

EDITORIAL

Stevens–Johnson syndrome and toxic epidermal necrolysis in children

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Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe forms of hypersensitivity reactions affecting the skin. Current terminology is based on maximal extent of epidermal detachment. SJS indicates cases with epidermal necrolysis that involve less than 10% of the body surface area, TEN with more than 30%, and overlap of SJS/TEN in between (1).

Clinically, SJS/TEN are characterized by polymorphic lesions like erythematous macules, papules, plaque, vesicles, and bullae with Nikolsky's sign positive. Oral, genital, and conjunctival mucosae are often involved in the form of erosion or ulceration (2). Fever and malaise are the first symptoms of the disease (3). Incidence of SJS/TEN is 0.05–3 persons per million populations per year (2, 4).

Several drugs are highly suspected to cause SJS/TEN in adults, such as anti-epileptics, anti-infective sulfonamides, non-steroidal anti-inflammatory drugs, nevirapin, allopurinol, and antimicrobials (cephalosporins, aminopenicillins, quinolones, tetracyclines, and imidazole antifungals) (4–12). The list of causative drugs may vary from country to country (4). In children, anti-infective sulfonamides, phenobarbital, carbamazepine, lamotrigine, and acetaminophen are frequently associated with SJS/TEN (12). However, SJS/TEN are rare in children with mortality rate of 7.5% (12).

In this article, evaluation of children with SJS/TEN, investigation of causative drug/drugs, treatment, clinical outcome, and complications are presented in three cases.

Case 1

A 6-year-old girl had developed TEN after parenteral administration of the fifth dose of procaine benzylpenicillin and second dose of ceftriaxone given for an upper respiratory tract infection, which she had tolerated few months before.

She had throat pain and fever (38.5°C). Throat swab revealed an infection with streptococcus beta-hemolytic, and therefore, she was administered intramuscular penicillin. Two days later, the child was afebrile. But on next day, her body temperature was 38.5°C again, and ceftriaxone was administered. On fifth day of penicillin therapy and second day of ceftriaxone therapy, she developed a generalized maculopapular rash, accompanied by fever and malaise. Both drugs were stopped. On admission, she looked severely ill. Her body temperature was 40°C. Within 3 days, lesions of the skin showed rapid confluence (Fig. 1). There were blisters with positive Nikolsky's sign, and epidermal detachment was observed in >70% of the body surface. Oral erosions, redness of eyes, prostration, arthralgias, and myalgias were present. Laboratory results showed leukocytosis ($20 \times 10^9/l$), positive

C-reactive protein (80 mg/l), and streptococcus beta-hemolytic in the throat swab. Serologic tests for acute infection (IgM) by Mycoplasma pneumoniae herpes viruses, Epstein–Barr virus (EBV), and cytomegalovirus (CMV) were negative. She received a short course of corticosteroid, intravenous immunoglobulin (IVIG), meropenem, fluid replacement with electrolyte and albumin solution, sedation, and analgesic therapy. Erosions were treated with octanisept and impregnated non-adhesive mesh gauze. Oral erosions were treated with disinfectant mouth wash. Anti-inflammatory eye drops were given. The child was discharged after 29 days, with extensive post-inflammatory hyperpigmentation.

Two years later, she underwent allergologic work-up. We administered patch tests with procaine benzylpenicillin and ceftriaxone (5% in petrolatum) according to the guidelines (13–15). Patch tests with procaine benzylpenicillin were only positive. According to the aforesaid guidelines (14), we performed intradermal test with ceftriaxone at concentrations of 2 mg/ml. Delayed-reading skin test was also positive.

In our patient, the development of TEN was associated with the administration of procaine benzylpenicillin and ceftriaxone, and resolution of the clinical manifestations was observed after discontinuation of these drugs. Very rarely infections caused by streptococcus beta-hemolytic have been mentioned as a potential cause of SJS. We exclude infection by mycoplasma, herpes viruses, EBV, and CMV as possible etiologic factors. We confirm offending drugs by positive patch test with procaine benzylpenicillin and delayed-reading skin tests to ceftriaxone.



Figure 1 Typical pattern of TEN in early stage. Small and large flaccid blisters arose on macules. Epidermal detachment was observed in >70% of the body surface.

Case 2

On the fourth day of therapy of an upper respiratory tract infection with ibuprofen, a 9-year-old girl developed SJS.

