



## Stevens-Johnson Syndrome: Case Presentation Related to the Use of Antiepileptic Medications

Nur Efe Iris<sup>1</sup>, Funda Simsek<sup>2</sup>, Taner Yildirmak<sup>2</sup>, Arzu Kanturk<sup>2</sup>, Muret Ersoz Arat<sup>2</sup>

<sup>1</sup> Istanbul Bilim University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

<sup>2</sup> Okmeydanı Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

### Abstract

*Stevens-Johnson Syndrome is an acute allergic reaction that can be life-threatening. Here we present a case of Stevens-Johnson Syndrome that has developed due to the use of combined medications. The 18-year-old female patient was hospitalized with the complaints of fever, chills and widespread eruptions all over her body. In her history she had generalized epileptic seizures that have been treated with valproate for the last five years; however, as the seizures could not be controlled, Lamotrigine was added to her treatment about a month ago. She was also on Paroxetine for her hallucinations. She had generalized desquamation on the face, exfoliating brown squames and plaques on the forehead and the cheeks, erythema and blurring around both eyes, redness, xerosis and desqua and white-coloured membranes of the lips, brown-pigmented and itchy papules and plaques and some vesicles on her back and hips that were also seen all around her body.. With these findings, the patient was evaluated as having drug eruptions (SJS) and transferred to the intensive care unit. With steroid treatment, the lesions regressed quickly. When Lamotrigine was added to her treatment regimen, she had been using valproate for 5 years; she had not developed skin lesions that are why valproate was not considered as an ethiological factor. Valproate is known to increase the viability of Lamotrigine by decreasing its glucuronidation. Use of Paroxetine is regarded as a risk factor for SJS also.. When combining medications, an attempt should be made not to combine such medications if possible.*

**Keywords:** Lamotrigine, paroxetine, Stevens-Johnson Syndrome, valproate

(Rec.Date: Nov 13, 2015)

Accept Date: Dec 04, 2015)

**Corresponding Author:** Nur Efe Iris, Istanbul Bilim University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

**E-mail:** nurefeiris@yahoo.com **Phone:** +902123145555

## Introduction

Stevens-Johnson syndrome presents itself with target lesions and bullae of the skin and the mucosae; it is an acute allergic reaction that can be life-threatening. The immunological reaction responsible for the disease is thought to be massive keratinocyte apoptosis [1]. Its etiology mostly includes sulphonamides, NSAIDS, anti-malarials and anticonvulsant drugs [2]. Here we present a case of Stevens-Johnson syndrome that has developed due to the use of combined medications.

## Case

The 18-year-old female patient was hospitalized with the complaints of fever, chills and widespread eruptions all over her body. In her history she had generalized epileptic seizures that have been treated with valproate for the last five years; however, as the seizures could not be controlled with this drug, Lamotrigine was added to her treatment regimen about a month ago. She was also on Paroxetine for her hallucinations. On her physical examination, her general condition was moderate, she was conscious and cooperative with full orientation. Her blood pressure was 100/60 mmHg, HR: 96/min. rhythmic, body temperature was 38°C. She had generalized desquamation on the face, exfoliating brown squames and plaques on the forehead and the cheeks, erythema and blurring around both eyes, redness, xerosis and desqua of the lips, white-colored membranes on the lip mucosa, brown-pigmented and itchy papules and plaques that did not change color by pressure and some vesicles on her back and hips that were also seen all around her body. There were palmar and plantar xeroses as well. Heart and respiratory sounds were natural upon auscultation. Abdomen examination was normal. Liver and spleen were not palpable. Traube space was open. Hemoglobin was:10.8, WBC:9500, Platelets: 204.000, CRP:36, AST:144, ALT:82, GGT:88, LDH:436, total protein:4.8, albumin:2.9 and globulin:1.9. With these findings, the patient was evaluated as having drug eruptions (SJS). Prednol was administered at a dose of 80 mg and local steroid therapy was initiated. As there was not any satisfactory improvement, the patient was transferred to the intensive care unit. With steroid treatment at the ICU, the lesions regressed very quickly. Anticonvulsants are important drug groups that can cause SJS (Figure 1 and Figure 2).



**Figure 1.**



**Figure 2.**

### **Discussion**

Stevens-Johnson syndrome is more common in adults than in children. It has a frequency of 0.4-1.6/1 million individuals per year [3] In our case, in addition to widespread skin involvement, the oral and ocular mucosae were also affected. In the literature, in cases in whom there is widespread body involvement, the mortality is reported as 3-18 % [2]. The use

of corticosteroids for the treatment of SJS is controversial [4]; however, we used steroids in our patient and observed their beneficial effects.

Anticonvulsants are important drug groups that can cause SJS. It is said that when combined antiepileptic medications are used, these compete with glucuronidation metabolism and increase each other's blood levels resulting in severe skin reactions [4]. A study from abroad showed that of 352 SJS cases, 73 (21%) were due to the use of antiepileptics. Of these 73, 36 were attributed to phenobarbital, 14 to phenytoin, 21 to carbamazepin, 13 to valproic acid and 3 to Lamotrigine. The risk of developing SJS was found to be highest within the first 8 weeks following the initiation of treatment while having valproic acid in the combination increased this risk [5].

