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Chronic bullous disease of childhood – A case report

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VERSITA

Abstract

Linear IgA bullous dermatosis is a chronic, acquired, autoimmune subepidermal vesiculobullous disease. Both children and adults are affected. It is characterized by direct immunofluorescence findings of linear immunoglobulins class A (IgA) deposits along the dermal-epidermal junction (basement membrane zone). In children, the disease is commonly referred to as chronic bullous disease of childhood and it mostly affects children between 2 and 5 years.

The onset of the disease is acute; the first episode is the most severe, while recurrences tend to wax and wane in severity and last till puberty or even longer. Diaminodiphenylsulfone is the treatment of choice, although systemic corticosteroids are reported to be very effective as well.

We report a 3-year-old boy with a vesiculobullous eruption which developed one week following administration of cephalexin for upper respiratory infection. He was referred to our Clinic from other health institutions as treatment failure for suspected *strophulus* or *impetigo bullosus*. On admission, the patient had fever and numerous vesiculobullous and erosive lesions distributed on the face and trunk. After immunohistological verification, the treatment with prednisone 25 mg/d was introduced, due to rapid progression of the disease and the fact that diaminodiphenylsulfone was not available. Improvement occurred after 2 weeks, so the dose was carefully tapered, taking into account the possibility of adrenal suppression. The medication was completely excluded within the next three months. No serious side effects were observed, except transitory hirsutism. The patient has had no relapses over the last 20 months of clinical follow-up.

Key words

Child, Preschool; Skin Diseases, Vesiculobullous; Cephalexin; Autoimmune Diseases; Chronic Disease; Disease Progression

Linear IgA bullous dermatosis (LABD) is an acquired, autoimmune subepidermal vesiculobullous disease affecting both children and adults. Historically, it has often been referred to as chronic bullous dermatosis of childhood (CBDC) (1). The disease is rare, with an estimated annual incidence of 1 per 500,000 children in the United Kingdom (2). The onset is usually between 2 and 5 years of age. Typically, it is characterized by large, often pruritic blisters arranged in a rosette fashion. In children, lesions commonly involve the perioral region, upper inner thighs, lower abdomen and the anogenital area with frequent involvement of the perineum. The disease is often misdiagnosed with bullous impetigo. Oral lesions are common, presenting in 50% of patients. Clinical course of the disease is usually benign and often self-limiting (3).

Case report

In January 2009, othertwise healthy 3-year-old boy, was admitted to the University Clinic of Dermatology in Skopje (Republic of Macedonia), with a two-week-history of widespread itchy blistering eruptions confined to the skin. The first lesions developed one week following oral intake of cephalexin for infection of the upper respiratory tract. Skin lesions had originally been thought to be due to *bullous impetigo* or *strophulus*. Systemic and topical antibiotic therapy, as well as antihistamines, did not produce any effect and the disease progressed.

The boy was systemically well, normally developed for his age. Skin examination revealed multiple vesicles and tense blisters arising from erythematous skin on his face (Figure 1), forearms and lower legs (Figure 2). The vesicles and blisters were seen at the edge of annular or polycyclic lesions, the appearance of which has been described as the "string of beads" sign (Figure 3). Some of them were grouped in a herpetiform pattern, described as the "cluster of jewels" sign. Within one week new blisters developed on the lower trunk, buttocks, thighs, groins and perineal surfaces. Large confluent lesions and extensive denuded surfaces were present on the back. (Figure 4). Ophthalmologic examination revealed conjunctivitis. Each flare of new lesions was associated with fever and leukocytosis. The oral mucosa was not involved.

