

# A Case of Stevens-Johnson Syndrome Triggered By Combined Use of Antiepileptics

## KOMBİNE ANTİEPİLEPTİK KULLANIMINA BAĞLI GELİŞEN STEVENS-JOHNSON SENDROMU

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### Summary

Stevens-Johnson syndrome (SJS) is a rare, life-threatening acute allergic reaction presenting with target lesions and blebs of epidermis. Etiology frequently comprises the use of sulfonamides, nonsteroid antiinflammatory drugs, antimalarial agents and anticonvulsant medication. Although anticonvulsant drugs have been considered as the primary factor in the etiology of SJS; the drugs responsible for SJS have not been clearly identified yet. However, combined use of these drugs have been reported to cause an increase in the blood levels of each other by competing with glucuronidation metabolism and lead to severe skin reactions. This report presents a SJS case triggered by combined use of anticonvulsant drugs.

A 19-year-old male patient applied to emergency clinic with skin eruption, especially on the face and trunk, and lesions around the mouth. The history of the patient revealed clonazepam use for the last seven months and concomitant use of acid valproic and lamotrigine for the last four months for generalized epilepsy and barbitone had been added to the treatment. However, lamotrigine dosage had been increased three weeks before the onset of symptoms due to the difficulties in controlling the epilepsy seizures. Dermatological examination revealed typical clinic picture of SJS. Lamotrigine and barbitone was stopped. While prednisolone 1mg/kg/day, antibiotic and topical care were started, steroid dosage was reduced within ten days. In addition to valproic acid and clonazepam, piracetam was given for myoclonic seizures. The condition of the patient rapidly improved through this treatment.

Clinicians should bear in mind the possibility that the drugs which increase the blood levels of each other, especially those which compete with glucuronidation metabolism, may lead to severe skin reactions.

**Key Words:** Stevens-Johnson syndrome, Anticonvulsants, lamotrigine

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### Özet

Stevens-Johnson sendromu (SJS) deri ve mukozalarda hedef lezyonlar ve büllerle seyreden, hayatı tehdit edebilen, nadir, akut allerjik bir reaksiyondur. Etiyolojisinde en sık sulfonamidler, nonsteroid antiinflatuar ilaçlar, antimalaryaller ve antikonvülzanlar gibi ilaçlar sorumlu tutulur. Antikonvülzanlar SJS'ye neden olan önemli bir ilaç grubu olmakla birlikte bu grup ilaçlardan hangilerinin sorumlu olduğu konusu hala tartışmalıdır. Kombine antiepileptik kullanımında bu ilaçların glukuronasyon metabolizması ile yarışa girerek birbirlerinin kan seviyesini arttırdığı ve şiddetli deri reaksiyonları oluşturduğu öne sürülmektedir. Burada kombine antikonvülzan kullanımı sonucu gelişen SJS sunulmaktadır.

Ondokuz yaşında erkek hasta, özellikle yüzde, gövdede kızarıklıklar ve ağız bölgesinde yaralar nedeniyle acil polikliniğine başvuran hastanın öyküsünde jeneralize epilepsi nedeniyle yedi aydır klonezepam, dört aydır valproik asit ve lamotrigine kullandığı ancak epilepsi nöbetlerinin kontrol edilememesi üzerine semptomlar ortaya çıkmadan üç hafta önce lamotrigine dozunun artırıldığı ve barbitoneun tedaviye eklendiği öğrenildi. Dermatolojik muayenesinde SJS'nin tipik klinik bulguları mevcuttu. Lamotrigine ve barbitone kesildi. Prednisolon 80 mg, antibiyotik, topikal bakım başlandı ve steroid dozu 10 gün içinde azaltıldı. Myoklonik nöbetleri için valproik asit ve klonezepam ek olarak pirasetam başlandı. Hasta bu tedavi ile hızla düzeldi.

Kombine antiepileptik kullanımını gerektirecek durumlarda her ilacın iyi takip edilmesi gerektiğini ve özellikle glukuronasyon metabolizması ile yarışa girebilecek ilaçların birbirlerinin kan seviyesini artırarak şiddetli deri reaksiyonlarına neden olabileceğini akılda tutmak gerekmektedir.

