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Acute Hemorrhagic Edema of Infancy

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KEY WORDS

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Summary

Acute Hemorrhagic Edema of Infancy is a small vessel leucocytoclastic vasculitis affecting young infants. It is characterized by large, target-like, macular to purpuric plaques predominantly affecting the face, ear lobes and extremities. Non-pitting edema of the distal extremities and low-grade fever may also be present. Extra-cutaneous involvement is very rare. Although the lesions have a dramatic onset in a twenty-four to forty-eight hour period, usually the child has a non-toxic appearance. In most cases there are no changes in laboratory parameters. The cutaneous biopsy reveals an inflammatory perivascular infiltrate. It is a benign and auto-limited disease, with complete resolution within two to three weeks leaving no sequelae in the majority of cases. No recurrences are described.

We report a case of a 42-day old girl admitted at our hospital with Acute Hemorrhagic Edema of Infancy.

Introduction

Acute Hemorrhagic Edema of Infancy (AHEI) is a rare leucocytoclastic vasculitis first described by Snow in 1913. It mostly occurs in children under two years of age and is characterized by acute development of purpuric, palpable, target-like skin lesions. The majority of children report a history of infection, drug-exposure or active immunization in the previous days. The lesions have a dramatic onset in twenty-four to forty-eight hours, and predominantly affect the face. Laboratory analyses are within normal values in the majority of patients.

It usually follows a benign course with spontaneous resolution in about three weeks, leaving no sequelae lesions. AHEI has common clinical features with Henoch-Schönlein Purpura (HSP) and it's considered by some authors as a variant of this syndrome. We report a case of AHEI admitted at our hospital and review the relevant literature.

Case Report

A 42 days-old previously healthy girl was admitted at our hospital for evaluation of a cutaneous vasculitis. The lesions affected primarily the face and rapidly progressed to the trunk and limbs within a twenty-four hour period. There were multiple erythematous palpable lesions, measuring between 0.5 to 4 cm in diameter, with well-defined peripheral edges (**figures 1 and 2**). Most presented centrifugal growth and some had central enlightenment (**figure 3**). Discrete non-painful edema of the feet was also noted on examination. The lesions were initially pink macular and later became purpuric in appearance. There was no fever, mucosal involvement or any medical state alteration. There was no personal history of previous infection, recent medications or immunization. Her father had a history of diarrhea ten days before the onset of the lesions.

Figure 1 - Multiple erythematous palpable face lesions at presentation**Figure 2** - Facial lesions with well defined peripheral edges

Laboratory tests performed were within normal limits: complete blood count, coagulation, electrolytes, liver function, kidney function and urinalysis. Immunoglobulin titers were normal, as well as C3 and C4 levels and anti-nuclear antibodies were negative. There was no rise in antibody titer to cytomegalovirus, parvovirus B19, herpes virus 6 and Epstein-Barr virus. Clinical features were consistent with Acute Hemorrhagic Edema of the Infancy. No therapy was initiated, and after four days there was a regression of the lower extremities edema and skin lesions started to disappear. Complete regression occurred after ten days. There were no relapses registered during the six months follow-up period.

Figure 3 - Centrifugal growth lesions with central enlightenment

Discussion

The reported case is consistent with the diagnosis of Acute Hemorrhagic Edema of Infancy (AHEI). It is a rare leukocytoclastic vasculitis first described in 1913 by Snow in the United States (1). The disease was later better characterized in Germany before the Second World War in 1929 by H. Finkelstein (2) and in 1939 by H. Seidlmayer (3).

It is an uncommon clinical identity with only about 300 cases reported in the literature hence the real incidence is not known (4,5,6,7). It is considered by some authors to be a variant of Henoch-Schönlein Purpura (HSP) and has been recognized under various terms: cockade purpura and edema of young children, acute benign cutaneous leukocytoclastic vasculitis of young children, and the eponyms Finkelstein disease, Seidlmayer disease, Finkelstein-Seidlmayer disease, purpura en cockarde avec edema or Henoch-Schönlein Syndrome of early childhood (4,7,8). AEHI occurs predominantly in the early childhood with 80% of cases occurring between six and twenty-four months (4,6). The mean age of presentation is approximately thirteen months (7). There is a male predominance described in the literature, with a male to female ration of approximately 2:1 (4,8).

