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ORIGINAL ARTICLE

Blistering eruptions in childhood Henoch-Schönlein syndrome: systematic review of the literature

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Abstract The occurrence of blistering eruptions in childhood Henoch-Schönlein syndrome has been so far addressed exclusively in individual case reports. To describe epidemiology, clinical presentation, and therapeutic options in Henoch-Schönlein patients ≤18 years of age with blistering eruptions, we completed a systematic literature search. For the final analysis, we retained 39 reports. Ten children with blisters were found in 7 (1.5%) case series containing a total of 666 unselected pediatric Henoch-Schönlein cases. We also found 41 individually documented cases of Henoch-Schönlein syndrome with blistering eruptions. Blistering eruptions and purpura were distributed very similarly, blisters developed concomitantly with palpable purpura or with a latency of ≤14 days, and 80% of the cases remitted within 4 weeks with a similar course in children managed expectantly and in those managed with steroids.

Conclusion: Blistering eruptions are rare in Henoch-Schönlein syndrome. They can be a source of diagnostic dilemma but do not have any prognostic value since they almost always spontaneously subside within 4 weeks.

What is known:
- *Textbooks and reviews marginally refer to the occurrence of blistering eruptions in children with Henoch-Schönlein syndrome.*

What is new
- *Blistering eruptions occur in <2% of cases.*
- *Blisters and purpura are distributed similarly, blisters develop concomitantly with purpura or with a latency of ≤14 days.*
- *Almost all cases remit within 4 weeks with a similar course in children managed expectantly and in those managed with systemic steroids.*

Keywords Blister · Colchicine · Glucocorticoids · Purpura · Schönlein-Henoch · Vasculitis

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Introduction

Blisters, either vesicles (≤0.5 cm in diameter) or bullae (≥0.5 cm in diameter), are a circumscribed swelling of the skin that contain watery fluid [1, 2]. Blistering disorders are often challenging because they occur in a wide variety of clinical settings, including physical injury, infections such as chickenpox, shingles, fever blisters, bullous impetigo and staphylococcal scalded skin syndrome, photosensitive disorders such as juvenile spring eruption, drug reactions, genetic disorders, and autoimmune disorders [1, 2].

In pediatric patients with Henoch-Schönlein syndrome, the most frequent childhood vasculitis [3], blistering eruptions are rare and have been addressed exclusively in individual case reports.

This study aimed to define the clinical picture of Henoch-Schönlein syndrome with blistering eruptions in childhood and to estimate its frequency.

Methods

Search strategy

Between January and April 2016, we completed a search with no date limits of the Medical Subject Headings terms (Henoch OR Schönlein OR anaphylactoid purpura OR immunoglobulin A vasculitis) AND (blister OR bulla OR vesicle) in the U.S. National Library of Medicine database, the Excerpta Medica database, and the Google search engine. We also scanned the references of all included articles and our personal files for additional reports. We applied the principles underlying the U.K. Economic and Social Research Council guidance on the conduct of narrative synthesis and the "Preferred reporting items for systematic reviews and meta-analyses" statement.

Selection criteria—data extraction—analysis

For the final analysis, we selected reports published as full-length articles or letters, which included Henoch-Schönlein cases with blistering eruptions in presumably immunocompetent subjects of both sexes ≤18 years of age, irrespectively of follow-up duration. Articles investigating the composition of blister fluid were also selected. Reports published in languages other than Dutch, English, French, German, Italian, Portuguese, or Spanish were excluded. The diagnosis of Henoch-Schönlein syndrome made in the original reports was reviewed using recognized criteria (palpable purpura together with at least one of the following findings—abdominal pain, acute arthritis or arthralgia in any joint, or renal involvement as evidenced by pathological hematuria, with or without associated pathological proteinuria). A skin biopsy demonstrating a leukocytoclastic vasculitis was not a prerequisite for diagnosis [3].

