CASE REPORT

ACUTE INFANTILE HEMORRHAGIC EDEMA: A CLINICAL PERSPECTIVE (REPORT OF SEVEN CASES)

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ABSTRACT

Acute infantile hemorrhagic edema (AIHE) is an uncommon cutaneous leukocytoclastic vasculitis characterized by large purpuric skin lesions, acral edema and fever. In spite of violent onset, spontaneous recovery without any sequelaes occurs within a few weeks. The causes of AIHE are unknown and there is no specific treatment. In this article, we have presented seven cases with AIHE admitted to our hospital between 2003-2006. We evaluated the effect of antihistaminic treatment on the course of the disease and we also reviewed the features of AIHE distinguishable from other purpuric diseases.

Keywords: Acute infantile hemorrhagic edema, Antihistaminic treatment, Immune system

AKUT İNFANTİL HEMORAJİK ÖDEM: KLİNİK BİR BAKIŞ (YEDİ VAKANIN SUNUMU)

ÖZET

Akut infantil hemorajik ödem (AIHE) nadir görülen bir kutanöz lökositoklastik vaskülit olup geniş purpurik deri döküntüleri, akral ödem ve ateş ile karakterizedir. Korkutucu başlangıcı olmasına rağmen haftalar içinde sekel bırakmadan spontan iyileşme görülür. AIHE'in etyolojisi belli değildir ve spesifik bir tedavisi yoktur. Bu makalede, hastanemize 2003-2006 tarihleri arasında başvuran ve AIHE tanısı konan yedi vakayı sunduk. Biz antihistminik tedavinin hastalığın seyri üstündeki etkisini araştırdık ve AIHE'in diğer purpurik hastalıklardan ayırıcı özelliklerini gözden geçirdik.

Anahtar Kelimeler: Akut infantil hemorajik ödem, Antihistaminik tedavi, İmmün system

INTRODUCTION

Acute infantile hemorrhagic edema (AIHE) is a benign leukocytoclastic vasculitis that is confined to the skin without visceral involvement. It is usually seen in children younger than 3 years. Since it was first described in 1913, fewer than 120 cases have been reported [1-11]. Cases of AIHE have also been described in our country[2,4-6,10]. It is characterized by fever, large purpuric skin

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lesions and acral edema. The causes of AIHE are unknown. The disease is usually seen during winter months and it has frequent association with upper airway infection, vaccination or drug intake[1] . It is also considered as a variant of leukoclastic vasculitis with many similarities to Henoch-Schönlein Purpura (HSP) by many authors. Routine laboratory tests are nondiagnostic and there is no specific treatment[3,12,13]. The diagnosis of AIHE is based on clinical features and skin biopsy is not usually required for all cases[3,12-14]. Herein, we describe seven cases with AIHE. Our aim is to emphasize the effect of antihistaminic treatment on the course of the disease and discuss the features of AIHE distinguishable from other purpuric diseases.

CASE REPORTS

Seven cases with AIHE were admitted to Selcuk University, Meram Medical Faculty, Department of Pediatrics, between 2003 and 2006. Their ages varied between 7 months to 4 years at the time of diagnosis. The diagnosis of AIHE was based on clinical features and laboratory findings (Tables I, II). All the patients admitted to our clinic with large purpuric skin lesions, especially on lower limbs, and acral edema. (Figure **1**) On initial physical examination; round or oval, ecchymotic, purpuric plaques with edema distributed particularly on the lower limbs and face were seen. (Figure 2) The edema was nontender. Two of the cases (case 1 and 3) also had the plaques on their ears which is uncommon. One of them was a girl with Down's syndrome (Case 6) (Figure 3). On admission,all the cases had fever (38,2-38,5 ºC). Five patients had upper airway infections and two patients had lower airway infections. (Case 2 and 5). Other physical examination findings were normal in all cases. All of the patients had leukocytosis and elevated C-reactive protein values at initial analysis which decreased systematically within a week. Also the sedimentation rate was found to be increased, except in one patient. (case 4) EBV EBNA IgM and IgG were positive in the patient with Down's syndrome, but EBV VCA IgM and IgG were negative. In the other patients, viral and bacterial serologies (EBV, CMV, HBV, HCV, HIV, Rubella, Parvovirus, Leptospiroz, Brucella and Salmonella) were negative. Blood, urine, stool and nasopharyngeal cultures were also found to be negative. Also the peripheral blood flow cytometric analysis of the patient with Down's syndrome was normal. All of the families refused the skin punch biopsy for histopathologic examination. Antibiotherapy was only given to patients 2 and 5 for pneumonia. Antihistamines (hydroxyzine HCI or diphenhydramine HCI) were randomly given to 4 cases. (Case 1, 4-6) The acral edema resolved in all patients within three days. In the group which received antihistamines, except for the case with Down's syndrome, the cutaneous lesions disappeared faster than (mean 10 days) in the patients who were not given antihistaminic treatment (mean 14 days). The mean recovery period with antihistamines was four days shorter than in the other group. Fundamentally, the lesions disappeared in all cases within 2 or 3 weeks. The patients were followed up for between 5 months to 2 years and only the patient with Down's syndrome had a recurrence a week after discharge.

