Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 6 (55) No. 2 - 2013

# LAMOTRIGINE-INDUCED *STEVENS-JOHNSON* SYNDROME

**L. NEDELCU [1] C. ALIONTE [2] D. DRĂGUŞ[2]**
**L. ANDREI [2] G. POP[2]**

***Abstract:*** *The doctors issuing prescriptions to the patients must warn them about the possible adverse reactions. Although the drug adverse reactions are rare, sometimes they can endanger the life of the patient. One of the drug induced complications - including Lamictal - is the Stevens-Johnson syndrome, a potentially lethal status that is manifesting mainly at the level of the tegument and mucosa but can affect other vital organs. Most Stevens - Johnson syndrome cases, being linked to Lamictal, have happened early at the treatment start, when the dosage was rapidly increased, disregarding the progressive increase of the medicine. Many types of drugs were proven to be efficient in treating the syndrome and the use of corticotherapy is contested in some studies and encouraged in others. The care of the patients with Stevens - Johnson syndrome consists of treatment of the symptoms.*
*We describe in this paper a SJS case, manifested at a epilepsy patient, of whom Convulex treatment followed for 19 years was replaced with Lamictal. The treatment scheme was dome by reducing the Convulex dosage and introducing fast increasing Lamictal doses and in the 4$^{th}$ week the SKS appeared. The evolution of the disease was slowly favorable by treating the associated symptoms cu corticotherapy.*
*In conclusion, although the incidence of the Stevens-Johnson syndrome is low (2-6 persons from 1000000), the doctors must aware of the possibility of its occurrence and the use of the corticotherapy, albeit controversial, can lead to the cure of the disease alongside the symptomatology treatment.*

***Key words:*** *drug adverse reactions, Stevens Johnson Syndrome, epilepsy, Lamictal (Lamotrigine), corticotherapy.*

## 1. Introduction and etiology

The therapy for the control of the epilepsy has made great advances, despite this, the adverse reactions, although rare, remain a major threat to the wellbeing of the patient.

Lamictal (Lamotrigine) in an antiepileptic used for treating the epilepsy. Cutaneous adverse reactions were reported, mostly in the first 8 weeks from the start of the treatment and rarely severe cutaneous reactions were reported, including Stevens-Johnson syndrome and toxic epidermal necrolysis. The global risk of cutaneous eruption can be closely linked with: 1. Initial high dose of Lamotrigine STADA and exceeding the recommended limit of dosage increase for Lamotrigine; 2. Concomitant use of Valproate. [6]

[1] *Transilvania* University of Braşov.
[2] County Emergency Clinical Hospital Brasov.

In the majority of the cases the time between the first intake and the development of the Stevens-Johnson syndrome is between 1 and 4 weeks.

## 2. Case review

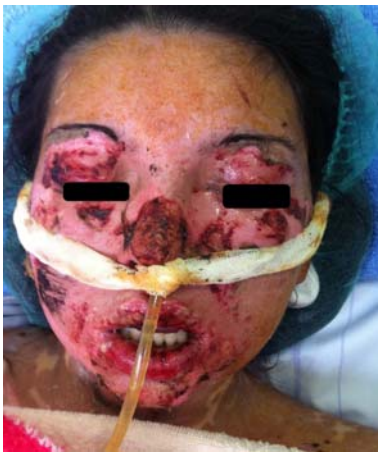


Fig. 1. *28 years female patient from urban area*

We present the case of a 28 years female patient from urban area.

Admission motives: fever, generalised polymorphous maculopapular-erythematous exanthem of face, torso and limbs, discretely pruriginous, very painful with the tendency to combine, with erosive lesions at the level of the mouth mucosa, with swallowing difficulties, vesiculobullous elements (with serum citrine content) very painful at the level of the soles and palms.