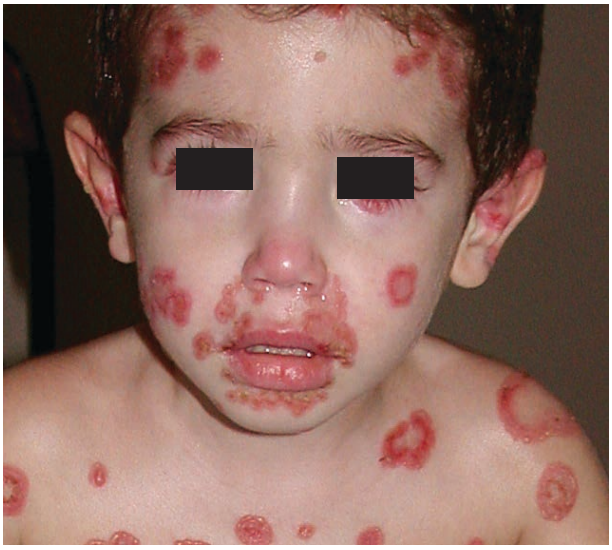

Figure 1. Facial lesions resembling bullous impetigo

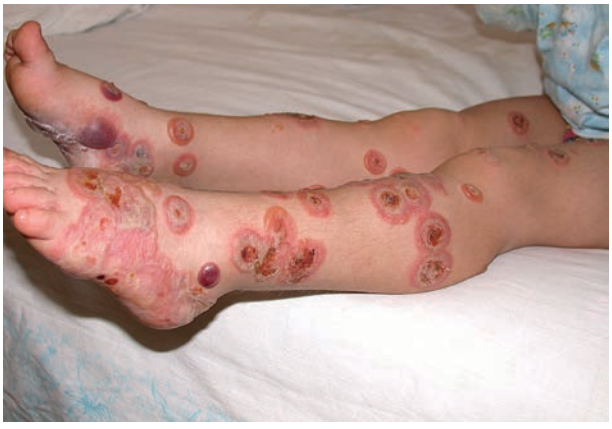

Figure 2. Tense blisters and vesicles

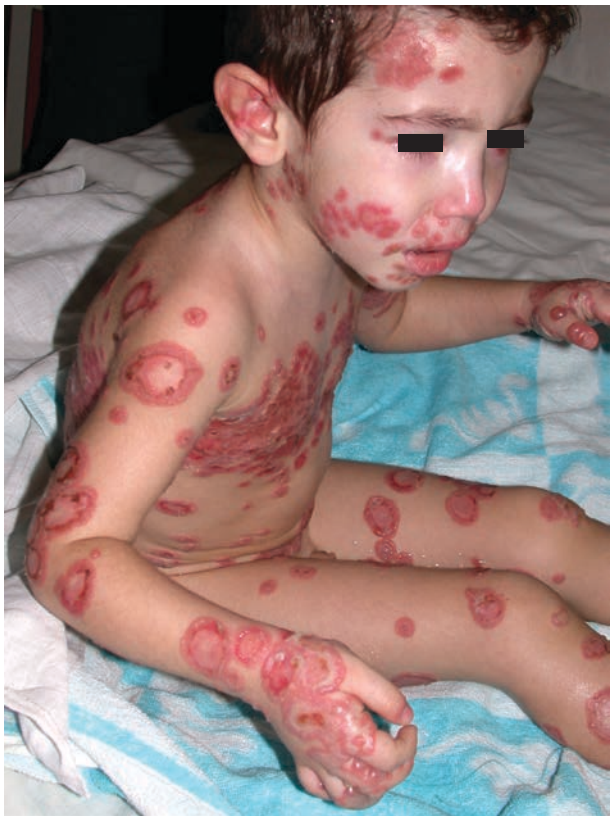

Figure 3. New blisters around old lesions

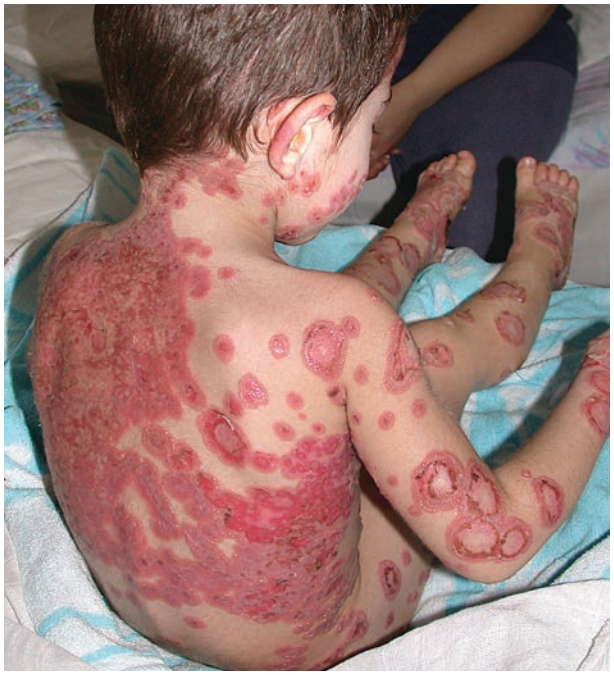

Figure 4. Extensive denuded surfaces on the back caused by peripheral extension and confluence of lesions

Laboratory investigations revealed the following abnormalities: white blood cell count was elevated to 22 x 10^9/L followed by increase up to 40 x 10^9/L, with neutrophylia and thrombocytosis. The skin swab was positive for *Staphylococcus aureus*, while hemoculture was negative.

