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1 **Accurate diagnosis of acute hemorrhagic edema of infancy: a French multicenter**
2 **observational study**

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1 **Abstract**

2 ***Purpose***

3 To highlight clinical signs that are either suggestive of or against the diagnosis of AHEI to
4 improve diagnosis and management.

5 ***Methods***

6 The medical records of children under 3 years old diagnosed with AHEI were retrospectively
7 reviewed. Clinical data and photographs were reviewed by three independent experts, and the
8 cases were classified as probable, doubtful or unclear AHEI.

9 ***Results***

10 Of the 69 cases of children diagnosed with AHEI included in 22 centers, 40 were classified as
11 probable, 22 as doubtful and 7 as unclear. The median age of patients with probable AHEI
12 was 11 months [IQR 9-15] and they were in overall good condition (n=33/40, 82.5%). The
13 morphology of the purpura was targetoid in 75% of cases (n=30/40), ecchymotic in 70% of
14 cases (n=28/40) and affected mostly the legs (n=39/40, 97%), the arms (n=34/40, 85%) and
15 the face (n=33/40, 82.5%). Edema was observed in 95% of cases and affected mostly the
16 hands (n=36/38, 95%) and feet (n=28/38, 74%). Pruritus was absent in all patients with
17 probable AHEI and described for 6/21 with doubtful AHEI (29%). AHEI was the original
18 diagnosis in only 24 patients (n=24/40, 60%). The major differential diagnoses were purpura
19 fulminans and urticaria multiforme.

20 ***Conclusions***

21 AHEI, which the diagnosis is made on clinical findings, is often misdiagnosed. Purpuric
22 lesions localized on the face/ears, arms/forearms, and thighs/legs with edema of the hands
23 without pruritus in a young child with a good overall condition are highly suggestive of
24 AHEI.

25

1 **What is Known:**

- 2 • Acute hemorrhagic edema of infancy (AHEI) is a cutaneous leukocytoclastic vasculitis
3 affecting children under 3 years old.
- 4 • Appropriate diagnosis is important to distinguish this benign disease from more
5 serious diseases to avoid investigations and treatments, iatrogenic harm and
6 unnecessary follow-up.

7 **What is New:**

- 8 • AHEI is an uncommon disorder often misdiagnosed by pediatricians and
9 dermatologists.
- 10 • Purpuric lesions localized on the face/ears, arms/forearms, and thighs/legs with edema
11 of the hands without pruritus in an infant with a good overall condition are highly
12 suggestive of AHEI

13

14 **Keywords:** acute hemorrhagic edema of infancy, observational study, leukocytoclastic
15 vasculitis, pediatric dermatology, purpura, Finkelstein-Seidlmayer vasculitis

16

17 **Abbreviations**

18 AHEI, acute hemorrhagic edema of infancy

19 IgAV, IgA vasculitis

20

1 **Introduction**

2 Acute hemorrhagic edema of infancy (AHEI) is a cutaneous leukocytoclastic vasculitis
3 usually affecting children under 3 years old.¹⁻³ The clinical presentation is often alarming with
4 a sudden appearance of large targetoid purpuric lesions, typically on the face and extremities,
5 associated with painful edema and fever in a previously healthy child.^{3,4} The diagnosis is
6 usually based on clinical manifestations and can be supported by a skin biopsy when
7 appropriate.⁵ AHEI is a self-limited disease with spontaneous resolution within a few weeks.
8 Possible triggers include infectious agents, especially viruses.^{3,6}
9 AHEI has been documented in small retrospective case reports^{3,7-16} and in one prospective
10 case series including 18 patients.¹⁷ This uncommon disorder is often underrecognized and is
11 frequently confused with IgA vasculitis (IgAV),^{3,5,8,9,18} purpura fulminans^{7,19,20} or urticaria
12 multiforme.^{2,3,5,17,21,22} In 1996, Krause *et al* suggested non-validated clinical criteria for the
13 diagnosis of AHEI as follows: (1) age < 2 years, (2) purpuric or ecchymotic target-like skin
14 lesions with edema on the face, ears and extremities, (3) lack of visceral involvement and (4)
15 spontaneous recovery within a few days or weeks.²³ Appropriate diagnosis is important to
16 distinguish this benign disease from more serious diseases to avoid superfluous investigations
17 and treatments, iatrogenic harm and unnecessary long-term follow-up.
18 The main objective of this study was to develop a diagnostic consensus for AHEI based on
19 the opinions of expert dermatologists. The secondary objective was to compare the
20 characteristics of AHEI classified as probable, doubtful and unclear.

