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Acute Hemorrhagic Edema of Infancy: Case Report and Comparison with Meningococcemia

Edema agudo hemorrágico da infância: relato de caso e comparação com meningococcemia

Edema agudo hemorrágico de la infancia: relato de caso y comparación con meningococcemia

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This paper aims at reporting the case of a 1 year and 8 months old child who was in a bad general state, and was admitted at the emergency room while going through hypovolemic shock, with acute hemorrhagic edema of infancy (AHEI) or its variant: Henoch - Schoenlein purpura (HSP). Information was obtained through a review of medical records, an interview with the patient, a photographic register of the diagnostic methods to which the patient was submitted. A literature review was also conducted. The reported case and the publications researched bring to light and discuss the diagnosis of a complex situation, which involves the menigococcal disease and the AHEI in its various forms, also discussing the proper therapy in urgent cases.
Descriptors: Schoenlein-Henoch Purpura; Vasculitis; Meningitis.

O presente trabalho tem como objetivo relatar o caso de uma criança com 1 ano e 8 meses, em mau estado geral e choque hipovolêmico, atendidoatendida na urgência com edema agudo hemorrágico da infância (EAHI), ou a sua variante: Púrpura de Schoenlein-Henoch (PHS). As informações foram obtidas por meio de revisão de prontuário, entrevista com mãe do paciente, registro fotográfico dos métodos diagnósticos ao quais o paciente foi submetido e revisão da literatura. O caso relatado e as publicações pesquisadas trazem à luz a discussão do diagnóstico de uma situação complexa que é a doença meningocócica e o EAHI em suas várias formas, bem como na terapêutica mais adequada em momento de urgência.
Descritores: Púrpura de Schoenlein-Henoch; Vasculite; Meningite.

El presente trabajo tiene como objetivo relatar el caso de un niño de 1 año y 8 meses, en mal estado general y shock hipovolémico, atendido en urgencia con edema agudo hemorrágico de la infancia (EAHI), o su variante: Púrpura de Schoenlein-Henoch (PHS). Las informaciones fueron obtenidas por medio de revisión de historia clínica, entrevista con la madre del paciente, registro fotográfico de los métodos diagnósticos a los cuales el paciente fue sujeto y revisión de la literatura. El caso relatado y publicaciones investigadas, traen a la luz la discusión del diagnóstico de una situación compleja que es la enfermedad meningocócica y el EAHI en sus varias formas, bien como en la terapia más adecuada en un momento de urgencia.
Descriptores: Púrpura de Schoenlein-Henoch; Vasculitis; Meningitis.

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INTRODUCTION

The acute hemorrhagic edema of infancy (AHEI) is a rare condition of which there are about 100 cases described in literature, although it is believed that it may not have been diagnosed in some past occasions, as it can be mistaken with the Henoch-Schönlein Purpura (HSP) in its childhood form.

It affects infants between 4 and 24 months of age, and it is generally preceded by a non-specific infection. The disease is benign, in spite of presenting a dramatic skin condition, together with a sudden emergence which, in some cases, can be similar to meningococcemia, sepsis, or other febrile exanthematic conditions.

Meningococcemia has a fast evolution and a hight mortality rate, and therefore, demands precise and rapid measures. Extreme attention is necessary regarding this differential diagnosis. The AHEI diagnosis is essentially clinic and can be confirmed by a biopsy which shows a small vessel leukocytoclastic vasculitis. Its etiology is yet to be defined and its treatment is symptomatic, considering the favorable clinical evolution of this disease[1,2].

METHOD

The information presented in this report was obtained through a review of medical records, an interview with the parents, a clinical examination of the patient, a review of sequential laboratory tests from all hospitalizations, including the photographic records of some diagnostic methods to which the patient was submitted, not to mention the a literature review. The patient was hospitalized in the pediatric ward at the General Hospital of the Federal University at the Triângulo Mineiro (GH/UFTM), from 08/05/15 to 08/15/15.