**Anahtar Kelimeler:** Steven-Johnson sendromu, Antikonvülzanlar, Lamotrijin

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Stevens-Johnson Syndrome (SJS) is a rare life-threatening hypersensitivity reaction. Non-steroidal anti-inflammatory drugs, antimalarials,

anticonvulsant agents, and sulphonamides are the common factors of etiology (1,2). Anticonvulsant agents pose relatively greater risks than many other

drugs and each one may lead to SJS alone. Particularly, in combined use there has been ongoing debate as to which anticonvulsant drugs are responsible for SJS. In addition, some of these drugs are known to be metabolized through glucuronidation; thus, increase the blood levels of each other and cause cutaneous complications when used concomitantly (2,3).

Barbexaclone (BBS), a propylhexedrine salt, has been used in uncontrollable generalized epilepsy treatment. Despite presenting fewer side-effects compared to phenobarbital, it has lost its popularity and is a rarely used phenobarbital derivation. The drug is metabolized in the liver through glucuronidation. As with phenobarbital, BBS frequently cause sedation, depression, and alcohol-dependency like effects on central nervous system. Its cutaneous side effects are usually maculopapular eruptions (4-7). No serious mucocutaneous complications like SJS or toxic epidermal necrolysis (TEN) due to BBS have been reported.

Lamotrigine (LTG), a new anticonvulsant drug, belongs to triazine family and has chemical properties different from those of other antiepileptics. LTG may prove effective especially in resistant generalized epilepsy cases. It may be used alone or in combination with another antiepileptic agent (8,9). Since its concomitant use is frequent, it is highly difficult to interpret the possible side effects. In 3-5% of the cases, there are skin eruptions, but they resolve after the withdrawal of the drug. The eruptions usually occur in the form of late hypersensitivity reaction and are in erythematous or maculopapular manner. There are reports of SJS cases especially with the use of high doses of LTG and combined use with valproic acid (3,10-12).

Clonazepam is the first choice of treatment in all myoclonic epilepsies and provides benefits due to its sedative effects with considerably less skin reactions (6).

Valproic acid has always been the first choice of drug treatment in generalized epilepsy, myoclonic epilepsy and tonic-clonic epilepsy. The side

effects are usually on the liver, hematologic system, and central nervous system. Cutaneous side effects are usually very rare and lead to twisted hair, thinning, and rarely to alopecia (6). This study presents an SJS case which is triggered by combined use of antiepileptic drugs.

### Case

A 19-year old male applied to emergency clinic with hyperaemia of the trunk and especially of the face and lesions around the mouth. The history revealed epilepsy of three years. For his myoclonic seizures, he had initially used valproic acid for six months and quit. However, within the last two years, the seizures had become generalized tonic and absence seizures in nature. When the seizures could not be suppressed, he had been given another treatment protocol in the neurology clinic of another institution. This protocol comprised the use of clonazepam (0.75 mg/day) for the last seven months, valproic acid (2400 mg/day), and Lamotrigine (50 mg/day) for the last four months. Nevertheless, epilepsy seizures could not be controlled and barbexaclone had been added to this combined drug treatment protocol three weeks before the onset of epidermal and mucosal complaints and LTG dosage had been increased to 250 mg/day.

Dermatological examination revealed severe bilateral conjunctivitis, erosion of the lips with hemorrhagic crusts, pale erythematous papules, bullae and erosion on the ears (Figure 1), gingivitis, and severe erosions of the pharynx. There were pale erythematous typical target macules tending to combine with each other and scattered Nikolsky's sign positive blisters on the trunk and acral areas. In the physical examination the patient had poor general appearance, a fever of 39.4°C, a pulse of 100 beat/min., and a blood pressure of 110/70 mm/Hg. Laboratory findings were as follows: WBC 3300 /  $\mu$ L, RBC 38.1 million /  $\mu$ L, hemoglobin 13.5 g/dL, platelet 325000 /  $\mu$ L, sedimentation 40/hr. In biochemical studies, fasting serum glucose level, renal function tests, electrolyte and bilirubine levels were normal, and in the liver



**Figure 1.** Bilateral conjunctivitis of the eyes, erythematous macules, bullae and erosion on face and ears, and hemorrhagic crust on lips.

function tests, the results were: AST 64 U/L (N:0-34) and ALT 82 U/L (N:5-30).