21

22 **Materials and methods**

23 ***Study design and setting***

24 This study was a French multicenter observational study that retrospectively reviewed all
25 cases of AHEI diagnosed between 1996 and 2021 in 22 centers.

1 ***Participants***

2 Children under 3 years old with a diagnosis of AHEI were included. The diagnosis was made
3 by hospital physicians (pediatric dermatologists, pediatric rheumatologists or pediatricians).

4 ***Data collection***

5 A questionnaire was sent to members of the Research Group of the French Society of
6 Pediatric Dermatology, members of the French Society for Pediatric Rheumatology and
7 Internal medicine; and pediatricians from five pediatric departments. The providers collected
8 the data of all patients from their hospital centers diagnosed with AHEI during the study
9 period, including demographic data, clinical characteristics, laboratory results, treatments and
10 follow-up data. Clinical photographs were collected. We excluded patients with missing data
11 for age, clinical features, investigations and clinical photographs. This non-interventional
12 research was conducted in accordance with the French Data Protection Agency.

13 ***Outcomes***

14 The primary outcome measure was the level of agreement among the panel of three
15 experienced experts (pediatric dermatologists) from hospital tertiary centers (authors AM, CB
16 and MP) on the diagnosis of AHEI in previously diagnosed patients. All cases were reviewed
17 independently. Data and photographs collected from the questionnaires were used to classify
18 each patient into probable, doubtful or unclear AHEI. The patient was classified into one of
19 these three categories when at least two of the three experts agreed on the same classification.
20 In cases of disagreement or incomplete data, the cases were classified as unclear AHEI. The
21 final classification determined by the consensus of experts was considered the gold standard.
22 Patients with an unclear diagnosis were excluded from further analysis. Because of no gold
23 standard for diagnosing the disease (which is the rationale for this study), experts were asked
24 to perform diagnosis based on history, photographs when available, clinical data and
25 complementary exams, with no pre-established diagnostic criteria. The clinical criteria

1 suggested by Krause et al²³ were known by the experts but were not used to classify AHEI.
2 Indeed, these criteria are not sensitive and would have excluded potential patients with AHEI.
3 The secondary outcome was to compare demographic characteristics and clinical
4 manifestations between the children with probable and doubtful AHEI to highlight clinical
5 signs that were either suggestive of or against the diagnosis of AHEI.

6 *Statistical analyses*

7 Descriptive statistics are expressed with mean (range) or median (Q1–Q3) for quantitative
8 data and number (%) for categorical data. Chi-square or Fischer test was used to analyze
9 categorical outcomes. A Wilcoxon-test was used to analyze continuous outcomes. The Fleiss
10 kappa index was calculated to evaluate the degree of agreement among the experts. All tests
11 were two-tailed and p values less than 0.05 were considered significant. No methods were
12 used for missing data. Statistical analyses involved use of R 3.5.1 (R Foundation for
13 Statistical Computing, Vienna, Austria).

14

15 **Results**

16 *Participants and experts*

17 The study screened 85 children, of which 16 were excluded (one duplicate patient and 15 with
18 missing data). **Figure 1** shows a flow chart of the process of patient inclusion. Overall, the
19 data from 69 children were evaluated by the experts.

20 The experts classified the patients into probable AHEI in 40 cases (58%), doubtful AHEI in
21 22 cases (32%) and unclear AHEI in seven cases (10%). Patients diagnosed by dermatologists
22 were classified as probable AHEI, doubtful AHEI and unclear AHEI in 69%, 28%, and 3% of
23 cases, respectively and those diagnosed by pediatricians in 47%, 38% and 15% of patients.
24 Photographs of the lesions were available in 38 cases (55%), mostly performed by

1 dermatologists (27/38, 71%). Among the 69 patients included, 14 (20%) had skin biopsies
2 performed both by pediatricians (7/14) and dermatologists (7/14).

