Background: **Acute hemorrhagic edema of infancy (AHEI) is a rare leukocytoclastic vasculitis of the small vessels occurring at a young age and considered as a benign self-limited disease. Due to its low prevalence, there are limited data on the presentation and complications of this disease.**

Methods: **All computerized files of children who were hospitalized at a tertiary pediatric center due to AHEI over a 10 year period were reviewed. Clinical, laboratory and histopathological data were collected.**

Results: **Twenty-six patients were included in our study, accounting for 0.7 cases per 1000 admissions of children aged 2 years or less. Mean age was 12.9 months. More than two thirds of the children had preceding symptoms compatible with a viral infection. Upon admission, all patients presented with typical findings of a rash and edema. Edema was most profound over the lower extremities (73%). Concomitant viral or bacterial infections were found in six children. Skin biopsy was performed in six patients revealing leukocytoclastic vasculitis. Thirteen children (50%) had systemic involvement including joint involvement (*n*=9), gastrointestinal hemorrhage (*n*=4), microscopic hematuria (*n*=1) and compartment syndrome of the limb (*n*=1). The latter was diagnosed in a patient with familial Mediterranean fever.**

Conclusions: **Our largest data series highlighted what is known regarding clinical and histological findings in children with AHEI. However, contrary to what was previously reported, we found a higher rate of systemic involvement. Although AHEI is a rare entity, pediatricians should be familiar with its presentation, management and our reported complications.**

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Original article

Background

Acute hemorrhagic edema of childhood, also called acute hemorrhagic edema of infancy (AHEI) or Finkelstein-Seidlmayer disease is a vasculitis of small blood vessels first described by Snow in 1913.[1] While its true prevalence is as yet unknown, the disease rarely occurs. The majority of cases are in the age group of 4-24 months old, with approximately 300 cases reported hitherto.[2]

The etiology of the disease is unknown, but various reports in the literature indicate precursor triggers[3,4] including a preceding infectious disease in over 75% of cases (usually an upper respiratory tract infection, urinary tract infection, pneumonia or acute otitis media), use of medications, such as antibiotics or antipyretics, especially paracetamol, and a combination of vaccines like diphtheria, tetanus, and pertussis.[4,5]

Diagnosis is based upon clinical and histological characteristics. The classic clinical triad includes a rash, which can appear as target lesions, a palpable purpuric rash or petal-like lesions (rosette) about 1-6 cm in diameter on the face and extremities, edema usually occurs over the limbs, eyes, ears, lips and genitalia, and mild fever. Histological features include leukocytoclastic vasculitis of small cutaneous blood vessels with infiltration of neutrophils.[3] The disease is usually benign and spontaneously resolves in 1-3 weeks. However, there are reports of complications with systemic involvement including gastrointestinal

manifestations (intussusception), arthritis and various degrees of renal involvement.[6]

Recent publications on AHEI mainly focus on disease complications whereas there are no large scale series of patients which can truly expand our knowledge regarding the common presentation of the disease. Focusing on the unusual cases may mislead as to the true nature of the disease and might overestimate its abnormal characteristics and complications.

Herein, we describe our tertiary center experience of AHEI patients hospitalized over a 10-year period.

Methods

The computerized medical records of a tertiary, university-affiliated pediatric medical center, Schneider Children's Medical Center, Petah Tiqva, Israel, were retrospectively reviewed for all hospitalized children clinically diagnosed with AHEI between January 1, 2003 and December 31, 2012. Institutional review board approval was obtained from the ethics committee of the Schneider Children's Medical Center. Cases were included according to the ICD 9 diagnosis code 287.8 (other specified hemorrhagic conditions) together with a typical clinical presentation.

The following data were collected: patient's age and sex, preceding symptoms and signs before admission, signs at presentation including type and location of rash and edema, laboratory findings at presentation including white blood count, platelet count, and C-reactive protein levels. Additional data, including infection serology, cultures, immunoglobulin and antinuclear antibody levels were also collected. These tests are not routinely performed but were undertaken according to the judgment of the medical team. Reported complications and further disease-related hospitalizations were also recorded.

Statistical analysis

Descriptive statistics were formulated. Variables were compared using the Mann-Whitney *U* test, independent Student's *t* tests, or CHI square test according to the distribution of variables. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

During the study period, 26 children were diagnosed with AHEI, which accounted for 0.3 cases per 1000 hospitalized children and 0.7 cases per 1000 hospitalized children <2 years of age. There were no relatives among the patients. Mean age was 12.9 months (range: 6-30) with 73% male predominance. Although winter was the dominant season in which most were diagnosed (39%), seasonal variation did not reach statistical significance (P=0.45, Table 1).

The study group experienced a wide variety of symptoms prior to hospitalization (Table 1), which in the majority was compatible with a viral infection. Fever was the most common (65%) symptom. Majority of the children were well appearing at presentation although we did not consider it as diagnostic criteria.