Pathogenesis

The etiopathogenesis is still not fully understood. Approximately 70% of cases are preceded by an infection, drug exposure and/or active immunization. Most frequently there is a personal or familiar history of mild upper respiratory tract infection, an acute diarrheal disease or a urinary tract infection (4,6,7,8,9). A season variation with a peak in the winter months, related to the frequency of upper respiratory tract infections, has been postulated (7). Cunningham et al reported a case of AHEI in a

newborn to a mother who had severe gastroenteritis six weeks prior to delivery (10). In our case the father of the girl reported a personal history of acute diarrhea ten days before the onset of the child lesions. Specific pathogens have been identified in association with AHEI: cytomegalovirus, coxsackie B4, rotavirus and herpes simplex virus (6,11-14).

Medication such as antipyretics, non-steroidal anti-inflammatory agents or antibiotics have also been implied in the pathogenesis of AIEH (4,8,12,15,16). However, there are no recurrences experienced after re-expositions to these agents, indicating that probably drug exposure alone was not responsible for the vasculitis (8). Approximately ten percent of cases are preceded by an active immunization (4,6,8,11,12).

Clinical features

AHEI has a rapid onset presentation and is characterized by the triad of fever, edema and cutaneous purpura (4,8,11,12). The cutaneous lesions are the most consistent aspect of the disease. They develop rapidly in twenty-four to forty-eight hours, starting with small erythematous macules, papules or urticariform plaques that progress to large (1-5 cm in diameter), round purpuric, palpable, target-shaped lesions. The colour may evolve from red or purple to brownish-yellow once the extravasated blood is degraded (4,7,8,11-19). The lesions have a symmetrical distribution and are mainly located on the face (mostly ears, cheeks and eyelids) and extremities, although other locations can also be involved (4-9,11-12). Mucosal membranes are only rarely involved, although cases affecting the conjunctiva, buccal mucosa or palate have been described (4,12,13,19,20).

Edema is classically asymmetrical non-pitting (mainly tender), affecting the auricles, face and extremities (frequently dorsum of the hands and feet). Other locations such as the scrotum in boys may also be involved (4,7-9). Fever typically is low grade and is present in about 50% of children and general symptoms such as irritability and pruritus may also be present (4,8).

Clinically what is most impressive is the contrast between the dramatically rapid development of the lesions and the good general, non-toxic appearance of the child (4,7,11,12,20). The average time interval between the possible causative agent and AEHI is seven to fifteen days (16,17,19).

In the case we report the cutaneous component was predominant, with lesions present mainly on the face but also affecting the trunk and limbs. Non-pitting edema of the feet was also present at admission.

Visceral involvement is rare occurring in less than 5% of children but there are document cases of abdominal pain, arthralgia and renal involvement. Proteinuria and haematuria may be present but are usually mild and transitory and unlike in HSP renal function is preserved (4,6,7,16).

Laboratory findings and histopathology

Routine laboratory tests are non-specific and non-diagnostic. Most children have normal C reactive protein and erythrocyte sedimentation rate, normal or mild leucocytosis with neutrophilia or eosinophilia and thrombocytosis, as in other vasculitis. Coagulation tests are generally normal as well as stool sample. Urinalysis is normal in most children but it can reveal microscopic haematuria or proteinuria indicating renal involvement (4,6-8,21).

Antinuclear antibodies, antideoxyribonucleic acid antibodies and rheumatoid factor are usually negative and immunoglobulin (IgA, IgM and IgE) levels may be normal or elevated. Serum complement levels are normal in the majority of patients but cases with transient low levels of C1q, C4 and CH50 have been reported (4,6-15,22,23).

Histopathologic analysis reveals a leukocytoclastic vasculitis of the small dermal vessels. The perivascular infiltrates are mainly composed of neutrophils with fragmented nuclei and occasionally eosinophils. There may also be endothelial edema with fibrin deposits in the vascular wall with a fibrinoid degeneration and erythrocyte extravasation (7,6,11,12). When direct immunofluorescence is performed, immunoglobulin A deposits may be found in approximately one-third of cases (4,8,12,24).