Table I: The clinical features of the patients

Case No.	Age (mo.) /Sex	Prodromes*	Clinical features	Duration of eruptions (days)
1	30/ M	URI**	Fever, edema of feet and face, purpuric lesions on upper and lower limbs, face and auricles IM Sefuroxim axetil was given before admission.	11
2	7 / F	LRI***	Fever, edema of feet and purpuric lesions on lower limbs. Crepitan rales were heard. IV Seftriaxon was given during hospitalization.	15
3	11/M	URI	Fever, edema of feet, purpuric lesions on upper and lower limbs, face and auricles. Right tympanic membrane was hyperemic.	13
4	24/M	URI	Fever, couch with nasal secretion, purpuric lesions on lower limbs and face Edema of feet and face.	10
5	10/F	LRI	Fever, edema of feet and face, purpuric lesions on upper, lower limbs and face. Pharynx was hyperemic and rales were heard. IV Seftriaxon was given during hospitalization.	9
6	48/F	URI	Down syndrome. Fever, edema of feet and face. Purpuric lesions on upper, lower limbs and face. One recurrence occurred.	19
7	8/M	URI	Fever, edema of feet and purpuric lesions on lower limbs.	14

1 *Active infection on admission
2 **Upper respiratory tract infection
3 ***Lower respiratory tract infection

Table II: The laboratory findings of the patients

Case No.	Admission			Control		Antihistamines
	*WBC (mm^3)	Sedimentation rate (mm/saat) (0-20)	CRP (mg/L) (0-10)	Sedimentation rate (mm/saat) (0-20)	CRP (mg/L) (0-10)	
1	16.000	56	38,6	21	9,8	Hydroxyzine HCI
2	16.500	43	28	9	8,7	-
3	21.200	118	23,6	13	4,4	-
4	16.700	13	25,3	8	4	Diphenhydramine HCI
5	22.600	24	27,5	20	14,9	Hydroxyzine HCI
6 (Down's syn.)	18.000	33	61,3	15	11	Hydroxyzine HCI
7	20.100	28	36,7	13	7, 3	-

*White blood cell count

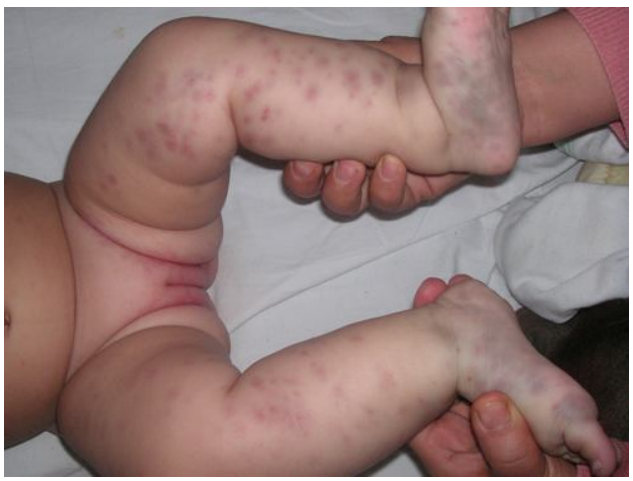

Figure 1: Large purpuric, ecchymotic skin lesions and edema on the lower limbs. (case 2)

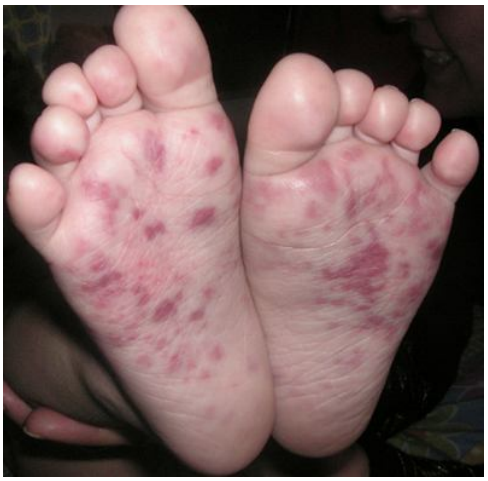

Figure 2: Purpuric lesions on the feet (case 1)