From each individually reported case of Henoch-Schönlein syndrome with a blistering eruption, data on gender, age, family history, pre-existing chronic conditions, acute illnesses or vaccinations preceding the skin lesions by ≤10 days, cutaneous, mucous membrane, abdominal, articular or renal involvement, course, management, and bioptic findings were excerpted with the use of a prospectively defined schedule. The *c*utaneous (non-vesicular), the *a*bdominal, the *a*rticular, and the *r*enal involvement were scored on the *CAAR* grading scale (Table 1) and a simple disease activity index calculated by adding the four items together [4]. The literature search and the data extraction were carried out independently by two investigators (V.R. and M.G.B.) and a consensus was reached on all items.

Since data for the study were acquired through previously published work, consent and institutional ethical review were not required. Results are given either as frequency or as median and interquartile range (which includes half of the data points), as appropriate. Cohen's index was applied to assess the agreement between investigators on the application of the inclusion and exclusion criteria, Fisher's exact test to compare dichotomous variables, and the Mann–Whitney–Wilcoxon rank-sum test to compare continuous variables. Statistical significance was assigned at $P < 0.05$.

Results

Search results

The literature search process is depicted in Fig. 1. The chance-adjusted agreement between the two investigators on the application of the inclusion and exclusion criteria was 0.91. For the final analysis, we retained 39 scientific reports [5–43] published between 1959 and 2016 in English ($N = 33$), German ($N = 3$), Dutch ($N = 1$), French ($N = 1$), and Portuguese ($N = 1$). Among them, 17 reports were from Europe (UK, $N = 6$; Switzerland, $N = 2$; the Netherlands, $N = 2$; Turkey, $N = 2$; Belgium, $N = 1$; France, $N = 1$; Germany, $N = 1$; Italy, $N = 1$; Spain, $N = 1$), 10 from Asia (Japan, $N = 3$; South Korea, $N = 2$; India, $N = 1$; Israel, $N = 1$; People's Republic of China, $N = 1$; Thailand, $N = 1$; Republic of China, $N = 1$), 10 from North America (USA, $N = 8$; Canada, $N = 2$), 1 from Africa (Tunisia, $N = 1$), and 1 from South America (Brazil, $N = 1$). The reports described 51 pediatric cases of Henoch-Schönlein syndrome with blistering eruptions. Ten cases were found in seven case series containing unselected cases of Henoch-Schönlein syndrome [5–11]. These cases were listed and not described in detail, allowing only analysis of prevalence. The remaining 41 cases, presented in 29 articles, were well documented [12–40]. Finally, we found three reports analyzing exclusively the composition of blister fluid [41–43].

Table 1 CAAR grading for *c*utaneous (non-vesicular), *a*bdominal, *a*rticular, and *r*enal involvement in Henoch-Schönlein syndrome [42]

*C*utaneous score
Absent: no skin lesions
Mild: skin lesions located on buttocks and lower extremities alone
Moderate: skin lesions located on (a) buttocks and lower extremities *and* (b) either trunk *or* upper extremities
Severe: skin lesions located on (a) buttocks and lower extremities, (b) trunk, *and* (c) upper extremities
*A*bdominal score
Absent: no symptoms, no findings
Mild: mild abdominal pain (medically elicited)
Moderate: moderate abdominal pain (transient complaints brought to medical attention)
Severe: severe abdominal pain and/or melena, and/or hematemesis, and/or intussusception
*A*rticular score
Absent: no symptoms, no findings
Mild: symptoms or findings of articular involvement but no functional abnormalities
Moderate: symptoms and findings of articular involvement causing functional reduction (e.g. limping)
Severe: symptoms and findings causing functional loss (e.g., inability to walk)
*R*enal score
Absent: normal urinalysis
Mild: pathological hematuria, normal proteinuria [stick negative or (+), urinary protein/creatinine <20 g/mol, respectively <0.2 g/g]
Moderate: pathological hematuria, mild-moderate proteinuria (stick + to ++, urinary protein/creatinine 20–200 g/mol respectively 0.2–2.0 g/g)
Severe: pathological hematuria, severe proteinuria (stick +++ to ++++, urinary protein/creatinine >200 g/mol respectively >2.0 g/g)

The grading scale was classified as absent (=0), mild (=1), moderate (=2), or severe (=3)

Clinical data

Prevalence of bullous lesions among Henoch-Schönlein children

Seven case series of childhood Henoch-Schönlein syndrome specifically addressed the possible occurrence of blistering eruptions. The aforementioned lesions were reported in 10 (1.5%) out of 666 cases.