Histopathology revealed subepidermal blistering (Figure 5) and immunohistochemical examinations demonstrated linear deposition of IgA along the basement membrane zone of the epidermis (Figure 6). The diagnosis of chronic bullous dermatosis of childhood (CBDC) was confirmed on the basis of clinical, histological, and immunofluorescence findings.

The patient was initially treated with prednisolone 25 mg/daily, and concomitant antibiotic treatment for *Staphylococcus aureus* infection. Treatment with steroids was indicated due to the widespread disease, and current deficiency of diaminodiphenylsulfone at the Clinic. After 2 weeks, the initial dose of prednisolone was reduced to 15mg/day. Skin lesions improved (Figure 7), although during the first two months, occurrence of new vesicles and itchy erythematous patches was observed (Figure 8). After 4 months, the maintenance therapy was discontinued, and the patient has had no relapses over the last year. No side effects were observed.

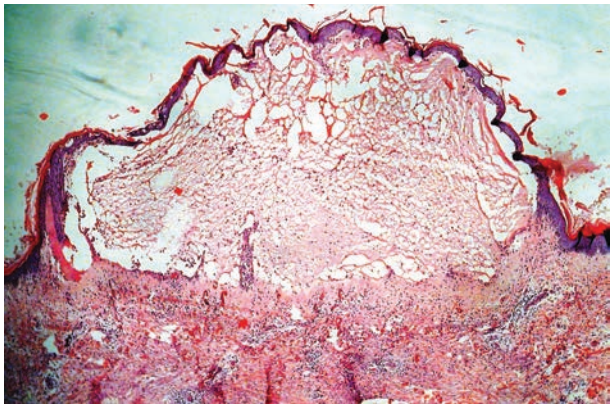

Figure 5. H&E-stained section showing subepidermal bulla (hematoxylin and eosin, x100)

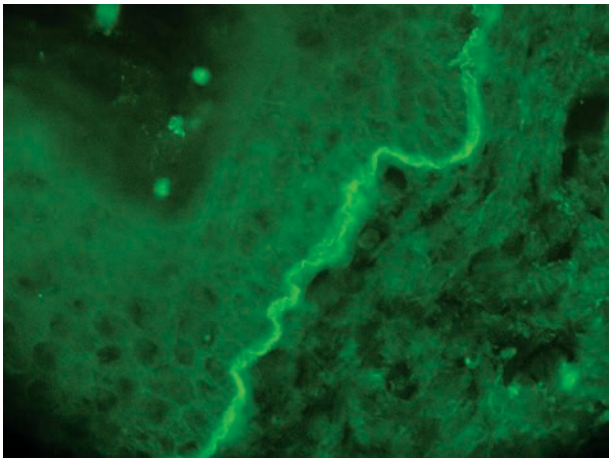

Figure 6. Direct immunofluorescence showing linear IgA deposits along dermal-epidermal junction

Discussion

In 1975, based on immunopathological findings, Chorzelski & Jablonska first suggested that linear IgA bullous dermatosis (LABD) represents a separate entity (4). On a molecular basis, some authors consider CBDC and LABD the same disease, only occurring in different age groups (2). The autoantibodies found in the diseased are IgA, directed against the certain number of different target antigens within the adhesion complex. They include two that may be