RESULTS

Describing the case

Male child, 20 months old, from the rural area of the city Campina Verde - MG, presented symptoms akin those of an upper airways infection (UAI) and tonsillitis; Amoxicilin was prescribed for seven days as a result. Four days after the beginning of the treatment, the child evolved with an intense gingival edema, local ecchymosis and nodules in the hard palate, which led to the suspension of the Amoxicilin and the prescription of topic nystatin. The case was registered at the system "SUS Fácil" and the original city reported there was Uberlândia-MG.

In view of the fast evolution of the child's situation, the parents have chosen to look for care in the emergency room of a children's hospital. The child was cared for in 08/05/14, and the parents reported the sudden emergence of pappillary erythema lesions (similar to insect bites) in the left auricle, which fastly evolved into red and purple lesions in both auricles, in the upper and lower limbs, associated to edema, prostration and fever (38.3ºC), followed by signs of shock with need for expansion. After that, the child was transfered to the GH-UFTM for a better investigation and conduction of the case.

Due to the situation reported, the child was admitted under the suspicion of meningococcemia - an infectious disease which quickly evolves into shock, multiple organ failure and death -, and isolated from all contact, as this disease can be transmitted through intimate contact with other people and through nasopharynx secretions[3,4].

The patient was very irritated, with an important edema in both upper and lower limbs, especially on the fists, hands, ankles, with local heat and hyperemia, as well as ecchymoses in the region of the elbows, knees, back, and thighs. The patient also presented intense ecchymosis of necrotic appearance in the left auricle, purple maculopapular rashes of different aspects in upper and lower limbs and face, torso and genitals, though not in the abdomen.

A therapy with antibiotics began, with the use of ceftriaxone, clindamycin, chloramphenicol, as part of a protocol to deal with hemorrhagic fevers (among which is the Rocky Mountain spotted fever) and to prevent an aggravation of the patient's state, considering the disease suspected by the physicians.

The patient evolved without sighs of fever since the admittance, accompanied by a good urine output and an unaltered gastrointestinal tract (GIT). One day later, there was an emergence of new lesions with hyperaemia disseminated through the body, including torso and abdomen, though not in the genitals; there was also an increase in the size of one of the first lesions, in the back of the right foot, near the 5th metatarsus. On the 3rd day of hospitalization, the child was in a good general state, playing, without any irritability or prostration. The lesions progressively diminished.

On 08/12/15 (7th day of hospitalization), came the result of the biopsy undergone in the first day of admission (08/05/15), which showed leukocytoclastic vasculitis. The infant evolved with a steady remission of the lesions, and was discharged on 08/15/15, with just one crusted lesion in the left auricle, in an unaltered general state. The child still used Chloramphenicol for seven days and Ceftriaxone, together with Clindamycin, for 10 days.

The child was discharged while waiting for the results of exams for Dengue Fever, Leptospirosis, Yellow Fever, Hantavirus, Hepatitis A, and Rocky Mountain spotted fever; the results for these diseases were given in a later consultation, on 08/22/15. The results were negative for Yellow Fever, Dengue fever, Hantavirus, and Leptospirosis. There was also no confirmation of Hepatitis A or Rocky Mountain spotted fever.

Biopsy report

Material: skin from the right arm. *Macroscopy:* light-brown skin ellipse measuring 0.8x0.5x0.2 cm. No macroscopic alterations present. *Microscopy:* skin fragments with unaltered epidermis. In the dermis, one can see and intense inflammation composed mostly by neutrophils with leukocytoclasia, which are disposed around vessels with a tumefacient endothelium and fibrinoid necrosis on the wall. A scarce extravasation of erythrocites was noted. *Diagnosis:* Leukocytoclastic vasculitis *Note:* Considering the clinical and pathological aspects, the patient's condition fitted that of an Acute Hemorrhagic Edema of Infancy.