Presentation, course, and management

The characteristics of the 41 individually documented Henoch-Schönlein patients are given in Table 2. They were 38 previously healthy children and 3 with a pre-existing chronic condition [2, 10, 29]: hepatitis B and each one child with dominant and recessive bullous epidermolysis, respectively. No further cases of vasculitides were reported within the families of the patients. The disease severity score (5 [3–6]) ranged from 2 to 8. Hemorrhagic blisters on the hard palate were observed in one case [48]. The clinical diagnosis of Henoch-Schönlein syndrome was supported by a skin biopsy in 25 cases (including the 3 cases with a pre-existing chronic condition). Vascular immunoglobulin A deposits were not found in nine cases.

In 40 cases (21 ♂ and 19 ♀), blistering eruptions developed ≤14 days (median 4 days) after the purpuric rash. Both purpura and blisters located on buttocks and lower extremities were noted in all cases. The distribution of blisters and purpura was very similar (Fig. 2). Blister eruptions developed after several insect bites and scratching in a 6-year-old Japanese boy with Henoch-Schönlein syndrome [31]. However, no temporal association with insect bites was reported in the remaining cases.

No drug management was administered in ten patients. Systemic steroids were given in 17 and colchicine in 2 cases (no detailed information on either management or course was available for the remaining cases). Patients managed expectantly and patients managed with steroids did not significantly differ with respect to age, gender, disease activity index, and clinical course, as given in Table 3.

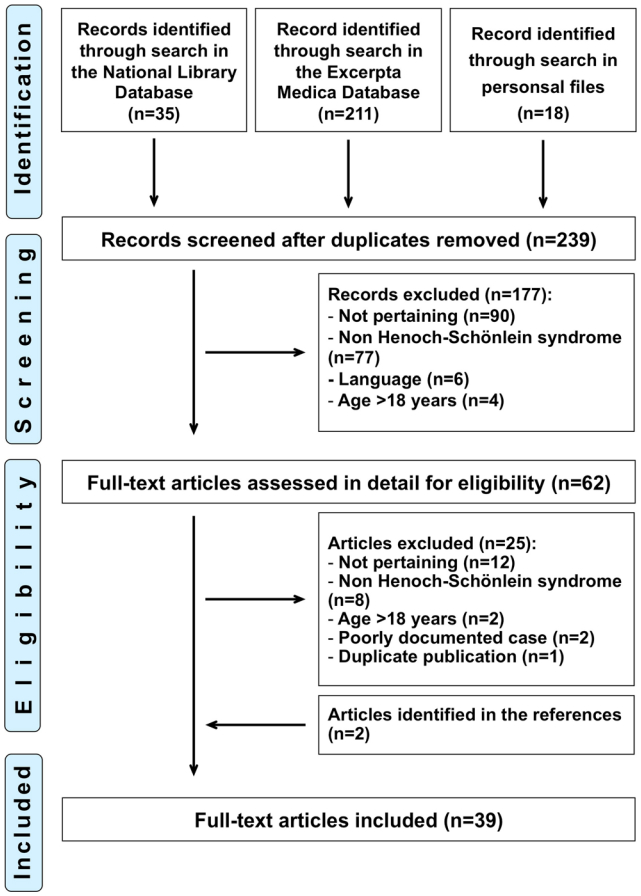

Fig. 1 Blistering eruptions in childhood Henoch-Schönlein syndrome. Flowchart of the literature search process

Table 2 Characteristics of 41 Henoch-Schönlein patients 18 years or less of age (range 3.0–16 years) with blistering eruptions (data are given either as relative frequency and percentage or as median and interquartile range)

