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Immune deposits in skin vessels of patients with acute hemorrhagic edema of young children: a systematic literature review

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Abstract

Background

Acute hemorrhagic edema of young children is a benign skin-limited vasculitis mainly affecting children 2 to 24 months of age, which is often considered the infantile variant of immunoglobulin A vasculitis, also termed Henoch-Schönlein purpura. The diagnosis is most often made on a clinical basis without a skin biopsy.

Methods

To test the prevalence of vascular immune deposits in the skin of patients with acute hemorrhagic edema of young children, we performed a systematic review of the literature.

Results

Testing for vascular immune deposits was performed in 75 cases (64 boys and 11 girls aged from 3.5 to 72, median 11 months) published between 1970 and 2018. Vessel wall deposition of complement C3 was seen in 40 cases. Immunoglobulin M (N=24), immunoglobulin A (N=21), immunoglobulin G (N=13) and immunoglobulin E (N=3) were less frequently detected. Gender, age, clinical features and disease duration were not statistically different in cases with and without vessel wall deposition of immunoglobulin A.

Discussion

This analysis points out that immune deposits in skin vessels, most frequently complement C3, are common in subjects with acute hemorrhagic edema of young children. Furthermore, it substantiates that acute hemorrhagic edema, immunoglobulin A vasculitis and pauci-immune vasculitides are different entities.

Background

Purpuric targetoid skin lesions, non-pitting edema and absent systemic involvement characterize acute hemorrhagic edema of young children, a self-limited small-vessel vasculitis mainly affecting children 2 to 24 months of age. The condition is mostly preceded either by a simple febrile illness or by an immunization.[1,2]

Acute hemorrhagic edema of young children, which is rather uncommon, is often considered to be the infantile variant of Henoch–Schönlein purpura[1-3]. In Henoch–Schönlein purpura, there is a distinctive vascular deposition of aberrantly glycosylated immunoglobulin A1[1]. The objective of this study was to test the prevalence of vascular immune deposits in the skin of patients with acute hemorrhagic edema of young children.

Methods

Starting in the early 1980s, our group has been systematically collecting the literature on acute hemorrhagic edema of young children[2-4]. Recently, we developed the **a**cute **h**emorrhagic **e**dema **bi**bliographic **d**atabase **AHEBID**[4], which progressively integrates all the original articles on acute hemorrhagic edema that appeared in Dutch, English, French, German, Italian, Portuguese, Spanish and Turkish after the first report by Snow in 1913[1-3]. The United States National Library of Medicine, the Excerpta Medica Database and especially our files were utilized. To identify further potential references, the bibliography of each article was also scanned. On August 31, 2018, the

database contained 270 reports: 14 published between 1918 and 1970, and 256 (including 472 patients) published later.

Eligible for the present study were cases published between 1970 and 2018 with both the clinical and the histological diagnosis of acute hemorrhagic edema, who also had undergone testing for immune deposits in lesional biopsies. The diagnosis of acute hemorrhagic edema made in the original reports was reviewed using recognized clinical (not-ill-appearing infant; purpuric targetoid lesions predominantly over the cheeks, ears, and extremities; often tender non-pitting edema of the face, auricles, and extremities; no pruritus or excoriations; no evidence for articular, abdominal or renal involvement; recovery within 21 days) and histological (non-granulomatous small-vessel leukocytoclastic vasculitis) criteria.[1,5,6] Patients presenting features consistent with the diagnosis of Henoch-Schönlein purpura (palpable purpura predominantly on the lower extremities and buttocks associated with at least one of the three following characteristics: abdominal pain, arthritis or arthralgia, or renal involvement) were not included[1,5].

For patients meeting the inclusion criteria, information on demographics, prodromes, clinical features and disease duration and immune deposits was obtained. Attempts were occasionally also made to contact authors of original articles to confirm the accuracy of reported data or provide missing data. The prevalence of immune deposits was separately evaluated in subjects ≤6, 7-12, 13-24 and ≥25 months of age. For statistics, the Fisher exact test with the Bonferroni adjustment and the rank sum test for two independent

samples were used. Significance was assumed when $P<0.05$.

Results

Testing for vascular immune deposits was performed by immunofluorescence in 73 and by immunohistochemistry in 2 patients (64 boys and 11 girls aged from 3.5 to 72 months, median 11 months), who had been reported in 45 different articles. A vessel wall deposition (table 1) of complement C3 occurred in two-thirds of the cases (N=40). Immunoglobulin M (N=24), immunoglobulin A (N=21), immunoglobulin G (N=13) and immunoglobulin E (N=3) were less frequently detected. No age-dependent deposition was observed.

Gender, age, clinical features and disease duration were not statistically different in 47 (69%) cases without as compared with 21 (31%) cases with vessel wall deposition of immunoglobulin A (table 2).

Discussion

Since the diagnosis of acute hemorrhagic edema of young children is mostly made on a clinical basis, the histology and especially the presence of immune deposits have been only sporadically characterized.[3,5] This survey points out that immune deposits in skin vessels, most frequently complement C3, are common in this condition. These data differentiate acute hemorrhagic edema of young children from vasculitides without substantial immune deposits such as microscopic polyangiitis, granulomatosis with polyangiitis and

eosinophilic granulomatosis with polyangiitis, which are often referred to as pauci-immune[7].

Immune deposits in small skin blood vessels characterize both acute hemorrhagic edema of young children and Henoch-Schönlein purpura. In the latter condition, the histological findings include a leukocytoclastic vasculitis and deposition of immunoglobulin A in all cases. Deposition of complement C3, immunoglobulin G or immunoglobulin M is also detected in many cases[1,5]. However, these deposits sometimes disappear with time due to proteolysis and phagocytosis[1,5]. Consequently, the term immunoglobulin A-associated vasculitis has been recently recommended[1,5]. In this survey, immunoglobulin A deposits were not detected in the vast majority of children affected by acute hemorrhagic edema, proving that acute hemorrhagic edema of young children and Henoch-Schönlein purpura are different entities.

Demographics and clinical data were similar in cases without and with vessel wall deposition of immunoglobulin A. Immunoglobulin A deposition does not occur exclusively in Henoch-Schönlein purpura and Berger disease.[1,5,8] For example, mesangial immunoglobulin A deposition may also be detected in some children with idiopathic nephrotic syndrome, in healthy renal kidney donors and in autopsy cases without known kidney disease[9-11]. Furthermore, vascular immunoglobulin A deposits sometimes occur in clinically normal skin[12]. Consequently, deposition of immunoglobulin A is a necessary but insufficient prerequisite for the diagnosis of Henoch-Schönlein purpura and Berger disease (IgA nephropathy)[1,5,8].

Henoch-Schönlein purpura and Berger disease are characterized by the deposition of aberrantly glycosylated immunoglobulin A1[1,5,13]. Standard laboratory techniques that are currently used to detect immunoglobulin A in tissue do not distinguish neither immunoglobulin A1 from immunoglobulin A2 nor normal immunoglobulin A1 from aberrantly glycosylated immunoglobulin A1. Further studies are needed to characterize the immunoglobulin A that is found in vessel wall of some children with acute hemorrhagic edema.

The main limitation of the present review results from the small number of published cases, which were reported over a period of about 50 years.

More than 100 years after the first description, acute hemorrhagic edema of young children appears more and more to be a distinctive immune-mediated leukocytoclastic small-vessel vasculitis characterized by immune deposits, mostly complement, on skin biopsy. Surprisingly, this condition has not been included in the recent update on classification on the nomenclature for cutaneous vasculitides[14].

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Declarations

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