

Stevens–Johnson Syndrome Prevalence due to Antiepileptic Drug Therapy at Aydın Province University Medical Faculty Hospital



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Aydın Bölgesi Üniversite Tıp Fakültesi Hastanesi'nde Antiepileptik Kullanımına Bağlı Stevens-Johnson Sendromu Prevalansı

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Summary

Objectives: This study aimed to determine the prevalence of Stevens–Johnson syndrome (SJS) due to anti-epileptic drug use among patients at Aydın province epilepsy clinic.

Methods: The records of 2112 adult epileptic patients treated at outpatient clinics of Adnan Menderes University Hospital departments of neurology, pediatric neurology, and dermatology were studied retrospectively.

Results: Two of 2112 epileptic patients who had used lamotrigine had a history of SJS.

Conclusion: The prevalence of SJS due to antiepileptic drug therapy among patients at Aydın province epilepsy clinic was 0.021%.

Keywords: Antiepileptic drugs; epilepsy; Stevens–Johnson syndrome.

Özet

Amaç: Bu çalışmada Aydın bölgesinde epilepsi polikliniğimizde antiepileptik kullanan hastalarda Stevens-Johnson sendromu (SJS) prevalansını incelemeyi amaçladık.

Gereç ve Yöntem: Adnan Menderes Üniversitesi Nöroloji, Çocuk Nörolojisi, Pediatrik Nöroloji Kliniği'nce antiepileptik tedavi ile izlenen 2112 epilepsi hastasının dosyaları geriye dönük olarak tarandı.

Bulgular: Sadece iki tanesinde SJS görüldüğü saptandı.

Sonuç: Antiepileptik kullanımına yönelik Aydın bölgesinde SJS prevalansı %0.021 olarak saptandı.

Anahtar sözcükler: Antiepileptik ilaçlar; epilepsi; Stevens-Johnson sendromu.



Introduction

Stevens–Johnson syndrome (SJS) is a rare, acute, frequently self-limiting, mucocutaneous vesiculobullous disease. Antibiotics such as anti-epileptics, sulfonamide, penicillin, ampicillin, and isoniazid; nonsteroidal anti-inflammatory drugs such as salsalate and allopurinol; others such as nevirapine; and also some infectious agents such as herpes simplex and streptococcus may play an important role in the pathogenesis of this disease. The apoptosis of keratinocytes is the main reason for severe epidermal damage. Various topical and systemic agents can be used to treat the disease; however, the most important treatment is the support treatment after discontinuing the suspicious drug.

Materials and Methods

The records of 2112 adult epileptic patients treated at outpatient clinics of Adnan Menderes University Hospital departments of neurology, pediatric neurology, and dermatology were studied retrospectively. The demographic features of the patients and the names and doses of the anti-epileptics they used were evaluated.

Results

SJS was detected in only 2 of the 2112 analyzed epilepsy patients.

Case 1 (AT)– A 67-year-old male had been using diphenylhydantoin for tonic–clonic seizures, which had occurred four to five times in a year since 25 years. The patient, who used 1×1 tablet and had his last seizure 2 years ago, visited the clinic with impaired balance complaint. Since no pathology was found on evaluating the age and bone structure of the patient, the reason behind the imbalance in this patient was thought to be related to his diphenylhydantoin treatment, and a transition to lamotrigine treatment was planned. It was suggested to add lamotrigine 1×25 mg/day to diphenylhydantoin 1×1, and then diphenylhydantoin was discontinued. However, the patient was hospitalized in the dermatology clinic due to the development of maculopapular eruptions on the mucosa and skin and redness in the conjunctiva in the third week of the additional therapy. The treatment was continued in the intensive care clinic due to edema, opening of the bullae, expansion of the hemorrhagic area, and fever.

Case 2 (HY)– A 21-year-old male patient had generalized tonic–clonic seizure that started during the examination and repeated three times in 4 months. The lamotrigine treatment was not started after the first seizure. Instead, valproate treatment was started after the second seizure. He had his third seizure after 1 month when he was under valproate treatment. Therefore, the lamotrigine treatment was started, since it had no effect on the loss of attention during the examination and did not cause weight gain. The patient visited the clinic with skin and mucosal lesions (maculopapular lesions), redness, conjunctival lacrimation, and conjunctival lesions in the third week of lamotrigine supplementation treatment, which was administered at an increasing dose of 25 mg/day every week. He was directly hospitalized due to the seriousness of his lesions.

Both cases were treated in the intensive care unit, their antiepileptic drugs were discontinued, and they were discharged in 7–10 days with an oral steroid, antihistaminic, and support treatment. The clinical conditions of the patients were shared after taking their consents at later stages of their treatments.