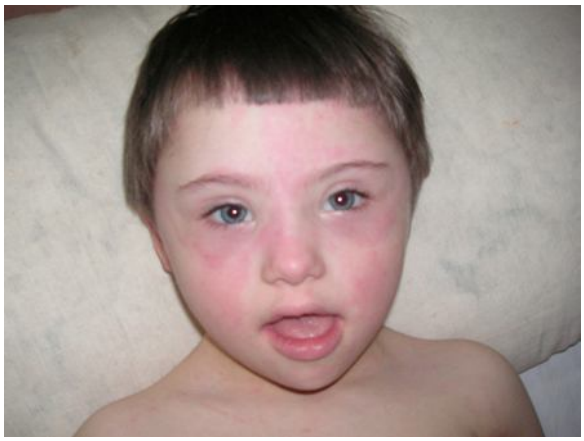

Figure 3: Large purpuric skin lesions and edema on the face of the girl with Down's syndrome. (case 6)

DISCUSSION

Acute infantile hemorrhagic edema (AIHE) is classified as a small vessels' leukocytoclastic vasculitis such as Henoch-Schönlein Purpura (HSP). Rosette-shaped purpuric plaques which rapidly expand to form multiple plaques on the face and limbs are typical skin lesions of the disease[1,2]. The causes of AIHE are unknown. Many of the authors consider the disease as an immunologic reaction after an antigenic trigger. Infections, drug intake and immunization are the main etiologic factors as in 75 % of the cases[1,2,6]. It has been reported in association with pneumococcal bacteremia, pulmonary tuberculosis, adenovirus infection, urinary tract infections, bronchopneumonia, neck abscess and bronchitis[5,9,10,15-17]. Our patients had upper and lower airway infections as trigger factors at admission.

There are no diagnostic criteria for the disease[1,3,4,12-14]. Despite the extent of the skin lesions, the children are often nontoxic. The diagnosis of the disease was based on clinical features and laboratory findings. All of our patients had fever, acral edema, purpuric and ecchymotic lesions, localized particularly on the extremities and face (Table I). Elevated C-reactive protein (CRP) with leukocytosis was detected in all patients (Table II). There was an infective focus in all cases at admission. However, nasopharyngeal, blood, urine and stool cultures were found to be negative. EBV EBNA IgM and IgG serologies were positive only in the case of Down's syndrome. But, EBV VCA IgM and IgG were found to be negative. It was evaluated as a subacute infection. Also this could be a trigger factor for recurrence in this case.

In AIHE, the histopathologic examination of the skin punch biopsies demonstrates leukocyte and eosinofile infiltration on the vessel wall. In the study of Saraclar et al., perivasculer fibrinogen, C3, IgM, IgG, IgA and IgE were detected 100%, 100%, 78%, 22%, 33% and 33% respectively, by a direct immunoflourescent study[5]. The IgA deposition appeared in only one patient out of nine in the study of Legrain et al.[1]. However, a skin biopsy is not usually required for diagnosis[3,12-14]. In our cases, the skin biopsies could not be done, but AIHE was diagnosed in the light of the clinical and laboratory findings.

Differential diagnosis is required for AIHE from HSP, meningococcemia, septicemia, Kawasaki disease, purpura fulminans, urticaria, erythema multiforme and other diseases leading to cockade eruptions. From a clinical point of view, the most urgent need is to exclude the possibility of meningococcemia. For this reason; age, characteristics and localization of the lesions, accompanying symptoms, duration of the illness, immunohistologic and laboratory findings should all be considered. AIHE is usually seen in the chidren of under 3 years, typical cockade, annular, targetoid and purpuric lesions appear on the face, ears and extremities with acral edema. The edema is non tender and may be asymmetrical[3]. Also involvement of the internal organ systems is rare. Spontaneous recovery without any sequelaes occurs within a few weeks[3,10]. It is considered as a distinct entity, on the basis of the typical picture and the excellent prognosis.

No specific treatment is available for AIHE, because the skin lesions usually resolve

spontaneously within 2 or 3 weeks. But their appearance is very terrifying. In our patients, the cutaneous lesions regressed in meanly 4 days, while the edema disappeared in 2 or 3 days. Full recovery occurred in a 2 week period in all patients except for the girl with Down's syndrome. Antihistamines (hydroxyzine HCI or diphenhydramine HCI) were randomly given to 4 patients. On follow up, the lesions disappeared earlier in the antihistamines group (mean 4 days) than in the others. In this group resolution of the lesions occurred within 19 days despite the antihistamines therapy only in the patient with Down's syndrome, and also one recurrence was observed after her discharge. All these clinical observations remind us that there may be an immunologic insufficiency in this patient. However, immunoglobulin values and peripheral blood lymphocyte subtype analysis were normal. It is known that AIHE is a small vessel leukocytoclastic vasculitis that appears after an immunologic trigger. Thus it is believed to represent an immune complex-mediated disease. Occasionally some T and B cell dysfunctions can accompany the Down's syndrome[18,19]. So, in our patient with Down's syndrome an unknown dysfunction of affected T and B cells may be associated with the long progress of the disease. Also this supports the view that of AIHE as an immune complex-mediated disease caused by immunologically affected T and B cells.