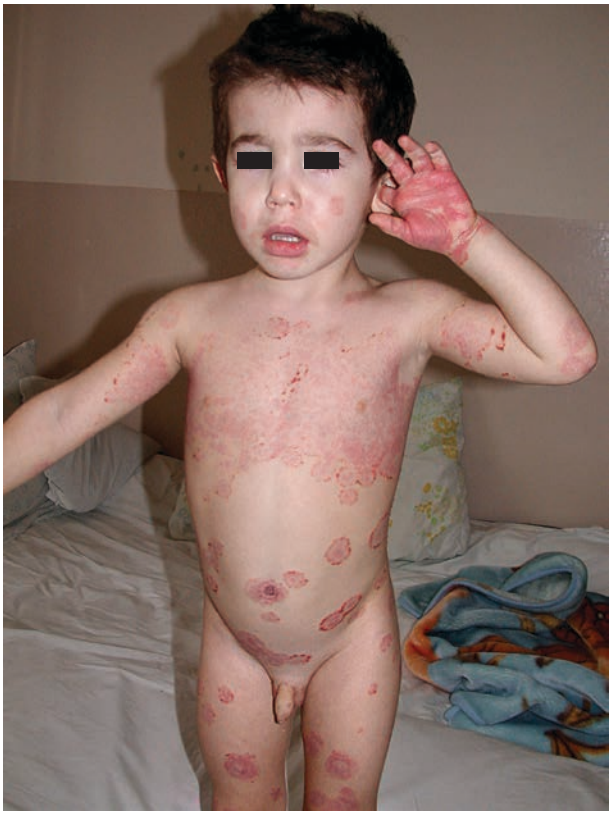

Figure 7. Improvement after 2 weeks

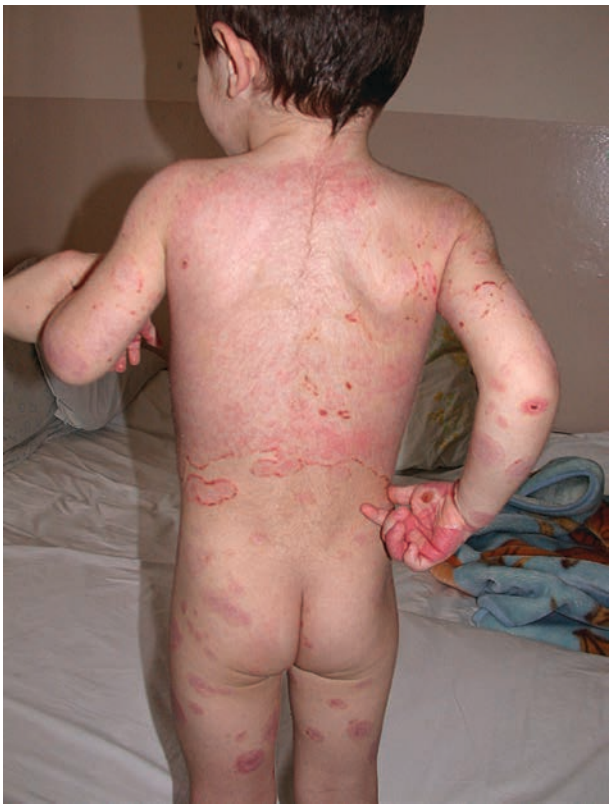

Figure 8. Improvement after 2 weeks

unique to linear IgA disease with molecular weights of 285 kD and 97/120 kD, bullous pemphigoid antigens BP 230 and BP 180 antigens, collagen VII, the anchoring fibril component, as well as some antigens uncharacterized yet (5-7).

Three distinct clinical lesions characterize this disease: large tense blisters as seen in bullous pemphigoid, grouped vesicles as seen in dermatitis herpetiformis, and lesions similar to those seen in erythema multiforme. One lesion type may predominate, or a combination of the tree may be found. Bullae arise on normal or inflamed skin; they are often arranged in a rosette manner; as new blisters cluster around the older lesions, they form a "cluster of jewels" sign. Healing is rapid, with hyperpigmentation, but without scarring (1).

Our patient developed polymorphic itchy lesions, single or grouped vesicles and bullae, showing "string of beads" patterns. He did not have mucosal involvement. The clinical features included: abrupt onset of the disease, presence of great number of vesicles and blisters, extensive denuded surfaces associated with fever and elevated number of leukocytes in the peripheral blood. Immunofluorescence findings confirmed the diagnosis and provided its differentiation from multiple causes of blistering in children. The treatment of CBDC was directed towards reducing the frequency and severity of outbreaks.

The disease is very responsive to sulfapyridine (35 mg/kg PO bid; not over 100 mg/kg/d) or diaminodiphenylsulfone (1-2 mg/kg PO qd initial; not over 3-4 mg/kg/d).