She had fever (38.3°C), cough, and nasal blockage, for which was administered ibuprofen, as she had tolerated ibuprofen a month before. A day later, the girl was subfebrile with appearing redness of neck and face. On next day, she was afebrile, but she developed a rash. Within 2 days, skin lesion included a diffuse violet macular rash with erythema and multiple bullous lesions (Fig. 2). Blisters were with positive Nikolsky's sign. Oral erosions were present. Her body temperature was 41°C, and she had shivers and pain. Ibuprofen was stopped, and resolution of the clinical manifestations was observed after discontinuation of the drug. Laboratory results showed mild leucopenia and elevated transaminases. Serologic tests for acute infection (IgM) by EBV and CMV were positive; unfortunately, PCR is not available in our country. Epidermal necrolysis involved less than 10% of the body surface area. She received a short course of corticosteroid, IVIG, intravenous fluids, and analgesic therapy. Erosions were treated with octanisept. Oral erosions were treated with disinfectant mouth wash. The girl was discharged after 26 days without any problem.

Six months later, she underwent allergologic work-up. We administered patch tests with ibuprofen, as recommended by Brockow et al. (16), which was positive.

The clinical history together with the positive results in patch tests, the positive serologic test, and skin biopsy (full-thickness necrosis and detachment of the epidermis, a sparse inflammatory infiltrate of the dermis) indicates that our patient had experienced a SJS to ibuprofen and infection by EBV and CMV.



Figure 2 Stevens–Johnson syndrome (SJS) characterized by a diffuse violet macular rash with erythema and multiple bullous lesions.

In our case, the time latency between beginning of ibuprofen use and onset of the SJS was a few days and was accompanied with simultaneous viral infection. The hypothesis that viral infection and medication can interact in the occurrence of the drug reactions remains very popular because of a very high rate of rashes induced by aminopenicillins during infectious mononucleosis (1). This hypothesis was never supported by clear evidence concerning SJS/TEN.

Case 3

A 3-year-old boy had developed overlap of SJS/TEN 3 weeks after commencing carbamazepine following a first incidence of seizure. After 15 days of drug therapy, he developed a macular eruption on the face which extended to neck and trunk. His body temperature was 38.3°C, C-reactive protein concentration was 25 mg/l, and a white cell count was $12.9 \times 10^9/l$; therefore, ceftriaxone and paracetamol were administered. Within a few days, the child was afebrile, but macular eruption extended to extremities. Five days later, body temperature was very high (39.6°C) again and skin lesions showed rapid confluence. On examination, the child was febrile, ill, and toxic. There were blisters with positive Nikolsky's sign and quickly result in widespread detachment of the epidermis and erosions (>10% and <30% of body surface) accompanied by malaise, arthralgias, myalgias, and confusion. Conjunctival, oral, and anogenital mucosae were involved. All drugs were stopped. During hospitalization, our patient experienced numerous complications, including septicemia (*Escherichia coli*-positive blood and urinary cultures), for which he received systemic antimicrobial (meropenem), anemia requiring packed cell transfusion, complications of gastrointestinal tract (vomiting and diarrhea), dehydration, and hypoalbuminemia, which was treated with fluid replacement with electrolyte and albumin solution. He also received corticosteroid, IVIG, sedation, and analgesic therapy. Erosions were treated with octanisept and impregnated non-adhesive mesh *gauze*. Oral erosions were treated with disinfectant mouth wash. Anti-inflammatory eye drops were given. The child was discharged after 25 days.

Ten months later, he underwent allergologic work-up. According to the aforesaid guidelines (14), we administered patch tests with carbamazepine, paracetamol, and ceftriaxone. Patch tests with carbamazepine were only positive. We also performed intradermal tests with ceftriaxone and paracetamol, according to the guidelines (13–15). Delayed-reading intradermal skin tests were negative.

In our patient, the development of overlap of SJS/TEN was associated with the administration of carbamazepine, and resolution of the clinical manifestations was observed after discontinuation of the drug. We confirm offending drug by positive patch test with carbamazepine. Carbamazepine is on the list of causative drugs that are highly suspected to cause SJS/TEN in children and also in adults (4, 12). Acetaminophen is on that list as well, but in our case, we excluded the possibility of paracetamol to be an offending drug. Cephalosporins as antibacterials have been reported as a possible cause of SJS/TEN (4, 7–9, 11); however, in our case, we excluded the

possibility that the patient's overlap of SJS/TEN was due to ceftriaxone.