Gender, ♂/♀	21:20
Age, years	7.9 [6.0–10]
Pre-existing chronic disease, *N* (%)	3[a]
Prodromal respiratory illness, *N* (%)	13[b]
Non-blistering skin involvement	
Mild, *N* (%)	18 (44)
Moderate, *N* (%)	13 (32)
Severe, *N* (%)	10 (24)
Abdominal involvement	
None, *N* (%)	13 (32)
Mild, *N* (%)	19 (46)
Moderate, *N* (%)	6 (15)
Severe, *N* (%)	3 (7)
Articular involvement	
None, *N* (%)	12 (29)
Mild, *N* (%)	25 (61)
Moderate, *N* (%)	2 (5)
Severe, *N* (%)	2 (5)
Renal involvement	
None, *N* (%)	25 (61)
Mild, *N* (%)	6 (15)
Moderate, *N* (%)	8 (19)
Severe, *N* (%)	2 (5)
Disease severity score	5 [3–6]
Skin biopsy findings	
Vasculitis without immunoglobulin A search, *N* (%)	1 (4)
Vasculitis without immunoglobulin A deposits, *N* (%)	9 (36)
Vasculitis with immunoglobulin A deposits, *N* (%)	15 (60)

[a] Hepatitis B (*N* = 1), dominant (*N* = 1) respectively recessive (*N* = 1) bullous epidermolysis

[b] Acute otitis media (*N* = 7), pharyngitis (*N* = 5), or mycoplasma pneumoniae respiratory infection (*N* = 1). None of the cases was preceded by a vaccination

In a 5-year-old French boy, a severe and relapsing form of blistering Henoch-Schönlein syndrome persisted for 10 months despite various courses of steroid therapy. Oral colchicine (1.0 mg/day) was followed by a marked improvement of skin manifestations within a few days. Discontinuation of colchicine and an attempt to decrease the dosage to 0.5 mg/day, respectively, were always followed by a relapse within 3 days. Colchicine was finally stopped when the boy was 8 years old without any relapse in the following 6 months [39]. In a 14-year-old Chinese boy, a hepatitis B carrier, both purpura and blisters resolved within 2 weeks after starting colchicine (dosage not reported) and did not recur [22].

The 41st case, a 9-year-old Scottish girl, is worthy of particular mention. She developed a rather mild form of purpuric Henoch-Schönlein syndrome mainly affecting the lower extremities that persisted over 2 years despite treatment with steroids and dapsone. Since the family was desperate, the decision was made to have a trial of the Q-switched Nd:YAG laser. Three days later, the patient developed severe blistering eruptions to the treated areas that healed spontaneously in 7 days [24].

The disease course was characterized by recurrent episodes of bullous Henoch-Schönlein syndrome in the two patients affected by bullous epidermolysis [28, 30]. No recurrences were reported in the remaining cases.

Blister fluid analysis

Blister fluid analysis, performed in 7 of the 41 cases, disclosed large amounts of matrix metalloproteinases, especially matrix metalloproteinase 9 and human leukocyte elastase.

Discussion

This literature review on blistering eruptions in Henoch-Schönlein syndrome in childhood showed that (a) blistering eruptions occur in <2% of patients, (b) purpura and blisters are distributed very similarly, (c) blistering lesions develop concomitantly with palpable purpura or with a latency of ≤14 days, (d) almost all cases remit within 4 weeks with a similar course in children managed expectantly and in those managed with systemic steroids, and (e) two anecdotal observations suggest that colchicine might be prescribed for severe long-lasting cases.

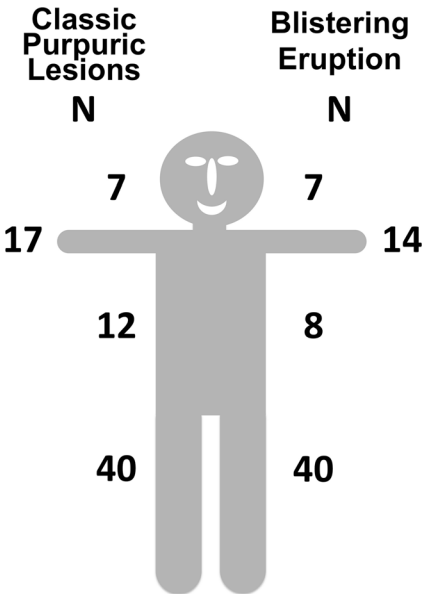

Fig. 2 Distribution of skin lesions among 40 pediatric cases (21 ♂ and 19 ♀) of Henoch-Schönlein syndrome with onset of blistering eruptions ≤14 days after the classic purpuric lesions