Our study is a clinical observation of our patients who were consistent with the diagnosis of AIHE. The typical lesions in our patients with AIHE regressed with antihistamines earlier than in the natural progress. However, the major limitation of the study is the small number of cases. We suggest that antihistamines may be useful to shorten the duration of the skin lesions in the course of the disease. But to improve this suggestion, new case control studies with a large number of patients are needed.

REFERENCES

1. Legrain V, Lejean S, Taieb A, Guillard JM, Battin J, Maleville J. Infantile acute hemorrhagic edema of the skin: study of ten cases. J Am Acad Dermatol 1991; 24: 17-22.
2. Ince E, Mumcu Y, Suskan E, Yalcinkaya F, Tümer N, Cin S. Infantile acute hemorrhagic edema: A variant of leukocytoclastic vasculitis. Pediatr Dermatol 1995; 12: 224-227.
3. Odom RB, James WD, Berger TG. Cutaneous vascular diseases. In: Odom RB, James WD, Berger TG, eds. Andrews' Diseases of the Skin, Clinical Dermatology, 9th ed. Philadelphia: W. B. Saunders; 2000: 1035-1036.
4. Caksen H, Odabas D, Kosem M, et al.Report of eight infants with acute infantile hemorrhagic edema and review of the literature. J Dermatol 2002; 29: 290-295.
5. Saraclar Y, Tinaztepe K, Adalioglu G, Tuncer A. Acute hemorrhagic edema of infancy (AHEI) - a variant of Henoch-Schönlein purpura or a distinct clinical entity? J Allergy Clin Immunol 1990; 86: 473-483.
6. Bozaykut A, Pulat-Seren L, Ozahi-Ipek I, Vardar-Tuncel G. Acute infantile hemorrhagic edema as a differential diagnosis of purpura: Report of three patients. Çocuk Sağlığı ve Hastalıkları Dergisi 2005; 48: 147-150.
7. Snow IM. Purpura, urticaria and angioneurotic edema of the hands and feet in a nursing baby. JAMA. 1913;61:18-19.
8. Paradisi M, Annessi G, Corrado A. Infantile acute hemorrhagic edema of the skin. Cutis 2001; 68:127-129.
9. Di Lernia V, Lombardi M, Lo Scocco G. Infantile acute hemorrhagic edema and ratovirus infection. Pediatr Dermatol 2004; 21: 548-550.
10. Parlak AH, Kavak A, Alper M, Özyurek H, Kocabay K. Acute infantile hemorrhagic edema: A case report. Çocuk Sağlığı ve Hastalıkları Dergisi 2002; 45: 326-329.
11. Di Lernia V, Ricci C. Skin manifestations with Rotavirus infections. Int J Dermatol 2006; 45: 759-761.
12. Weston WL, Orchard D. Vascular reactions. In: Schachner AL, Hansen CR, eds. Pediatric Dermatology, 3rd ed. Spain: Elsevier Limited: 2003: 824.
13. Taieb A, Legrain V. Acute hemorrhagic oedema of the skin in infancy. In: Harper J, Oranje A, Prose N, eds. Textbook of Pediatric Dermatology. Volume 2. USA: Philadelphia, Blackwell Science Ltd : 2002: 1569-1573.
14. Soter NA. Cutaneous necrotizing venulitis. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. Fitzpatrick's Dermatology in General Medicine, 6th ed. Volume 2. USA: Philadelphia, The McGraw-Hill Companies:2003: 1731.
15. Jeannoel P, Fabre M, Payen C, Bost M. Acute hemorrhagic edema in infants: Role of adenoviruses? Apropos of a case. J Am Acad Dermatol. 1997; 37: 673-705.
16. Morrison RR, Saulsbury FT. Acute hemorrhagic edema of infancy associated with pneumococcal bacteremia. Pediatr Infect Dis J 1999; 18: 832-833.
17. Millard T, Haris A, MacDonald D. Acute infantile hemorrhagic oedema. J Am Acad Dermatol 1999; 41: 837-839.
18. Scotese I, Gaetaniello L, Matarese G, Lecora M, Racioppi L, Pignata C. T cell activation deficiency

associated with an aberrant pattern of protein tyrosine phosphorylation after CD3 perturbation in Down's syndrome. Pediatr Res 1998; 44: 252-258.

19. Cuadrado E, Barrena MJ. Immune dysfunction in Down's syndrome: primary immune deficiency or early senescence of the immune system? Clin Immunol Immunopathol. 1996; 78: 209-214.