Exams

EXAM	08/05/2014	08/06/2014	08/08/2014	08/14/2014
HMG	SV: 3,9/10,9/32,8 SB: 10.090 (2/57/0/0/29/12) PLAT. 207.000	SV: 3,91/10,9/33,3 SB: 11.730 (4/47/3/0/36/10) PLAT. 297.000	SV: 3,9/10,9/33,7 SB: 8.970 (1/30/1/0/60/8) PLAT. 448.000	SV: 4,2/11,9/37,2 SB: 9.870 (1/37/1/0/58/3) PLAT. 586.000
UR/CR	---	8,4 / 0,39	14,6 / 0,37	---
ALBUMINE	---	---	3,31	---
LDH	385	---	---	---
PT	56,2% (RNI: 1,39)	---	---	---
APTT	35,9 sec.	---	---	---
FIBRIN.	286	---	---	---
ELETROLITES	---	Na: 140 / K: 3,9	Na: 137 / K: 4,89	---
CRP	---	7,9	---	0,1
AST/ALT	---	---	25,5 / 10,5	---
CSF	Cells: : 2/mm3 He: 10.000/mm3 (neut. 20%/ Linf. 70%/mon. 10%) Glucose: 84 Protein: :18 Cl: 720	---	---	---
CSF CULTURE	TWNBG	---	---	---
BLOOD CULTURE	TWNRG	---	---	---
URINE 1	Bilirubin +/ Frequent Epithelial Cells	---	---	---
URINE CULTURE	TWNBG	---	---	---

DISCUSSION

The AHEI was described for the first time by Snow, in 1913, as a condition of "purpura, hives, and angioedema on the hands and feet of an infant". It was lated named post-infectious purpura in cockade by Seidlmayer,

and finally, in 1938, Finkelstein named it acute hemorrhagic edema of infancy[1].

Approximately 100 cases were described; however, this condition is believed to be underdiagnosed, as many authors deem it as a manifestation of Henoch-Schoenlein purpura (HSP) in infants[2].

The acute hemorrhagic edema of infancy AHEI is a rare and benign form of leukocytoclastic small vessel vasculitis, which affects children between 4 and 24 months of age, being characterized by the triad: fever, edema of the extremities, and clearly delimited purpura spots, symmetric, and located especially in the face, the auricles, and the extremities, scarcely affecting the torso[1-5].

The vasculites happen due to an inflammatory vascular process, immunologically mediated, which causes functional and structural damage to the wall of the vessels. According to the predominant cell type in the inflammatory process, the vasculites are classified as neutrophilic, lymphocytic and granulomatous.

They can also be classified according to their location, and to the size of the vessels involved (small, medium and/or large). The necrotic vasculitis is characterized by segmented areas of transmural neutrophil infiltration, rupture in the architecture of the walls of the vessels, and it is associated to fibrinoid necrosis. The histopathological expression used to indicate this set of alterations is leukocytoclastic vasculitis. The endothelial edema and the leukocytoclasia are frequently seen, but are not a necessary part of the diagnosis[6].

Other occasional manifestations are reticular purpura, necrotic lesions, especially on the ear, and hives. The occurrence of purpuric lesions in the mucosa (both conjunctival and the soft palate) has also been described. Visceral involvement is rare, and in the few cases in which it was described, it consists of discrete and transient renal involvement, as well as gastrointestinal changes. Some authors consider the absence of visceral involvement and of a systemic illness as an essential criteria for the diagnosis of AHEI[5].

The benign evolution itself, together with the improvements with the use of corticosteroid therapy, is a factor that confirms this diagnosis[7-9].

In spite of the dramatic nature of the cutaneous symptoms and of the fast emergence, the prognostic is favorable, with a spontaneous resolution within 1 to 3 weeks. The association of fever and purpuric lesions is a challenge to the physician[1].

Among the diseases in which this association happens, one must always remember the Henoch-Schöenlein Purpura, the multiform erythema and the hypocomplementaemic urticarial vasculitis (all of which are benign), as well as the menigococcemia and the sepsis - all among the main differential diagnosis of AHEI[2,6,10].

The highest prevalence of AHEI happens during the winter, which might be related to the higher chance of vasculitis occurring after infectious episodes. Studies show that 75% of the cases were preceded by infections (Streptococcus, Mycoplasma, E. coli, Staphylococcus), vaccination (measles, DPT, Hib), or drugs (penicilin, cephalosporin, trimethoprim/sulfamethoxazole, paracetamol)[1,5].