Family medical history: without significance;

Physiologic medical history: menarche - 13 years, menstrual cycle - 28 days with 4 days of duration, last menstruation 18.02.2012, 1 pregnancy with therapeutic abortion (fetus with malformation);

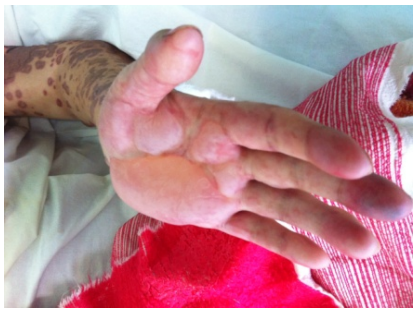
Pathologic medical history: epilepsy (in treatment with Convulex 500 mg for 19 years), B virus hepatitis (detected 1 year ago);

Life and work conditions: adequate;

Behavior (smoking, alcohol): Smoking for 10 years – 5-6 cigarettes/day, denies alcohol consumption;

Treatment administered before admission: Convulex 500mg 2x1 tab/day (for 19 years), Lamictal 50mg (for 4 weeks.), Diane 35, 1 tab Phenoxymethylpenicillin, 1 tab Paracetamol.

Disease history: the patient, ages 28 years, smoker, known with epilepsy fro 9 years of age, with chronic treatment with Convulex 500 mg 2 tab/day, presented a pregnancy a year ago, stopped by therapeutic abortion for fetal malformation; at the same time being discovered with B virus hepatitis. Subsequently, the patient goes to a new physician consult desiring a new pregnancy and the Convulex replacement is decided, being incriminated of the fetal malformation, with Lamictal. The treatment scheme was with the gradual decrease of Convulex and gradual introduction of Lamictal (progressive increased dosage but incorrectly established). Thus, being in the 4$^{th}$ week of treatment with Lamictal, the patient had sudden onset of fever (40°C), dysphagia, dry chough, hyperemic sclerae, conjunctivitis, photophobia, asthenia, myalgia, lack of appetite, reasons wherefore has taken ambulatory Phenoxymethylpenicillin and Paracetamol.



After 3 days the general status of the patient deteriorated as fever appeared, generalised polymorphous maculopapular-erythematous exanthem of face, torso and limbs discretely pruriginous, very painful with the tendency to combine, with erosive lesions at the level of the mouth mucosa, with swallowing difficulties, vesiculo-

bullous elements (with serum citrine content) very painful at the level of the soles and palms, being admitted at the Intensive Care Unit of Brasov County Emergency Clinical Hospital Brasov.

Physical examination at admission: altered general state; sclerae hyperemia; hot skin; generalized exanthema with fusion tendency, with vesiculobullous elements (with serum citrine content) painful, at the level of the palms, abdominal flanks, inguinal with involvement of the genital mucosa and soles; sialorrhea; dry, cracked lips; oral mucosa with aphthae lesions and ulcerations; saburral tongue with adherent white deposits; oral superficial breathing; AT=90/60 mmHg, HR= 120 bpm; hematuria, fever 40 $^{o}$C.

The laboratory values at admission: Hgb 13.6 g/dl; CK: 227 U/L (range: 26-174 U/L); CK-MB: 299 U/L (range: 0-24 U/L); Glicemia:130 mg/dl (range: 70-115 mg/dl); VSH: 20 mm/1 hour (range: 2-13 mm/1hour); TGO: 57.8 U/L (range: 0-38 U/L); TGP: 52.8 U/L (range: 0-41 U/L); Thoracic X-ray: describes bilateral accentuated interstitial markings; The blood culture was negative.