Discussion

Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) are usually a straightforward diagnosis. Difficulties may arise in two situations: viral or drug-induced macular eruptions on the one hand, which require the prediction whether they proceed to SJS/TEN or not; and on the other hand, other eruptions characterized by widespread erythema and detachment of skin. Differential diagnosis includes macular eruptions, herpes simplex-associated erythema multiforme, generalized bullous fixed drug eruption, physical and chemical injury, staphylococcal scalded skin syndrome, AGEP, and acute graft-versus-host disease (4).

Diagnosis of severe non-immediate hypersensitivity reactions is difficult, and the diagnostic value of current allergologic tests is not well defined in this situation. There is no reliable laboratory test to determine the offending drug. Diagnosis rests on the patient's history, the empirical risk of drugs to elicit SJS/TEN, and *in vitro* and *in vivo* tests to culprit drugs. Provocation tests, as the gold standard, are contraindicated because re-exposure can elicit a new episode of SJS/TEN of increased severity (4).

The ENDA devised a diagnostic algorithm for *in vivo* allergologic evaluation of non-immediate reaction to β -lactams, which combines patch tests and skin intradermal tests with a common panel of reagents and suspect β -lactam. Patch tests should be administered with suspect β -lactams or other drugs (5% in petrolatum) following the recommendations of Brockow et al. (15). Reading of patch test should be made according to the recommendations of Barbaud et al. (13), 15 min after removal of the strips and 24 h later. Intradermal testing should be performed by the injection of 0.02 ml of the hapten solution. Reading of delayed reactions should be taken after 48 and 72 h. Any infiltrated erythema with a diameter larger than 5 mm should be considered a positive reaction (14, 15).

Patch tests can be performed with any form of commercial drugs and are safer than intradermal tests. It should be used as the first line of investigation; in case of positive results, intradermal testing can be avoided. However, patch tests are less sensitive, but more specific than delayed-reading intradermal tests, and their sensitivity may vary, depending on the vehicle used. Patch test sensitivity also varies with the type of eruption (higher in eczematous, maculopapular, and acute generalized exanthematous pustulosis (AGEP); lower in urticaria, SJS, and TEN; and nil in vasculitis) as well as with the drug involved (higher with diltiazem, abacavir, β -lactam antibiotics, anticonvulsants, tetrazepam, and pseudoephedrine) (13–15, 17). The sensitivity of patch testing alone is low (range of 10.8–37.5% depending on previous publications) (17). False-negative results in drug patch tests may be due to insufficient penetration of reagents into the epidermis and/or to the fact that the concentration used is too low, or due to fact that a drug metabolite is actually responsible for the reaction or that concomitant factors, such as viral infections, are no longer present (13, 14). False-positive results were observed by

Barbaud and colleagues in patch testing with colchicine at 10% in petrolatum, misoprostol at 30% in petrolatum, and drugs containing sodium lauryl sulfate (13). We performed patch testing using vehicles and drug concentrations according to the recommendations of ENDA (European Network on Drug Allergy) and ESCD (European Environmental Contact Dermatitis Research Group) (13, 15). With respect to the recommended drug concentrations that are not irritating, false-positive results were excluded in all our patients. Two different drugs (penicillin and cephalosporin) are incriminated in the first case. Considering the literature data, the cross-reactivity between cephalosporins and penicillins seems to be very rare for T-cell reactions, but patch tests can help to study the ability of drugs to elicit symptoms due to cross-reactivity, for example, between β -lactam antibiotics, as in our first case (14). Delayed-reading intradermal tests appear to be somewhat more sensitive than patch tests (14). The negative predictive value of drug skin tests is approximately 90% (18).

The lymphocyte transformation test (LTT) has been shown to be useful in the diagnosis of T-cell-mediated delayed hypersensitivity reactions. We did not perform LTT, because recent studies showed that LTT is of poor relevance. A positive LTT is useful in confirming the diagnosis, and a negative test cannot exclude drug hypersensitivity (14, 15).