There was no bacterial growth in nasal, throat, urine, and fecal cultures. LTG and BBS were stopped due to severe cutaneous reaction risk posed by high dose of LTG and BBS being the latest treatment modality. As the result of neurological consultation, the diagnosis was established as juvenile myoclonic epilepsy in accordance with the International League Against Epilepsy-1981 (ILAE-1981) criteria (13). The treatment comprised clonazepam (0.75 mg/day) and acid valproic (2400 mg/day), and diazepam was available for any seizure risk. In addition to the basic constituents of the treatment, i.e. valproic acid and clonazepam, piracetam was given. Additional treatment involved fluid replacement, prednisolone (1mg/kg/day), oral antibiotic; ampicilin and sulbactam combination, antibiotic eye drop and ointment, steroid ointment for lips, mupirocin ointment for skin, bicarbonate and chlorhexidine mouth wash for oral mucosal lesions, wet dressing for epidermal surfaces. When the total blood count, biochemical values, general condition of the patient improved and there were no new lesions, the steroid dosage was gradually reduced and completely stopped. The patient had two myoclonic seizures during treatment, and the seizures were controlled with diazepam.

## Discussion

SJS, a rare mucocutaneous reaction, has an incidence of one in two or three million per year. Despite many etiological factors, usually certain drugs rank the first. The mostly accused forms of drugs are antibiotics (40%), antiepileptics (11%) and analgesics (5-23%). Among antiepileptics the mostly accused ones are phenytoin, carbamazepine, phenobarbital, and recently lamotrigine (1,2,11). The risk arises most frequently within the first 2-8 weeks of antiepileptic treatment. Following this 8 weeks, short term, no increase in risk is expected with continued antiepileptic alone. There are, on the other hand, no reports of increased SJS development risk in either short or long term use of valproic acid use. In patients with SJS/TEN and a drug history of concomitant short-term and long-term use of antiepileptics, a suggested initial approach has been to withdraw only antiepileptics with short-term use and continue those with longer use (2,11).

Although the role of LTG in SJS etiology is not clear, there are two hypotheses on this issue. In immunological hypothesis, drug metabolites have been claimed to assume the role of hapten and lead to immunological reactions, particularly to T-cell originated reactions and cell associated cytotoxicity. Showing the infiltrations of CD8+ T cells into epidermis and CD4+ T cells into dermis by lymphocyte transformation test and immunohistological examinations have proved this hypothesis. Severe cutaneous reaction following LTG treatment can occur even when low starting dose is slowly increased (10). The other hypothesis claimed VA may interfere with the metabolism of LTG by inhibiting that the glucuronides, leading to approximately 100% increased of LTG blood levels; thus severe skin reactions are observed (10,11). That's why the patients who will administered LTG and it is combined with VA, should be followed for especially severe skin reactions. The severe skin reaction has been reported to increased with high dosages LTG administration and VA combination. The potential pharmacokinetic interaction of LTG, especially when used in combined with the drugs escalating for glucuronidation, the

dose of VA should be decreased. Severe skin reactions may prevent by avoiding of concomitant use of drugs that can metabolize in the liver, slow dose escalation, and routine evaluation of LTG blood levels (3,7,9,12).

Our case had used only VA for 6 months previously, and later on a constant dose of VA in the last four months in his new treatment protocol. He had also used constant dose of clonazepam for seven months. Therefore, these two drugs were not considered as etiological factors. However, we believe that the increase in the dosage of LTG from 50mg/day to 250mg/day and addition of BBS, which metabolizes through glucuronidation, to the treatment protocol might have increased LTG blood level and caused skin reaction. Another possibility may be that BBS alone might have led to these reactions. In conclusion, in the cases requiring combined antiepileptic drug use, the effects of both drugs should be well-observed. Clinicians should bear in mind the possibility that the drugs which increase the blood level of each other, especially those which compete with glucuronidation metabolism, may lead to severe skin reactions.

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