## 3. Management

*Diagnosis*: Stevens – Johnson Syndrome

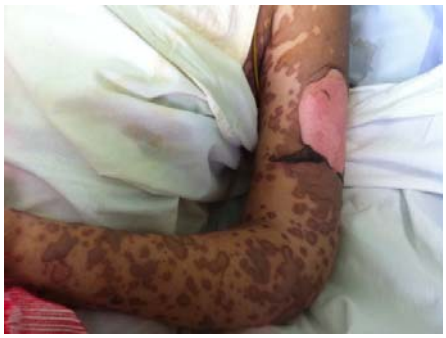
*Differential Diagnosis*: erythema multiform (EM), toxic epidermal necrolysis (TEN), Ritter disease, burns, chemical toxicity (methotrexate), DIC with skin necrosis, purpura fulminans, graft-versus-host disease.

It has been proven that the early diagnosis can decrease the mortality rate. First of all the relationship between the medicine intake and the onset of the adverse reaction, including the evolution after the discontinuation of the incriminated medicine from the therapy. A good history taking of the patient is very important.

All the cases suspected of SJS and TEN should be confirmed via skin biopsy for histology and immunofluorescence examinations. The first lesions have a suprabasal layer of apoptotic keratinocytes. Later the lesions become necrotic and will separate the epidermis from the dermis.

90% of SJS and TEN have also mucosa membrane involvement, its absence should determine an alternate diagnosis to be considered.

The polymorph erythema could be easily mistaken for SJS because both have cutaneous exanthema and mucosa erosions.



*Denomination of the table* Table 1

| EM | SJS |
|---|---|
| Etiology: infection with Herpes Simplex virus | Etiology: drug related |
| Mycoplasma Pneumoniae | Macular lesions |
| Erythematous papular lesions | |
| Specific lesions | "Shooting target" lesions |
| 70% the mucosae are affected but usually limited to the oral mucosa | Initially has face an proximal limbs involved, the mucosae are affected in more than 90% of the cases |
| Fever and altered general state | Fever, cephalea, myalgia |
| Affects < 10% of the body surface | Epidermic necrosis extension |
| Favorable evolution, recovery in 1-4 weeks | High mortality in severe cases |
| Frequent recurrence and many are related to the infection with Herpes Simplex virus | Less frequent recurrence, only if the SJS inductor drug is retested |

A high number of important diseases mimic SJS, thus the histology evidence is very important in our opinion.

*High risk medications* to cause the SJS adverse reaction, reported in studies are: Allopurinol, Carbamazepine, Lamotrigine, Oxicam (NSAID), Phenobarbital, Phenylbutazone, Phenytoin, Sulfamethoxazole, Sulfasalazine, Sulfonamide.

## 4. Treatment

During the admission the Lamictal treatment was suspended and the patient received parenteral alimentation, diet and hygiene, rehydration, and restoration of hydro-electrolytic balance (according to the electrolytes and Astrup values) treatments, also rigorous skin lesion cleaning and complex medicine treatment: systemic antibiotic therapy; Convulex 500 mg for the management of the epilepsy; local anesthetics (to decrease the pain), antihistamines, steroidal anti-inflammatory drugs, anti-itching drugs, analgesics, antipyretics, anticoagulants, gastric and protection, intestinal anti-infective drugs, antifungal, ointment and ophthalmic drops.

In the management of SJS a good nutrition is required because the energy and protein dietary requirements are high.

The oral intake is often difficult due to the impairment of the superior gastrointestinal tract. Initially, when the dysphagia and odynophagia are present, the parenteral feeding is considered very important. When we can switch to oral feeding it is important to take into account the temperature and acidity (hot, cold, acid cause pain), soft and mushy foods are recommended to the detriment of hard and gritty ones. It is important to encourage the oral feeding to avoid superior gastrointestinal tract adhesions. Maintaining the glycemia in normal parameters can be difficult due to stress and corticotherapy. As the hyperglycemia is a risk factor for a negative prognosis, it is recommended to closely monitor the glycemia.

**4.1. The skin care** involves careful exposed dermis protection and early re-epithelization of the skin to prevent further separation; these are the objectives for a prosperous evolution. Daily baths and use of sterile, non-adhesive dressings are required. The lesions must be observed and, if necessary, samples for microbiological cultures will be taken to prevent infections.