Table 3 Influence of drug management with systemic steroids on blistering eruptions in Henoch-Schönlein syndrome (results are given either as median and interquartile range or as relative frequency)

	No systemic steroids	Systemic steroids
N	10	17
Gender, ♂/♀	5:5	11:6
Disease severity score	4 [3–5]	5 [4–6]
Duration of vesicular lesions		
Total duration		
Days	21 [14–28]	20 [14–28]
Duration >28 days, *N*	2	4
Duration before steroids, days	NA	7 [3–10]
Duration after steroids, days	NA	13 [8–20]

NA Not applicable

Although not supported by the results of well-designed trials, there is a general agreement that, in Henoch-Schönlein syndrome [3] and acute hemorrhagic edema, its infantile variant [44], the skin rash does not respond to systemic steroids. As a consequence, management of cutaneous Henoch-Schönlein syndrome is largely supportive. This analysis does not support the prescription of steroids in childhood Henoch-Schönlein syndrome with blistering eruptions. Circumstantial reports suggest colchicine or dapsone may hasten the resolution of the rash in Henoch-Schönlein syndrome. Two observations included in this review confirm that colchicine might have a role in Henoch-Schönlein syndrome with blistering eruptions.

Blister fluid analysis disclosed large amounts of matrix metalloproteinase 9 and human leukocyte elastase. In vivo and in vitro studies point out that these molecules are critically involved in the induction of blisters [2]. It is currently unclear, however, why a very small minority of Henoch-Schönlein children develop blistering eruptions, whereas most have only palpable purpura. Since some patients with recurrent blistering eruptions included in this survey were affected by a genodermatosis, we speculate that a pre-existing skin fragility and susceptibility might be a primary factor in many cases. This observation, taken together with the temporal association with insect bites and scratching noted in a Japanese child and with laser therapy noted in a Scottish girl, prompts us to speculate that exogenous factors might also be involved as triggers of blistering lesions.

Blistering eruptions can sometimes be difficult to distinguish clinically and therefore challenging [1, 2]. Unsurprisingly, therefore, a diagnostic skin biopsy was performed in many cases. Vascular immunoglobulin A deposits were not detected in some cases, confirming the existence of Henoch-Schönlein cases in which immunoglobulin A testing is negative. Negative testing occurs mainly if the biopsy is obtained from the middle of a lesion where the presence of proteolytic enzymes can result in negative staining [45].

Some limitations of this analysis should be mentioned. First, it results from the very small number of published cases, often with a brief (or even without) follow-up. Second, the mechanisms by which some Henoch-Schönlein children develop blistering eruptions are so far undemonstrated. Third, it is currently unclear whether this cutaneous variety mainly develops in Henoch-Schönlein patients with high disease severity score. Finally, since diagnostic and therapeutic recommendations can be uneasily inferred from the accumulation of individual case reports, suggested diagnostic and therapeutic recommendations arise from low-quality evidence.

In conclusion, in childhood Henoch-Schönlein syndrome, blistering eruptions represent an unusual but well-recognized manifestation. They appear concomitantly or soon after the characteristic cutaneous manifestation of Henoch-Schönlein syndrome. They can be a source of diagnostic dilemma but do not seem to have any prognostic value since they almost always spontaneously subside within 4 weeks. Confirmation of the suspected diagnosis of Henoch-Schönlein syndrome by skin biopsy, which is normally unnecessary, is recommended for clinically unclear cases.

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Authors' Contributions – Study concept and design: V.R., S.A.G.L., M.G.B., G.P.R.
– Acquisition, analysis, and interpretation of data: V.R., S.A.G.L., G.D.S., M.G.B., G.P.M.
– Statistical analysis: G.D.S., M.G.B., G.P.M.
– Drafting of the manuscript: V.R., S.A.G.L., M.G.B., G.P.R.
– Critical revision of the manuscript: V.R., S.A.G.L., G.D.S., M.G.B., G.P.R., G.P.M.

Compliance with ethical standards The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest The authors declare that they have no competing interests.

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