3 *Primary outcome results*

4 The degree of agreement between the experts for probable AHEI was moderate with a
5 category-wise kappa of 0.45. There was a low degree of agreement on the classifications of
6 doubtful and unclear AHEI cases (category-wise kappa of 0.36 and 0.15 respectively) (**Table**
7 **1 online**). One expert classified 25 cases as unclear compared to 6 and 9 for the two other
8 experts and partially explained the moderate and low consensus obtained.

9 *Secondary outcome results*

10 Demographic characteristics and clinical manifestations in children with probable and
11 doubtful AHEI are shown in **Table**. Triggering factors were evidenced in 43 patients (28
12 patients with probable AHEI [70%] and 15 patients with doubtful AHEI [68%]); and were
13 acute infections and vaccination. The mean duration between the onset of infection and
14 diagnosis of AHEI (41/43 patients) was 6.8 days (range 0-20, missing data for three patients).
15 Between the vaccination and disease onset (2/43 patients), data was available for one patient
16 and was four days. The overall condition was good in 83% (n=33/40) and 91% (n=20/22) of
17 children with probable and doubtful AHEI, respectively. Clinical signs significantly
18 associated with probable AHEI were purpura localized on the face, ears, arms/forearms or
19 thighs/legs, and edema localized on the hands with the absence of pruritus. The morphology
20 of the purpura and the localization of the purpura on the hands or feet were not distinguishing
21 features of probable versus doubtful AHEI (**Figures 2 and 3**).

22 A sensitivity analysis, which was not initially planned, was conducted to analyse clinical
23 characteristics of patients with clinical photographs provided (**Table 2 online**). Results were
24 similar to the main analysis, except for triggering factors, which were significantly more

1 frequent with probable AHEI, and pruritus, which was more frequent but not significantly
2 with doubtful AHEI.

3 In children with probable AHEI, the diagnosis was delayed by a mean of 2.7 days (0-11 days).
4 AHEI was the original diagnosis in 60% of patients (n=24/40). Other initial diagnoses were
5 purpura fulminans in 10 patients treated by antibiotics and discontinued after negative culture
6 results, IgAV in two patients, drug-induced anaphylaxis in two patients treated with
7 antihistamines and corticosteroids, a viral infection in one patient treated with antibiotics and
8 corticosteroids, and bullous impetigo in one patient due to a bullous purpura.

9 C-reactive protein (CRP) level was obtained for 29 of 40 patients and was elevated in 23
10 (58%; range 16 to 183 mg/l; median 54 mg/l). In 6 patients, CRP levels were above 100 mg/l,
11 with negative bacteriological cultures. No data on leukocytes, sedimentation rates, D-dimers
12 were available. Creatinine level was normal in all 17 patients who were tested. Proteinuria
13 was investigated in 29 patients and was found slightly positive in one case, at 0.5 g/24h. The
14 following bacteriological tests were performed in 22 patients among 40 (55%): blood culture
15 in 12 (30%), mycoplasma serology in eight (20%), spinal puncture in six (15%),
16 meningococcal PCR in four (10%) and urinary culture in five (13%). All bacterial tests were
17 negative except for one urine sample positive for *Escherichia coli*. Viral tests were performed
18 in 16 patients (40%). Nasal swabs of two patients were positive for rhinovirus, and the
19 cerebrospinal fluid of one patient was positive for enterovirus. Skin biopsies were performed
20 in 13 patients (33%) with probable AHEI and showed a leukocytoclastic vasculitis with
21 presence of C3 on direct immunofluorescence in 6 out of 9 patients. Sixty percent of children
22 (n=24/40) were hospitalized for 1 to 11 days (median 3 days, missing data for 16 patients) in
23 pediatric departments, including two patients in an intensive care unit. One patient with a
24 urinary tract infection was treated with antibiotics. Four patients received H1-anti histamines
25 and 1 patient oral corticosteroids. For 34/40 patients, no treatment was initiated for managing

1 AHEI. The purpura and edema completely resolved without sequelae in all cases within 2 to
2 44 days (mean 17 days). Recurrences with new cutaneous manifestations occurred in two
3 patients 1 and 2 weeks later respectively. Eleven patients who were monitored at follow-up
4 with urinalysis had normal urine findings.