**4.2. The pain control** is an integral part of the SJS management, but is not widely published, excepting a guide on burns pain management [3]. The pain management should be customized depending on the clinical needs of the patient. The SJS patients should be treated in I.C.U. and when the patient accuses high level pain and is agitated short action opioids for the upper respiratory tract mucosa can be administered and anxiolytics such as benzodiazepines with short acting time.

**4.3. Frequent monitoring** of the vital signs is an important part of the SJS management because can offer the first signs of systemic worsening. The earliest sepsis signs are hypothermia, tachycardia, low blood pressure, confusion and diarrhea. These require a fast intervention.

For the temperature control the patients are treated in rooms with ambient humidity and temperature.

The careful monitoring of the hydric balance by measuring the amount of administered liquids and diuresis is essential, because the patients have significant liquid loses and in many cases they are dehydrated and have renal insufficiency. These aspects must be quickly prevented or corrected as being risk factor for an ominous progress.

The most common problem is the conjunctiva involvement. This involvement can be mild but can be sometimes severe leading to scars and other complications.

**4.4. The eyes care** is done with ophthalmic ointment (anti-inflammatory and anti-infective) for the exterior eyelids and ophthalmic drops (Tobramycin, Dexamethasone, Neomycin, polymyxin B) 1-2 drops every 4-6 hours in the conjunctival sacs. The possible long term complications are: xerophthalmia, ectropion, symblepharon. The main target of the eye care is keeping these ailments to a minimum.

A good hygiene and use of non-adhesive dressings are usually good to permit the healing of the genital mucosa erosions.

**4.5. The superior gastrointestinal tract care -** the food intake is encouraged to prevent adherences. Mouth cleaning, once every 2 hours with mouthwash, lubrication cream for lips hemorrhagic lesions, in the presence of aphthae the antifungal treatment is recommended. The lip lesions have a tendency to persist even after other skin areas have healed. Some authors have reported a respiratory tract involvement in 10-20% of the cases, requiring artificial respiratory aid. The infectious or aspiration pneumonia can be present at some patients requiring special care.

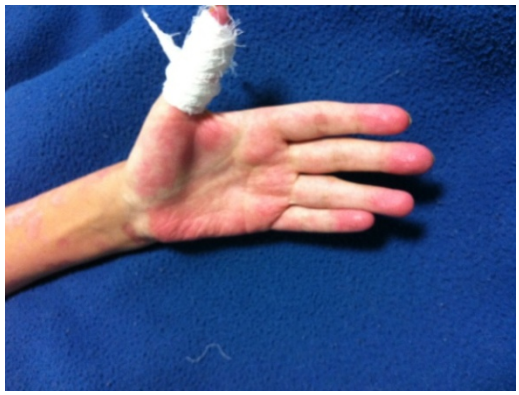
The use of systemic corticosteroids has remained controversial [2] in many studies, some authors considering a worsening of the bullous epidermolysis after corticotherapy (increasing the morbidity and the mortality) and are associated with a higher incidence of complications, some authors recommending high dosage in the initial stages of the disease as being useful. [4]

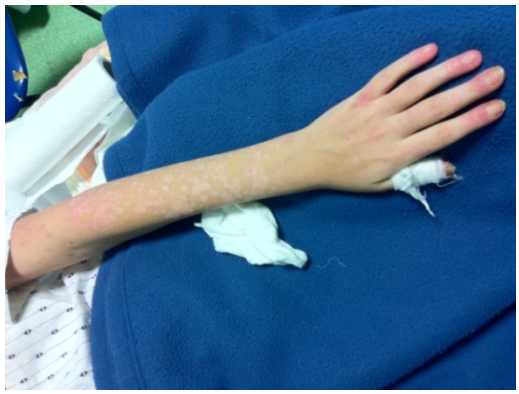
**4.6. Intravenous human immunoglobulins** have been described as useful in treatment and prophylaxis.