Clinical and laboratory characteristics upon admission

Upon admission, all patients presented with a rash, purpuric in 85% of the cases, combination of maculopapular rash and ecchymoses in 35% of the cases. In the vast majority of cases (96%), the distribution of the rash was on the lower extremities; 50% involved the palms and soles. The rash also appeared on other parts of the body including the upper limbs and face. In half of the cases, the rash was described as painful. In addition, all patients presented with a non-pitting edema at admission, appearing on the lower extremities in 73%, with 50% involving the

Table 1. Clinical characteristics of hospitalized children with acute hemorrhagic edema of infancy (n=26)

Variables	Value
Age	
Mean±SD (mon)	12.9±5.5
Range (mon)	6-30
Sex, *n* (%)	
Male	19 (73)
Female	7 (27)
Number of hospitalization days	
Mean±SD	4.6±3.8
Season at presentation, *n* (%)	
Summer	5 (19)
Winter	10 (39)
Spring	6 (23)
Autumn	5 (19)
Preceding symptoms and signs, *n* (%)	
Rhinorrhea	13 (50)
Cough	5 (19)
Diarrhea	3 (11)
Pharyngitis	6 (23)
Acute otitis media	7 (27)
Pneumonia	2 (8)
Conjunctivitis	6 (23)
Fever at admission (≥38.0°C), *n* (%)	21 (81)
Mean±SD	38.4±1.08
Min, Max	36.0, 41.0
Labs, mean±SD	
White blood cell (10^9/L)	14.9±4.0
Platelets (10^9/L)	540±190*
Hemoglobin (g/dL)	10.9±1.0
C-reactive protein (mg/dL)	5.2±5.0*

*: one sample *t* test compared to normal values, P<0.0001. SD: standard deviation.

palms and soles, and occasionally appearing in diverse areas including the face, ears, tongue and testicles. The edema was symmetrical in 58% of the cases (Fig.). Initial laboratory investigation revealed thrombocytosis of (540±190)×10^9/L and elevated inflammatory markers, specifically C-reactive protein 5.2±5 mg/dL, compared with normal values (P<0.0001, Table 1).[7]

Investigation and hospitalization course

During hospitalization, different infections were concomitantly diagnosed in 6 patients: *Escherichia coli* urinary tract infection (diagnosed in 1/5 children who had a urine culture done), rota virus gastroenteritis (diagnosed in 2/7 in which a rota antigen stool test was done), adenovirus (diagnosed in 1/5 in which a respiratory antigen for adenovirus was performed), *Streptococcus pyogenes* tonsillitis (diagnosed in 1/5 in which a throat culture for *Streptococcus pyogenes* was done) and primary herpes simplex gingivostomatitis (diagnosed in 1/2 in which polymerase chain reaction from a blister was performed). A skin biopsy performed in 6 cases revealed leukocytoclastic vasculitis.

Complications

As shown in Table 2, 50% of the children had involvement of another organ/system other than the skin. This included joint involvement: arthralgia or arthritis (35%), gastrointestinal hemorrhage at presentation: melena or hematochezia (15%), microscopic hematuria (4%) and compartment syndrome of the limb requiring surgical involvement. The last complication presented in a 19 month old male who was admitted due to mild fever, a swollen left calf and ankle and a petechial rash on both feet and hard palate. During his hospitalization period, foot pressure measurements were taken using an arterial line manometry connected directly to the needle. These were shown to be well above the commonly cited ranges of compartment syndrome and the diagnosis of compartment syndrome of the foot was established. Fasciotomy of all nine foot compartments was done. During his ambulatory follow-up, he tested positive for M694V and V726A mutations of the *MEFV* gene and was diagnosed with familial Mediterranean fever (FMF). Four patients (15%) had a secondary hospital admission due to one of the above complications.

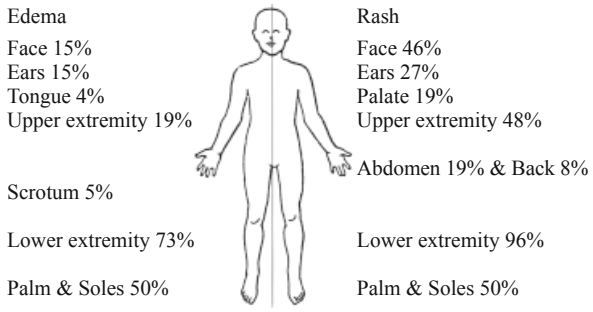

Fig. Clinical manifestations. 2/26 reported of pruritus. There were different types of rash purpura (n=22, 85%), ecchymosed (n=9, 35%), urticarial (n=3, 12%), maculopapular (n=6, 23%), and vesicular (n=2, 8%).