5 The diagnosis of AHEI was doubtful in 22 patients. Photographs were available in 14 cases
6 and were consistent with urticaria multiforme in 11 cases, isolated petechial purpura on the
7 lower limbs in two cases and IgA vasculitis in one case. One patient had a skin biopsy
8 showing a leukocytoclastic vasculitis. Eight patients had no photographs, but for seven
9 patients, the clinical history was consistent with urticaria multiforme and in 1 with IgAV.

10 The diagnosis of AHEI was unclear in seven patients; six of them due to incomplete data and
11 one due to expert disagreement. The latter was a 12-month-old patient with ecchymotic
12 purpura who was in good overall condition classified as probable AHEI by the first expert,
13 doubtful by the second expert due to purpura and edema affecting only the feet, and unclear
14 by the third expert due to incomplete data with no photographs.

15

16 **Discussion**

17 *Key results*

18 Our study found that AHEI is an uncommon disorder often misdiagnosed by both
19 dermatologists and pediatricians. Nearly 40% of cases were not considered as probable AHEI
20 by the experts. Urticaria multiforme was often mistaken for AHEI, and AHEI was often
21 misdiagnosed as purpura fulminans leading to unnecessary hospitalizations and procedures.

22 *Interpretation*

23 In agreement with previous studies,^{3,5,17} our study indicates that AHEI typically presents with
24 a triad of the sudden appearance of purpuric lesions, edema and fever in an otherwise healthy
25 boy with a median age of 11 months. The morphology of the purpura was typically targetoid

1 or rosette-shaped and/or ecchymotic and predominantly affected the arms, the legs, the face
2 and the ears with relative sparing of the trunk (**Figure 3a and b**). Edema predominantly
3 affected the hands and feet and could be painful. An infectious trigger was found in most
4 cases and was consistent with a recent study.²⁴ Pruritus was uncommon and was mostly
5 observed for patients with doubtful AHEI. Although visceral involvement is uncommon,²⁵
6 two patients with probable AHEI, for whom the diagnosis of IgA vasculitis was excluded, had
7 abdominal pain. Lesions in different stages at the same age were also observed with co-
8 existence of purpuric and post-ecchymotic lesions (**Figure 3c**).²⁶ However, the children in our
9 study had greater impaired general condition (17%) than reported in a previous study (general
10 appearance severely or mildly reduced in 8% of cases)³. This finding might be due to our
11 large recruitment from pediatric emergency departments (14/40, 35%, in the probable AHEI
12 group).

13 Most children classified as doubtful AHEI had clinical features consistent with urticaria
14 multiforme. Urticaria multiforme is a cutaneous hypersensitivity reaction more common in
15 young children and presents with large annular and polycyclic erythematous wheals with
16 dusky ecchymotic centers, sometimes in association with acral edema. Lesions are commonly
17 transient, diffuse and pruriginous, and treatment with antihistamines is usually
18 effective.^{2,3,5,17,21,22} IgAV also shares similar clinical features with AHEI, and some suggest
19 that AHEI is a benign variant of IgAV occurring in young children.^{3,5,8,9,18} Reports of the
20 simultaneous appearance of these two diseases in a brother and a sister suggest that AHEI and
21 IgAV may be variants of the same clinical entity.²⁷ However, IgAV and AHEI have important
22 differences, and the distinction between these two diseases is essential to avoid unnecessary
23 investigations, unjustified concern and long term renal monitoring. IgAV affects older
24 children between three and 12 years old. The purpuric lesions of IgAV are predominantly
25 localized to the lower extremities. IgAV can present with edema of the extremities and is

1 associated with abdominal, articular or renal involvement.²⁸ Purpura fulminans is another
2 differential diagnosis reported by several publications.^{7,19,20} In purpura fulminans, the purpura
3 typically starts on the lower limbs, quickly spreads to become extensive, ecchymotic and
4 necrotic, and the patients typically have a very poor overall condition.²⁹

5 AHEI can have a frightening appearance; therefore, children were hospitalized in 60% of
6 cases, and in two cases, the child was placed in an intensive care unit. These patients
7 underwent invasive procedures such as spinal puncture, received irradiation from radiological
8 exams and were given ineffective treatments. These superfluous investigations and treatments
9 increase the risk of iatrogenic harm. In our study, purpuric lesions localized on the face/ears,
10 arms/forearms, and thighs/legs, edema of the hands, and the absence of pruritus were the
11 distinguishing features between AHEI and other diagnoses, including urticaria multiforme and
12 IgAV. A good overall condition usually discriminates between purpura fulminans and
13 AHEI,^{7,19,20} but in cases of doubt, antibiotics and hospitalization are justified.