CBDC is also well corticosteroid-responsive. Remissions are usually induced within 6 - 12 months (2). Patients may still develop occasional bullae, but relapses are uncommon (1). Our patient responded well to systemic corticosteroid therapy with prednisolon and improvement was observed in 2 weeks.

The prognosis of CBDC is generally favorable. While recent reports have described a subset of patients with episodic recurrences that persisted until adulthood, in most patients eruptions usually resolve between 3 and 5 years (8).

Mild single vesicles and blisters or erythematous infiltrates were observed in the first 2 months after initiating the treatment. After 20 month-follow-up, we did not observe any recurrences. Our patient developed initial skin eruptions one week after receiving cefalexin for upper respiratory infection.

Cases of linear IgA dermatosis associated with gastrointestinal diseases, autoimmune diseases, malignancy and infections have been reported (9). The significance of these associations has yet to be determined, but they may play a role in the initial stimulation of the IgA mucosal immune system. On the other side, reports have shown that as many as two-thirds of all occurrences may be drug-induced. The most frequently implicated drugs were antibiotics, especially vancomycin, penicillin, amoxicillin-clavulanate, cephalosporin, sulfonamides, sulfamethoxazole/trimethoprim, non-steroidal anti-inflammatory drugs such as diclofenac, naproxen, piroxicam, antihypertensive drugs such as captopril, angiotensin converting enzyme inhibitor (ACE), and diuretics (10).

However, in contrast to adult patients, the role of possible precipitating factors in childhood cases of LABD, has been less commonly discussed in the

literature and only isolated reports on associations with underlying conditions exist. A 2-year-old boy developed LABD during amoxicillin-clavulonic acid therapy (11). Polat et al., published a case of a 5-year-old boy with acute lymphoblastic leukemia in remission, in whom CBDC developed after treatment with trimethoprim/sulfamethoxazole (12).

Conclusion

In conclusion, we present a 3-year-old boy in whom diagnosis of chronic bullous dermatosis of childhood was established according to clinical, histopathological and direct immunofluorescence findings. The patient developed initial skin eruptions one week after receiving cephalexin for upper respiratory infection. The clinical follow-up confirmed a benign nature of the disease. A follow-up of 20 months after discontinuation of treatment showed neither recurrence of the disease nor side effects of corticosteroid treatment.

As far as the world literature is concerned, this is the 3rd report on chronic bullous dermatosis of childhood associated with drug intake.

Abbreviations

ACE – Angiotensin-converting enzyme
BP - Bullous pemphigoid
IgA - Immunoglobulin class A
LABD - Linear IgA bullous dermatosis
CBDC - Chronic bullous dermatosis of childhood

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Hronična bulozna bolest kod dece – prikaz slučaja

Sažetak

Uvod: Linearna IgA bulozna dermatoza (LABD) je hronična, autoimuna, subepidermalna bulozna dermatoza, koja se javlja kod odraslih i kod dece. Za djagnozu odlučujući je nalaz linearnih depozita IgA u zoni bazalne membrane dokazanih direktnim imunofluorescentnim pregledom (DIF) perilezionekože ili sluznice. Bolest je u dečjem uzrastu poznata i pod nazivom hronične bulozne bolesti dece (HBBD). Javlja se najčešće između druge i pete godine života. Bolest je retka, sa godišnjom incidencijom u Velikoj Britaniji od 1/500 000 dece. Tipična klinička slika je pojava napetih bula na neizmenjenoj ili eritematoznoj koži. Pojava novih mehurova na periferiji starih, daje izgled poznat kao „gomile dragulja". Predilekcione regije su perioralno područje, perineum i donji deo trbuha. Kod 50% bolesnika lezije su oralno smeštene. Početak bolesti je akutan, prva epizoda je najteža a recidivi su uobičajeno sa lakšom kliničkom slikom. Bolest kod dece najčešće spontano prolazi posle 3 do 5 godina, iako su opisani slučajevi perzistencije bolesti i nakon puberteta.
Prikaz slučaja: Prikazujemo trogodišnjeg dečaka sa

vezikulobuloznom erupcijom, koja se javila nedelju dana po prekidu terapije infekcije gornjih respiratornih puteva cefaleksinom. Na našoj Klinici je hospitalizovan januara 2009. godine, posle dvonedeljnog neuspešnog lečenja u drugim zdravstvenim ustanovama, kao bulozni strofulus i impetigo sa sistemskim i lokalnim antibioticima i antihistaminicima.