In spite of being a benign disease, the AHEI can coexist with an infectious process, which can be an airway infection, parvovirus B19, hepatitis B and C, and streptococcus; this coexistence sometimes makes it more difficult to achieve a differential diagnosis. Several studies also point to a genetic susceptibility[11].

Its etiology is still unknown, and the pathophysiology, uncertain. However, some authors consider the AHEI to be a disease mediated by immune complexes[6].

The essentially clinic diagnosis is confirmed by a biopsy. In the peripheral blood, eosinophilia can occur, as well as leukocytosis and thrombocytosis. The erythrocyte sedimentation is normal or lightly elevated. The levels of serum complement are normal. The other tests, such as, coagulogram, urinary sediment, renal and hepatic functions, ASLO,

immunoglobulin A (IgA) and immunoglobulin M (IgM), antinuclear factor and VDRL, are all normal. Systemic involvement is rare, as is the recurrence of the lesions[1,4].

The histopathological findings indicate a leukocytoclastic vasculitis, compromising small vessels from the dermis and rarely reaching subcutaneous levels, fibrinoid necrosis, erythrocyte extravasation and interstitial edema.

Direct immunofluorescence (DIF) reveals deposits of complement 3 (C3), fibrinogen and IgM. IgA, immunoglobulin G (IgG) and immunoglobulin E (IgE) can be observed, though less frequently. Therefore, the clinical characteristics, the age and the evolution of the disease allow for a differential diagnosis, and the absence of IgA is not mandatory for achieving a diagnosis[1].

The conection between AHEI and HSP remains a controversial one. Both are small vessel leukocytoclastic vasculitis and usually develop after an infection[6].

HSP generally affects children from two to eight years old, and it manifests through purpuric lesions that do not present an annular target-like shape and affect mainly the legs, thighs, and gluteal regions, but not the face and the torso, rarely showing any underlying edemas. In addition, there are frequent extracutaneous (two thirds of patients present gastrointestinal and articulatory manifestations, from 20 to 100% with kidney involvement), lasts for an average of 30 days and there are frequent relapses (up to 50% of cases). Histologically, the fibrinoid necrosis is rare and the immunofluorescence reveals IgA, C3 and fibrin deposits - which suggests that the alternative path of the complement was activated. In contrast, the standard immunohistologic characteristics of the AHEI consist in the presence of IgA in only one third of cases, C1q, fibrinogen, C3, IgG, IgM and IgE deposits on the walls and around the small vessels[5].

The absence of visceral involvement and the good prognostic are characteristic of AHEI. Reports of atypical cases with symptoms characteristic of both diseases have been considered to be an overlap of AHEI and HSP; there is also disagreement on the question of whether or not AHEI is actually a different problem or a variation of HSP in infants. It has been suggested that the differences among both could be due to immune system maturity changes, mediated by IgA and related to the age[2].

No treatment must be conducted, as the disease is benign and self-contained, lasting from one to three weeks. There are no evidences that the use of systemic corticosteroids and antihistamines can shorten the length of the disease, in spite of their use as therapeutic measures. The warning for this vasculitis aims at assisting and quickening the discovery of a diagnosis, in order to avoid unnecessary treatments and concerns. There is only one reported case of AHEI which evolved due to a complicated ileum-ileum intussusception[6].

Other differential diagnoses include purpura fulminans, multiform erythema, menigococcemia, neonate lupus erythematosus, Swemenigococcemiaet syndrome (cutaneous erythematous plaques, fever, leukocytosis with neutrophilia and dermis with histological dense neutrophilic inflammation), Gianotti-Crosti disease (erythematous papulous eruption occurring symmetrically in the face, gluteus and extremities of children between 2 and 6 years of age) and Kawasaki disease. Among these, meningococcemia should be highlighted, due to its fast evolution and high mortality rates[2].

The symptoms of meningitis in infants are usually nonspecific. Irritability, apathy and refusal to eat, associated with fever, are symptoms which indicate it as a possibility. Signs of meningeal irritation are not frequent in this age group, and may appear only in later stages of the disease[3].