14 The diagnosis of AHEI can usually be made based on clinical manifestations; therefore, a skin
15 biopsy is not essential.^{3,5,17} However, misdiagnoses are common and the classification criteria
16 suggested by Krause *et al* are not sensitive, include an evolutive feature not present at the
17 diagnosis and are not validated. All skin biopsies performed in our series showed a
18 leukocytoclastic vasculitis, some with presence of C3 on direct immunofluorescence.³⁰

19 Although leukocytoclastic vasculitis can be found on the skin biopsies of patients with IgAV
20 ³¹, and purpura fulminans, skin biopsies can be helpful to differentiate between diagnoses
21 ^{31,32,33}. In urticaria multiforme, a skin biopsy shows diffuse dermal edema, perivascular and
22 interstitial lymphocytic infiltrate with variable number of eosinophils and/or neutrophils and,
23 rarely, a leukocytoclastic vasculitis.³³ IgA deposits on direct immunofluorescence are highly
24 suggestive of IgAV.³¹ A bacterial culture of the skin biopsy specimen can suggest purpura
25 fulminans even after the initiation of antibiotics.^{32,34}

1 In uncertain cases, an expert opinion may also be sought, in which case, photographs of the
2 cutaneous lesions become critical. In our study, patients were classified as probable AHEI in
3 69% of cases reported by dermatologists versus in 47% of cases reported by pediatricians.
4 This discrepancy was likely due to the lack of available photographs in cases reported by
5 pediatricians.

6 ***Limitations and strengths***

7 Our study is limited by its retrospective design; we could not avoid recall bias and incomplete
8 data, such as missing photographs. Moreover, the inter-expert disparity observed was
9 probably linked to the current lack of criteria for diagnosing condition, the lack of clinical
10 photographs for some patients and the missing data due to retrospective collection, although
11 we excluded patients with missing data for important data. However, we described the largest
12 series of AHEI published to date, with all cases of AHEI diagnosed by three independent
13 experts. Recent literature included case series with a lower sample size (16 and 26
14 patients)^{35,36} and systematic reviews of the Acute Hemorrhagic Edema Bibliographic
15 Database, but patients/reports included were not reviewed by experts.^{24,25,30} Indeed, the main
16 strength of our work is that we included only patients with a probable diagnosis of AHEI
17 defined by three experts. We believe that cases reported in the literature could be
18 misdiagnosed as AHEI, because in the present work, 32% of cases had doubtful AHEI. In
19 addition, we compared patients with probable and doubtful AHEI to highlight clinical features
20 that could help clinicians in the diagnosis of AHEI.

21 ***Conclusion***

22 In conclusion, AHEI, which the diagnosis is made on clinical examination, often
23 misdiagnosed causing unnecessary hospitalizations, procedures and treatments. Given its
24 dramatic presentation, it is essential to accurately diagnose AHEI to avoid any undue stress to
25 parents and medical staff. Clinical signs that can help distinguish AHEI from other diagnoses

1 are purpuric lesions localized on the face/ears, arms/forearms, and thighs/legs with relative
2 sparing of the trunk and edema localized on the hands in a young child (under 3 years old)
3 with good overall condition and the absence of pruritus. In uncertain cases, a photograph of
4 the lesions shared with an AHEI expert may be helpful. A urine test should be performed at
5 diagnosis, and other investigations (e.g., skin biopsy, blood sample) are not required, unless in
6 case of atypical features (e.g., impaired general condition). For the follow-up, urinary
7 investigation should be proposed in case of proteinuria at the diagnosis. A clinical evaluation
8 by a general practitioner pediatrician or dermatologist could be proposed to ensure resolution
9 of symptoms.

10

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7

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13 **Author Contributions**

14 All authors contributed to the study conception and design. Material preparation, data
15 collection and analysis were performed by Sophie Leducq, Annabel Maruani, Maryam Piram.
16 The first draft of the manuscript was written by Sophie Leducq, Annabel Maruani and
17 Maryam Piram and all authors commented on previous versions of the manuscript. All
18 authors read and approved the final manuscript.