Differential diagnosis

Prompt recognition of this rare disease is important to differentiate it from other serious disorders that require rapid therapy. The differential diagnosis includes sepsis (either meningococcal or non-meningococcal), Henoch-Schönlein Purpura, erythema multiforme, hemorrhagic urticaria, trauma-induced purpura, drug-induced vasculitis and child abuse (4,6,7,8,12).

Krause et al (12) suggested four diagnostic criteria for Acute Hemorrhagic Edema of Infancy that are summarised in **table 1**. The diagnosis is based either on clinical features, supported by a skin biopsy or both. A skin biopsy is not needed to formally confirm the diagnosis - clinical aspects and the natural course of the disease are generally sufficient (4,8).

The main differential diagnosis is with Henoch-Schönlein Purpura and has long been a matter of controversy. Some authors

Table 1 - *Diagnosis criteria for Acute Hemorrhagic Edema of Infancy proposed by Krause et al (12).*

- Age younger than two years old;
- Purpuric or ecchymotic skin lesions, with edema of the face, auricles and extremities with or without mucosal involvement;
- Lack of systemic disease or visceral involvement;
- Spontaneous recovery within a few days or weeks.

Table 2 - Clinical and laboratory differences between AHEI and PHS.

	AHEI	PHS
Age presentation	2-24 months	3-8 years-old
Skin lesions distribution	Predominantly face	Lower extremities, buttocks, thighs and legs
Visceral Involvement	Rare	Frequent
IgA deposits in skin biopsy	Rare	Very Frequent
Resolution	2-3 weeks	4 weeks

regard them as different clinical identities whereas some suggest that AEHI is a benign variant of HSP occurring in younger children. **Table 2** presents the major differences between these two leukocytoclastic vasculitis.

The distribution of the skin lesions is different. In AHEI the face is the predominant affected site whereas in HSP the lesions affect mainly the extensor surfaces of lower extremities, the buttocks, thighs and legs, generally sparing the face (4,8). Some authors relate the difference in lesion distribution to gravity - since most children with AHEI are less than six months of age, they spend most of their time lying down and gravity cannot be considered a factor. Children with HSP (generally older than four years old) spend most of their time standing up what would be consistent with lesion distribution predominantly on the lower extremities. Also the proportionally larger head of the small infant, with corresponding increase blood supply, would make them more susceptible for facial skin lesions (4,8,16).

Age presentation is also different - HSP typically occurs between two and eight years old while AHEI occurs in younger children, most of them less than two years old (4,8).

Classically the presence or absence of IgA deposits in skin biopsies is considered an important marker to differentiate the two identities - IgA deposits are found in almost 100% of children with HSP and only occasionally in AHEI (19,25). Some authors proposed that this difference is related to the physiologic immaturity of the immune system during infancy - IgA levels are low at birth and progressively increase through childhood. Young infants who present with AHEI have a physiological low circulating IgA level hence skin deposits are not normally found. As HSP normally occurs in children older than 5 years of age, the immune system has become reasonably mature and skin IgA deposits can be consistently found (8,25).

Other features that distinguish AHEI and PHS are rare visceral involvement in the former and the duration of skin lesions that normally regress within twelve days in AHEI and within four weeks in PHS (4,8,12).

The controversy remains, with some authors approving that AHEI and HSP are two variants of the same identity while oth-

ers agree that there are sufficient clinical and prognostic data to consider them as different clinical identities.

Course management and prognosis

Despite the rapid progression of lesions, Acute Hemorrhagic Edema of Infancy is generally a self-limited disease with skin lesions resolving in one to three weeks. Treatment remains controversial with some authors postulating benefit effects of anti-histaminics as well as topical or systemic steroids, while others state no role for these drugs in changing the course of the disease. With either treatment or conservative approach, AHEI resolves completely with no sequelae in the majority of cases (4,6,7,8). However, there have been reports of residual hyperpigmentation and slight atrophy of the skin (22).

In the case we report no therapy was started and the skin lesions resolve completely in ten days with no sequelae in a six month follow up period.

Conclusion

Acute Hemorrhagic Edema of Infancy is probably less rare than described in the literature. The benign and self-limiting course of the disease and its clinical similarities do HSP may contribute to its reduced reporting.

Early recognition of AHEI is important in order to avoid unnecessary or invasive medical investigation. The disease is self-limited with skin lesions resolving in about one to three weeks with no treatment. In most cases sequelae do not occur.

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