Objektivni status na koži i vidljivim sluznicama: Pregled je pokazao brojne vezikule i bule u predelu lica, perineuma, podlaktica i potkolenica. Prvih dana hospitalizacije, nove lezije su se javile u području ekstremiteta i tela. Promene su bile polimorfnog karaktera: veliki mehurovi, vezikule herpetiformnog i anularnog rasporeda, lezije sa izgledom „gomile dragulja". U predelu leđa, perifernim širenjem i konfluiranjem lezija, nastupila je denudacija velike površine. Sluznice nisu bile zahvaćene. Erupcija novih promena je bila praćena pruritusom i povišenom temperaturom.

Laboratorijske analize: Laboratorijska ispitivanja krvi su otkrila leukocitozu, neutrofiliju, eozinofiliju i trombocitozu. U brisu kože je identifikovan *Staphylococcus aureus*. Hemokultura je bila negativna.

Patohistološke analize: Svetlosnom mikroskopskopijom bioptičkog uzorka obolele kože, rutinski bojenim H&E, otkriven je subepidermalni rascep. Imunofluorescentnom mikroskopijom je pomoću direktne imunofluorescencije utvrđeno postojanje linearnih depozita imunoglobulina klase A – IgA, u zoni bazalne membrane. Na osnovu ovih nalaza, postavljena je dijagnoza HBBD.

Terapija: Zbog nedostupnosti diamunodifenilsullfona, lečenje je započeto prednizolonom, u dozi od 25 mg/dnevno. Posle dve nedelje nastupila je morbostaza, pa je doza smanjena na 15 mg/dnevno. Dalja redukcija doze bila je pažljiva, sa ukupnim trajanjem terapije od 4 meseca. U tom periodu bilo je nekoliko erupcija solitarnih vezikula i pruritičnih eritema, koji su spontano prolazili za 2-3 dana. Ove epizode nisu bile pridružene temperaturom i leukocitozom. 20 meseci posle prekda terapije nije registrovan recidiv. Nije bilo neželjenih efekata terapije, osim tranzitornog hirzutizma.

Diskusija: Uprkos izvesnim razlikama u kliničkoj slici i toku bolesti, većina autora smatra da su LABD i CBBD jedan isti entitet. U dijagnozi ovog oboljenja presudan je nalaz direktne imunofluorescencije koji omogućava razlikovanje HBBD od drugih buloznih dermatoza dečjeg uzrasta. Tri tipa lezija su karakteristična za ovu bolest: velike tenzione bule kao kod pemfigoida; grupisane vezikule kao kod herpetiformnog dermatitisa; lezije slične multiformnom eritemu. Kod našeg bolesnika lezije su bile polimorfne, pruritične, bez zahvatanja mukoze. Lek izbora za HBBD je diamunodifenilsullfon (1-2 mg/kg/d). U našem slučaju, zbog nedostupnosti ovog leka, bili smo primorani da terapiju započnemo prednizolonom. Morbostaza je nastupila za dve nedelje, a ukupna terapija je trajala 4 meseca. Jedan interesantan momenat našeg slučaja je moguća povezanost infekcije (akutni rinofaringit) i leka (cefaleksin) sa pojavom bolesti. Podaci iz literature prikazuju da LABD-odraslih može biti povezana sa bolestima gastrointestinalnog trakta, autoimunim bolestima, malignitetima i infekcija. Pretpostavlja se da ova stanja mogu da stimulišu IgA mukozalni imuni sistem. Postoje mnogobrojni izvestaji o povezanosti bolesti sa lekovima (vankomicin, penicilini, cefalosporini, kaptopril, naproksen, diklofenak, fenitoin). Za razliku od odraslih, kod dece, lek kao mogući okidač je opisan u dva slučajeva.

Zaključak: Prikazujemo slučaj hronične bulozne bolesti kod deteta koji, prema nama dostupnim podacima iz literature, predstavlja treći do sada u svetu objavljen slučaj u kome je lek imao ulogu mogućeg okidača.

Ključne reči

Predškolsko dete; Vezikulobulozne bolesti kože; Cefaleksin; Autoimune bolesti; Hronična bolest; Tok bolesti