Discussion

The side effects associated with skin infections in patients using antiepileptic drugs are the most common side effects. SJS or toxic epidermal necrosis is the most severe among these side effects. This clinical picture may be seen as a result of multiple drug use (antiepileptic drugs, sulfonamide, beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs, gold salts, allopurinol, nevirapine, and so forth). Drugs or their metabolites bind to the surface of keratinocytes and act like haptens. The drug-specific CD8+ T cells activate caspase enzymes through Fas/FasL or perforin/granzyme B pathways. Apoptosis of keratinocytes is triggered, and severe epidermal damage occurs. An increase in pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-6, IL-8, and IL-13 in SJS and toxic epidermal necrosis also plays a role in this damage.^[1]

Genetically, carriers of HLA-B 1502 mutation after the use of carbamazepine, diphenhydramine, and fosphenytoin are frequently found in populations of Asian countries such as India, China, Malaysia, Philippines, and Taiwan. Carriers of HLA-A 3101 mutation after carbamazepine use were also reported in Japan.^[2,3] Felbamate, gabapentin, levetiracetam, topiramate, tiagabine, and zonisamide have been

found to be safer in this regard.^[4] The use of lamotrigine, carbamazepine, ethosuximide, phenytoin, phenobarbital, and valproate as antiepileptic drugs has been reported in recent years.

Only two cases with SJS among 2112 cases were reported. This study aimed to discuss the prevalence of this rare syndrome among the patients who used antiepileptic drugs in Aydin Adnan Menderes University Hospital. No specific study related to this topic was found in the *Epilepsy journal* since 1995. Also, no specific information on its prevalence was available in the literature. Many studies on the side effects of antiepileptic drugs have been conducted in Turkey. Denizbasi and Eskazan conducted a large-scale study on the side effects of these drugs on skin in 1995. They reported the prevalence of treatment-related skin hypersensitivity reactions as 1.34% for phenytoin, 2.63% for carbamazepine, 0.39% for valproate, and 3.64% for lamotrigine.^[5] However, no SJS-specific studies were reported. The results of antiepileptic drug-related skin rashes were not shared, but the details of two cases with mucocutaneous lesions in the intensive care unit were discussed in the present study. The study by Denizbasi and Eskazan evaluated the cases according to their gender; the prevalence of skin reactions was found to

be 1.7% and 0.73% in male and female cases, respectively. Both SJS cases in this study were males.

The first case was an elderly patient who had been using phenytoin for years and was treated with lamotrigine in the clinic due to his impaired balance complaints. No abnormalities were revealed by his carotid–vertebral artery ultrasonography, routine biochemistry, hemogram analyses, B12 and folic acid levels, and infection parameters. A drug alteration was planned considering the risk of cerebellar degeneration due to diphenylhydantoin use. The second case was under valproate treatment, which was started in another center after his first seizure. Even though he had been using 3×1 valproate tablet, sufficient seizure control could not be achieved. Lamotrigine was prescribed, since the patient was under intensive examination and did not want to gain weight. Both cases had severe skin and mucosal rashes, fever, fatigue, lack of appetite, nausea, vomiting, and swallowing and chewing difficulties. The second case (who had psoriasis) also had arthralgia and sore throat (Figures 1 and 2). The cases were admitted to the intensive care unit, and the medicines t they had been using were continued. They were discharged after treating with steroid and anti-histaminic drugs and supportive medical treatments.



Figure 1. Case 1: Skin (a and c) and mucosal (b) eruptions.



Figure 2. Case 2: Skin (a and c) and mucosal (b) eruption.

Lamotrigine was preferred, since the second case in this study did not mention about his previous psoriasis treatment before lamotrigine treatment and no psoriasis was reported. However, if psoriasis was reported earlier, an anti-epileptic, which might cause common skin rash, would not be preferred. The importance of questioning other previous illnesses of the patient was highlighted in this case.

Infections (particularly varicella infections) should be considered in the differential diagnosis of rashes in antiepileptic drug users.^[6]

Nonprogressive conjunctivitis was detected in both the cases in this study. Another important issue is that artificial tears and pomades may sometimes not be sufficient when subepithelial symptoms develop in the eyes, such as symblepharon, entropion, trichiasis, distichiasis, and episcleritis after conjunctivitis. The eyelid sequels may even need surgery after the disease is treated. In some cases, penetrating keratoplasty may not provide desired benefits due to the development of corneal neovascularization.^[7] Another issue that demands the attention of clinicians is that the possibility of developing a cross-reaction is high during the use of aromatic antiepileptic drugs such as carbamazepine, ox-carbamazepine, lamotrigine, and phenytoin. These agents should be avoided when choosing and changing appropriate antiepileptic agents.

A common side effect of lamotrigine use is skin rashes (2.3%–8.2%).^[8] Another study conducted in Turkey reported the prevalence of skin rash with lamotrigine use as 4.3%. Unlike previous results and the findings of Denizbasi

and Eskazan,^[5] sex differences were not detected in this study.^[9]

Oral mucocutaneous lesions disrupt the patient's nutrition and hence require a prolonged treatment. Moreover, some painful vaginal or anal lesions and nasal mucosal lesions can be associated with similar symptoms in women. Although these lesions are rarely seen, the aim of the present study was to alert against this clinical condition whose death rate can reach up to 35%.^[4]

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