On the other hand, an increase in the intracranial pressure, which always happens in bacterial meningitis and manifests itself in older children through the occurrence of headaches, is manifested in infants through the bulging of the frontal fontanel and the suture diastase.

Changes in consciousness varying from obnubilation to coma may be a

symptom of meningitis for any age group, as well as neurological focal signs, which, when manifested in the moment of the diagnosis, can suggest a worst prognosis for the disease. Seizures affect from 20 to 30% of children with bacterial meningitis in their admission and first days of hospitalization, but are usually not related to the prognosis, as long as they only take place in the initial stage of the disease.

Among the systemic manifestations associated to bacterial meningites, one can quote arthralgias, myalgias, petechiae or purpura, and shock, all of which can occur because of any infectious agent, being, however, significantly more frequent with the menigococcus.

The meningococcal disease can manifest itself in three different ways: a) meningitis; b) meningococcemia; c) meningitis associated with meningococcemia. Typical cases of isolated meningitis are clinically indistinguishable from meningitis of different bacterial etiology.

Meningococcemia is an infectious and invasive syndrome, predominant in cold seasons, caused by *Neisseria meningitis*, and has a high rate of mortality. That means there should be a high level of suspicion regarding the possibility of this disease in infants who present nonspecific symptoms, which manifest in the first 4 to 6 hours with sudden high fever, drowsiness, nausea, vomit, irritability, lack of appetite, as well as petechiae and hemodynamic changes[3,12].

Skin changes are classic, and have a later onset, being characterized by the presence of skin petechiae and purpuric lesions, which can be preceded by maculo-papular exanthemata. The lesions are located mostly in the extremities of the limbs and on regions of the skin which are often subjected to pressure. The petechiae, which are initially superficial, can coalesce and get deeper, turning themselves in hemorrhagic suffusions and ecchymoses[13].

In the fulminant meningococcemia there is an extremely fast evolution associated to signs of shock (changes in consciousness, tachycardia, tachypnea, decreased pulse amplitude, slow capillary filling, arterial hypotension and oliguria) and disseminated intravascular coagulation (DIC). Therefore, the CSF initially tends to be normal. Recognizing and treating the shock early allows for a better outcome for the case. Fluid therapy is a common practice for kids which are suspected to be victims of the disease, to answer the first signs of shock[13].

Precocious intervention is based on two actions: aggressive fluid therapy and antibiotic therapy. Fluid therapy, as mentioned, must be started when there is any suspicion of meningococcal disease or signs of shock. The initial emergency treatment must include repeated 20ml/kg boluses of isotonic crystalloids or colloids until the case is solved. These children can need as much as 100 to 200 ml/kg. The importance of this treatment is such that, for each hour without treatment, the mortality rate gets at least two times higher[3,4].

The antibiotic therapy is as essential to the treatment as the fluid therapy, and must be started as soon as there is any clinical suspicion of the disease, that is, it should not be delayed by the clinical investigations. The initial treatment must be conducted with the use of broad-spectrum antibiotics that can easily penetrate the cerebrospinal fluid. In most health units, the third generation cephalosporins, whether intravenous or intramuscular, such as ceftriaxone and cefotaxime should be the first option in these cases[3,4].

CONCLUSION

The reported case and the published works mentioned bring to light a discussion about the situation of a complex pathology that frequently, since it is rare in children, can be mistaken by many other pathologies, whose treatment involves an understanding of its pathophysiology and of the evolution of the disease. Although it is a rare Pediatrics case, with sometimes dramatic lesions, the evolution of this pathology is most often benign, if correctly addressed.

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CONTRIBUTIONS

Mariana Figueiredo Caixeta was responsible for the bibliographical survey and for the writing of the article**. Jussara Silva Lima** guided, supervised and helped in the data collection and the writing of the article. **Valéria Cardoso Alves Cunali** wrote part of the text. **Vandui da Silva dos Santos** conducted the bibliographic survey and the discussion.

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