Table 2. Complications

Variables	n (%)
Complications	17 (65)
Arthralgia/arthritis	9 (53)
Gastrointestinal bleeding	9 (53)
Renal involvement	1 (6)
Compartment syndrome	1 (6)

Treatment

Since there is no defined treatment protocol, treatment varied among our patients. Upon admission, over half were treated with antibiotics due to an initial suspicion of a bacterial infection (specifically meningococcemia) until negative blood cultures. Several (23%) were treated with steroids, some as part of the treatment protocol for meningitis, and some due to edema and compartment syndrome. Only three patients were treated with non-steroidal anti-inflammatory drugs because of arthritis or fever.

Discussion

We present herein the largest series of children with AHEI treated in one pediatric tertiary center during a 10-year period. The disease was first reported in 1913. Since then, several case reports and a few reviews[4] have summarized the known features of this rare disease. The fact that most of our knowledge has been retrieved from case reports focusing on severe presentations and complications, may give a wrong impression on the disease characteristics.

The mean age in our study was 12.9±5.5 months with a range of 6 to 30 months is in accordance with previous reports.[2]

Several studies have endeavored to discover the cause of the disease.[2] These studies associate the winter season to the peak of the children arriving with suspected AHEI. They hypothesized that since infectious diseases are more prevalent during the winter, there might be a connection between the development of AHEI and an infectious etiology. We found that although winter was the dominant season (39%), no significant difference existed between winter and other seasons of the year. Nevertheless, most of our patients

had already been diagnosed with a preceding disease before being diagnosed with AHEI (62%). So far, no identifiable mechanism had been reported.

Since diagnosis is based on clinical presentation, there is a broad differential diagnosis of which Henoch-Schonlein purpura (HSP) is most prominent.[6,8] Some researchers argue that these two diseases are not distinct and represent a spectrum of one disease, but most researchers believe these are two different diseases with different clinical, laboratory and histological features.[8] It is important to distinguish between the two, since the medical approach to each disease is quite different. The features that may help differentiate HSP from AHEI include: age of onset, morphology, cutaneous distribution, relapses, complications, extra cutaneous involvement, and most importantly histology and immunohistologic characteristics [immunoglobulin A (IgA) deposition in HSP versus non-IgA deposition in AHEI].[4,8-10] All features describing AHEI are consistent with our patients' clinical presentation. Other less appropriate differential diagnoses include: Sweet's syndrome, erythema multiforme, neonatal lupus, Kawasaki disease, medication side effects and meningococcemia.[8,11] This latter threatening diagnosis might explain the high percentage of patients in our case series who were initially treated with antibiotics (23%).

Treatment of the disease is controversial. There are supporters of steroid and antihistamine therapy, while others believe in a conservative approach due to the benign pattern and spontaneous resolution.[5] When complications arise, there is an indication to treat with non-steroid anti-inflammatory drugs or steroids.[5] In our study, a few patients were treated with steroids (23%) and non-steroidal anti-inflammatory drugs (11%).

Fiore et al[2] has concluded that involvement of body systems other than skin in AHEI was rare and that most children recovered spontaneously without long term sequelae, similar to our findings. Yet there have been reported complications which include mild to moderate gastrointestinal bleeding, arthralgia or arthritis, renal function disturbances and genital complications (testicular torsion).[2,12,13] However, in our case series, the percentage of patients with complications was fairly high (50%). Moreover, we report a new complication which we first published last year as a case report of a compartment syndrome of the limb in a 19 month old male. Interestingly, this patient was eventually diagnosed genetically with FMF (M694V and V726A mutations in the *MEFV* gene).[14] Aksu et al[14] showed that FMF patients might be at an increased risk of developing vasculitis, with HSP and polyarteritis nodosa being the most common ones. Comparing isolated and FMF-associated HSP patients, those who were heterozygous for *MEFV* mutations were younger and with a higher frequency of arthritis, edema and gastrointestinal complications.[15,16] Since FMF was reported to be associated with small vessels vasculitis, it could have contributed to the complication in our patient. We therefore suggest that more attention should be paied on the patient's past medical history and a family history of FMF in cases of complicated AHEI.

There are several limitations in our study. The first is its retrospective manner and by its limited number of patients. Moreover our complications rate was far higher than assumed in previous studies. Yet, it should be noted that FMF disease is more prevalent in Israel which might explain complications rates.[17] Another limitation to our study is the lack of long term follow up. Further studies should be performed in order to achieve a larger database of patients with this disease.

In conclusion, we present detailed hospitalization data of the largest number of AHEI patients. We demonstrated various assumptions regarding the disease including its clinical presentation and its association with infectious diseases. It should be noticed that our complication rate was far higher than usually cited.

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Competing interest: None.

Contributors: Bilavsky E conceptualized and designed the study. Parker L drafted the initial manuscript. Shahar-Nissan K and Ashkenazi-Hoffnung L reviewed and revised the manuscript. Trivizki O supervised the statistics. Harel L and Amir J made critical revision of the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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