19 **Ethics approval**

20 This non-interventional research (retrospective research on previously collected data, other
21 than genetic data) was conducted in accordance with the French Data Protection Agency.

22 **Consent to publish**

23 The authors affirm that human research participants provided informed consent for
24 publication of the images in Figures 3.

25

26

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1 **Table.** A comparison between clinical characteristics of patients classified as probable (n=40)
 2 and doubtful (n=22) acute hemorrhagic edema of infancy

<i>Characteristics</i>	Probable AHEI n=40	Doubtful AHEI n=22	<i>P</i>
Age. months (median [IQR])	11 [9-15]	15 [9-19]	0.21
Sex (M/F)	29/11	12/10	0.25
Trigger, n (%)	28 (70)	15 (68)	>0.99
General symptoms, n (%)			
Fever	24 (60)	10 (45)	0.40
Impaired general condition	7 (17)	2 (9)	0.47
Pruritus*	0 (0)	6 (29)	0.001
Abdominal pain‡	2 (5)	1 (4)	>0.99
Purpura, n (%)	40 (100)	21 (95)	-
Localization of the purpura, n (%)			
Face	33 (82)	8 (38)	<0.001
Ears	22 (55)	3 (14)	0.002
Hands	16 (40)	4 (19)	0.10
Arms/forearms	34 (85)	9 (43)	<0.001
Feet	21 (52)	11 (52)	>0.99
Thighs/legs	39 (97)	14 (67)	0.002
Trunk	12 (30)	11 (52)	0.09
Aspect of the purpura, n (%)**			
Rosette-shaped	30 (75)	10 (56)	0.14
Ecchymotic	28 (70)	11 (61)	0.50
Petechial	5 (12)	1 (6)	0.65
Necrotic	4 (10)	1 (6)	>0.99
Bullous	3 (7)	0 (0)	0.54
Edema, n (%)	38 (95)	20 (95)	-
Localization of the edema, n (%)			
Forehead or eyelids	7 (18)	6 (30)	0.34
Hands	36 (95)	8 (40)	<0.001
Feet	28 (74)	16 (80)	0.75
Scrotal	2 (5)	2 (10)	0.60

3 AHEI: acute hemorrhagic edema of infancy, M: male, F: female, IQR: interquartile range

4 *Missing data for three patients in the group probable AHEI and one patient in the group
 5 doubtful AHEI

6 **Missing data for three patients in the group doubtful AHEI

7 ‡ For patients in the group probable AHEI, IgA vasculitis was excluded because of no IgA
 8 deposits for one patient and lack of complete clinical features and clinical photographs for
 9 another. In the doubtful AHEI group, a diagnosis of IgA vasculitis could not be excluded (no
 10 skin biopsy performed).

11

1 **Figure legends**

2 **Figure 1**

3 Flow diagram showing the selection of cases of acute hemorrhagic edema of infancy reported
4 by pediatricians, pediatric dermatologists and pediatric rheumatologists

5 *GRSFDP: Research Group of the French Society of Pediatric Dermatology, SOFREMIP:*
6 *French Society for Pediatric Rheumatology and Internal medicine*

7 **Figure 2**

8 Distribution of skin lesions in the 40 patients: frequency (%) of purpura (left) and edema
9 (right)

10 **Figure 3**

11 (a) Edema of the hands and feet associated with rosette-shaped purpura on the face and the
12 limbs in a 14-month-old boy diagnosed with acute hemorrhagic edema of infancy

13 (b) Purpura of the ear in an infant with acute hemorrhagic edema of infancy (*Coll Pr*
14 *Boralevi*)

15 (c) Coexistence of lesions of different stages: purpuric and post-ecchymotic lesions (*Coll Pr*
16 *Boralevi*)

1 **Supplemental file**

2 **Table 1:** Classifications and degree of agreement between the experts for the 69 cases of

3 AHEI

4 **Table 2:** Sensitivity analysis for comparison between clinical characteristics of patients with

5 clinical photographs classified as probable (n=24) and doubtful (n=14) acute hemorrhagic

6 edema of infancy