**4.7. The plasmapheresis and hemodialysis** have been endorsed by some authors to eliminate the metabolites and responsible cytokines from the blood stream but both have an arguable value.

## 5. The clinical and biologic evolution

Was favorable slowly, the admission period being from 28.02.2013 to 03.04.2013, with biologic and clinical parameters improved at discharge.





The morbidity and mortality of Stevens-Johnson Syndrome –was evaluated with the SCORTEN score: Age>40 years - 1p; Heart Rate>120 -1p; Initial percentage of skin detachment > 10% -1p; Urea level> 27 mg/dl -1p; Serum Glucose>250 mg/dl -1p; Bicarbonate< 20mmol/L -1p; Presence of neoplasms -1p. [5]

## 6. Prognosis

In accordance with this evaluation (SCORTEN) our case has a score of 2, therefore a mortality risk of 12.1%. More than 50% of the patients will have long term sequelae: symblepharon, scars, irregular pigmentation, vagina adhesion, et al.

The corticotherapy and the environment predispose to severe cutaneous infections and/or septicemia.

## 7. Conclusions

1. The most cases of antiepileptic drugs induced SJS manifested in the first 60 days of use.[1]
2. The Stevens-Johnson Syndrome is regarded as a immune mediated reaction to different medicines, over 100 drugs being reported as cause for this skin disease; involved with a greater frequency are: NSAIDs, antibiotics and antiepileptics. This hypersensitivity immune complexes mediated disorder can be induced by many drugs, viral infections and malignancies.
3. The onset of the disease is, usually, with an upper respiratory tract acute infection, fever, cephalea, myalgia; afterwards the typical manifestations of papule, vesicular, bullous and erosion plaques appear during the disease. The center of the lesion can become necrotic with tegument cropping. Aphthous stomatitis, urethritis, erosive vulvovaginitis, convulsions et al. can be associated.
4. The diagnosis was sustained by the history of the disease, with medicine association, onset as URTI, clinical panel, but also by the lack the skin biopsy the confirmation of the disease is missing.
5. The clinical and biologic evolution of the patient was favorable slowly, without complications, under treatment with corticotherapy and symptomatic treatment.
6. The case particularity was the association of three medications: Convulex, Lamotrigine and Diane 35, on the B virus hepatitis background.
7. As conclusion, even if the SJS incidence is small, the doctors must the aware of its possibility of occurrence and the adequate use of the corticotherapy, in our case, has lead to the symptoms remission and healing of the lesions.

## References

1. Mockenhaupt, M., et al.: *Risk of SSJ and toxic epidermal necrolysis in new users of antiepileptics*. In: Neurology Apr, 12, 2005.
2. Oppert, M., Schindler, R., Husung, C., et al.: *Low dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock.* In: Crit Care Med 2005; 33: 2457-2464.
3. Patterson, D.R., Hofland, H.W., Espey, K., et al.: *Pain management*. In: Burns 2004; 30: A10-A15.
4. Patterson, R., Grammer, L.C., Greenberger, P.A., Lawrence, I.D., Zeiss, C.R., Detjen, P.F., Ganz, M.A., Miller, T.P., Orfan, N.A., Sonenthal, K.R., Stoloff, R.S.: *Stevens-Johnson syndrome (SJS): effectiveness of corticosteroids in management and recurrent SJS*. In: Allergy Proc 2007; 13, 89-95.
5. Pitche, P., Padonou, C.S., Kombate, K., et al.: *Stevens-Johnson syndrome and toxic epidermal necrolysis in Lome (Togo). Evolutional and etiological profiles of 40 cases*. In: Ann Dermatol Venereol 2005; 132: 531-534.
6. Wolf, R., Orion, E., Marcos, B., Matz, H.: *Lifethreatening acute adverse cutaneous drug reactions*. In: Clin Dermatol., 2005; 23:171-181.