There is scant quality literature about management of SJS and TEN in children. Steroids and IVIG improve the outcome of patients with SJS/TEN, but results from different reports are variable (16). Our patients were given corticosteroids and IVIG. An increased rate of infections, the risk of masking septicemia, a delay of re-epithelialization, and a prolonged duration of hospitalization have been the arguments against the systemic treatment with glucocorticosteroids (4, 5). In recent years, steroid pulse therapy has been proposed in the acute stage of SJS/TEN. Mortality was not higher, and the time of re-epithelialization was not longer than expected and may help to prevent ocular complication (4, 19). Treatment is based on non-specific and symptomatic means. Erosions can be treated with octanisept and impregnated non-adhesive mesh gauze. Disinfectant mouth wash should be used to treat oral erosions, and mild ointment should be applied on bloody crusts of the lips. In case of eye involvement, anti-inflammatory eye drops should be given. Patients with SJS/TEN need fluid replacement with electrolyte and albumin solution. Sedation and analgesic therapy should be given in case of mucosal involvement and the extent of skin detachment. If clinical infection is suspected, anti-infective treatment should be started (3).

The time latency between beginning of drug use and onset of the SJS/TEN varies. Anti-epileptic drugs and allopurinol are frequently tolerated for several weeks, and antibiotics and anti-infective sulfonamides usually show a much faster reaction onset (4). In case 3, the time latency was 2 weeks, and in case 2 and case 1, it was a few days.

Barvaliya et al. show that duration of hospital stay (20.6 vs. 9.7 days) was significantly higher in TEN than SJS (2). In all our cases, duration of hospital stay was nearly 1 month (in TEN 29 days, in SJS 26 days, and in SJS/TEN overlap

25 days). Probably concomitant infectious factors and treatment influenced the resolution of the disease.

The hypothesis that viral infection and medication can interact in the occurrence of the drug reactions was never supported by clear evidence concerning SJS/TEN (1). In EuroSCAR study, authors found no evidence that viral infection was a risk factor by itself or by increasing the risk of medications (20). The prognosis of individual adult patient can be evaluated by applying SCORTEN. Seven independent factors including age, skin detachment, underline malignant diseases, tachycardia, and laboratory values such as serum urea, glucose, and bicarbonate are considered (4, 21).

Other factors associated with SJS/TEN are infectious diseases such as those caused by human immunodeficiency virus, herpes virus, *Mycoplasma pneumoniae*, and hepatitis A virus, and non-infectious conditions including radiotherapy, lupus erythematosus, and collagen vascular disease (22). It is often difficult to decide whether symptoms such as oronasal soreness, conjunctival injection, and fever are signs of an acute infection or the beginning of SJS/TEN (3).

Certain infections implicated in the pathogenesis of SJS/TEN such as those caused by *Mycoplasma pneumoniae*, herpes simplex virus, EBV, and CMV as possible etiologic factors were excluded in our case 1 because of the lack of compatible clinical findings, negative medical history, and negative serologic tests (IgM and IgG). However, our patient in case 2 had positive serologic test for acute EBV and CMV infection and positive patch test for ibuprofen. We can explain that through transient immunosuppression and the danger hypothesis (23), costimulatory signals provided by viral reactivation and/or drug sensitization could act as cofactors and enhance stimulation of an immune response to another protein conjugate and lead to development of severe cutaneous adverse drug reactions (24).

Dehydration and secondary infections are often complications of SJS. Management includes cessation of the responsible drugs, treatment of the precipitating infection, administration of intravenous fluids, topical anesthetics, and prevention of secondary infections. Transdermal fluid loss leads to hypovolemia, changes in electrolyte levels, and finally, to a catabolic

metabolism in TEN. The combination of septicemia and hypovolemia increases the risk of the development of shock and multiorgan failure. Hypoxemia, hypocapnia, and metabolic alkalosis point in need of mechanical ventilation increase the risk of death (4). During hospitalization, cases 1 and 3 experienced numerous complications, including septicemia, anemia, dehydration, and hypoalbuminemia. Ophthalmologic sequelae result in functional changes of the conjunctival epithelium. Ocular sequelae are severe and frequent (40%–50% of survivors) (12). Our patients had no ocular complications.

Conclusion

In summary, early recognition of SJS/TEN and prompt treatment can reduce the risk of infection and length of hospitalization. Patch tests and delayed-reading intradermal test are useful tools for evaluating offending drug. Ceftriaxone and ibuprofen should be considered as possible causes of SJS/TEN in children.

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