In the literature there was a case similar to ours; SJS had developed after the addition of Lamotrigine to the existing valproate treatment regimen in this case. This 6-year-old girl had been on valproate for 4 years while Lamotrigine was added during the last two weeks. She had admitted with the complaints of fever, widespread eruptions on the body, oral mucosa lesions and conjunctivitis and was treated with IVIG and steroids [6]. In another case presentation, in the 24-year-old male patient epileptic seizures could not be controlled with valproate and Lamotrigine was added to his treatment regimen. Instead of using the regular dose of 25 mg, the patient mistakenly ingested 200 mg. Couple of hours later, he developed an acute presentation with a body temperature of 40°C, painful ulcers and widespread erythematous plaques all over his body. He was diagnosed as SJS. In this study, it was emphasized that the interactions between Lamotrigine and valproate had contributed to the development of SJS [7]. Different than the cases in the literature, our patient was using three medications namely Valproate, Lamotrigine and Paroxetine with potentials to cause significant rashes at the same time.

When Lamotrigine was added to her treatment regimen, our patient had been using valproate for 5 years; she had not been confronted with side effects and had not developed skin lesions, that is why valproate was not considered as an ethiological factor in the development of Stevens-Johnson syndrome in this patient. Valproate is known to increase the viability of Lamotrigine by decreasing its glucuronidation. This explains why the risk for significant rashes increased when the patient was given Lamotrigine. Even very low concentrations of

valproate decrease the clearance of Lamotrigine. If the patient is to be administered with 500 mg/day dose of valproate, such an effect would be more significant [8]. This shows us that Valproate-Lamotrigine interactions contribute to the development of Stevens-Johnson Syndrome. We primarily think that Lamotrigine that was added to the treatment caused SJS by interacting with Valproate. In addition to Lamotrigine and Valproate, our patient also received Paroxetine. Although quite rarely, Paroxetine is known to cause severe cutaneous side effects like erythema multiforme, Stevens- Johnson Syndrome and toxic epidermal necrolysis [9]. Like Stevens-Johnson Syndrome, toxic epidermal necrolysis is defined as necrotic bullous reactions developing against different medications. The use of Paroxetine is regarded as one of the risk factors for the development of toxic epidermal necrolysis [9].

Paroxetine is a serotonin inhibitor, it demonstrates antidepressant activity during panic disorders, it specifically inhibits the uptake of 5 HT in cerebral neurons. In the literature, in a patient who was using Paroxetine and Sertraline for panic disorder, maculopapillary and erythematous rashes developed and these were thought to be due to a cross-reaction between the medications [10].

With Lamotrigine treatment, the risk for an adult to develop Stevens-Johnson syndrome is 0.3% with the risk of this being highest during the first month of the treatment [11]. However, with the combined use of antiepileptics the risk increases significantly. Therefore, there is the need to monitor each medication separately and for those medications that can compete with glucuronidation mechanism, we should keep in mind that they can increase each other's blood levels resulting in severe skin reactions. Moreover, as was the case in our patient, when using a concomitant medication having a high risk for severe rashes, such risks can be higher and one should be more attentive about these types of side effects in these instances. When combining medications, an attempt should be made not to combine such medications if possible.

### References

1. Murata J, Abe R, Shimizu H. Increased soluble Fas ligand levels in patients with Stevens Johnson Syndrome and toxic epidermal necrolysis preceding skin detachment. *J Allergy Clin Immunol.* 2010;125(3):703-10.
2. Forman R, Karen G, Shear NH. Erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis in children. *Drug Safety.* 2002;25(13):965-72.

3. Raujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med.* 1994;331(19):1272-85.
4. Yates AB, de Sharo RD. Allergic and nonallergic drug reactions. *South Med J.* 2003;96(11):1080-7.
5. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis during first weeks of antiepileptic therapy: a case- control study. *Lancet.* 1999;353(9171):2190-4.
6. Uğuz A, Berber Z, Haspolat Ş, Duman Ö, Yerebakan Ö, Taçoş Ş, Yeğın O. Stevens-Johnson Syndrome, Case presentation related to the use of Lamotrigine, Toxic Epidermal Necrolysis: *Türkiye Klinikleri J Peditr* 2005;14 (1): 36-9.
7. Famularo G, Simone C, Minisola G. Stevens-Johnson syndrome associated with single high dose of lamotrigine in a patient taking valproate. *Dermatol Online J.* 2005;11(1):25.
8. Gidal BE, Sheth R, Parnell J, Maloney K, Sale M. Evaluation of VPA dose and concentration effects on lamotrigine pharmacokinetics: Implications for conversion to lamotrigine monotherapy. *Epilepsy Res.* 2003;57(2-3):85-93.
9. Ahmed R, Eagleton C. Toxic epidermal necrolysis after paroxetine treatment. *NZ Med J.* 2008;121(1274):86-9.
10. Khairkar PH, Bang GM, Singh AB, Tiple PG. Possible cross sensitivity between sertraline and paroxetine in a panic disorder patient. *Indian J Pharmacol.* 2010;42(2):110-1.
11. Schatzberg A. *The American Psychiatric Publishing textbook of psychopharmacology.* 2007;787.