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Case Report

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A Case of Stevens-Johnson Syndrome Triggered by Combined Use of Lamotrigine and Valproic Acid

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ABSTRACT

Stevens-Johnson syndrome (SJS) was first described by Stevens and Johnson in 1922. It is an acute mucocutaneous hypersensitivity reaction, involving skin and mucous membranes. This is a rare but life-threatening syndrome. The use of non-steroid anti-inflammatory drugs, penicillin, antimalarials, sulphonamides, and anticonvulsants are common etiologic factors. In this report, we present a case of Stevens-Johnson syndrome related with concomitant use of lamotrigine and valproic acid. A 7 year-old boy referred to emergency clinic suffering from erythematous papules, predominantly on the face and neck, and lesions around the mouth. The patient was under valproic acid therapy for three years with the diagnosis of epilepsy. Because of poor control of the seizures, lamotrigine (25 mg/day) had been added to the treatment one month ago. Dose of the drug had been gradually increased to 50 mg/day in three-weeks period. After one week of this dose, skin eruptions had appeared. In conclusion, the clinicians should be aware of the fact that combined use of lamotrigine and valproic acid increases the risk of SJS especially in children. Patients who undergo anticonvulsant therapy should be informed about possible cutaneous adverse effects and treatment should be discontinued immediately if any rash appears.

Key words: *Child, Stevens-Johnson syndrome, valproic acid, lamotrigine*

ÖZET

Valproik Asid ve Lamotriginin Birlikte Kullanımının Tetiklediği Bir Stevens-Johnson Sendromu Vakası

Stevens-Johnson Sendromu 1922'de Stevens ve Johnson tarafından tanımlanmış, deri ve mukozaları tutan, akut bir aşırı duyarlılık reaksiyonudur. Bu sendrom nadir, ancak hayatı tehdit eden bir tablodur. Etiyolojisinde non-steroid antiinflamatuar ilaçlar, penisilin, antimalaryal ilaçlar, sulfonamidler ve antikonvülzan ilaçlar yer alır. Bu çalışmada lamotrigine ve valproik asid kullanımına bağlı bir Stevens-Johnson Sendromu vakası rapor edilmiştir. Yedi yaşında erkek hasta özellikle boyun, yüz ve ağız çevresinde gelişen eritemli papüller döküntüler ile kliniğimize başvurdu. Üç yıl önce hastaya epilepsi tanısı konulmuş ve valproik asid tedavisi başlanmış. Ancak nöbetlerin kötü kontrolü nedeniyle bir ay önce 25 mg/kg/gün dozunda lamotrigine eklenmiş ve kademeli olarak 50 mg/kg/gün dozuna artırılmış ve bu dozdan bir hafta sonra deri döküntüleri ortaya çıkmış. Sonuç olarak, klinisyenler özellikle çocuklarda valproik asid ve lamotrigin kombinasyonunu kullanmaları durumunda Stevens-Johnson sendromu riskinin artığını bilmelidirler. Antikonvülzan ilaç kullanan hastalar oluşabilecek yan etkiler hakkında bilgilendirilmeli ve herhangi bir döküntü gelişmesi halinde derhal tedavi kesilmelidir.

Anahtar Sözcükler: *Çocuk, Stevens-Johnson sendromu, valproik asid, lamotrigine*

Stevens-Johnson syndrome (SJS) is a rare but life-threatening acute mucocutaneous hypersensitivity reaction, usually related to some drugs. While mycoplasma and other infections may be responsible for SJS in children and in adolescents, drugs are always considered to be the reason in adults. Non-steroid anti-inflammatory drugs, antimalarials, penicillin, anticonvulsants, and sulphonamides are common etiologic factors (1, 2). Lamotrigine (LTG) is an antiepileptic drug (AED) recently released in several countries, and also bears a risk for skin reactions. The risk is largely confined to the first 8-weeks of treatment. Main adverse effects of LTG are simple morbiliform skin eruptions, occurring in 3-10% of the treated patients, but the incidence for development of Stevens-Johnson syndrome during lamotrigine therapy is low. The risk of cutaneous side effects is increased in patients receiving concomittant valproic acid (VA), probably by doubling the plasma half-life of LTG due to competition with hepatic glucuronidation. Conversely, the risk can be reduced by adding LTG in lower doses (3-5). In this report, we present a case of Stevens-Johnson syndrome due to concomitant use of lamotrigine and valproic acid.

CASE REPORT

A 7 year-old boy applied to emergency clinic with erythematous papules, especially on the face and neck, and lesions around the mouth (Figure 1). The patient was under VA (500 mg/day) therapy for three years with the diagnosis of epilepsy in the neurology clinic of another institution. Because of poor control of the seizures, lamotrigine (25 mg/day) had been added to treatment one month ago. Dose of the drug had been gradually increased to 50 mg/day in three weeks period. After a week of this dose, skin eruptions had appeared. Physical examination revealed: the patient had a fever of 38.7°C, a pulse of 108 beats/min, and blood pressure of 100/60 mm/Hg. Dermatologic examination showed erythematous papules, especially on the face and neck, and lesions around the mouth, hemorrhagic crust on lips, purpuric lesions on the trunk, extremities, and genital region (Figure 2).

Laboratory findings were as follows; WBC: 5250/µL, RBC: 4,940,000/µL, hemoglobin: 11.8 g/dl, platelet: 182,000/µL,

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sedimentation: 31/hr. The chest radiograph was normal. In biochemical studies, serum glucose level, renal function tests, electrolyte and bilirubin levels were in normal range, and liver function tests were; AST: 54 U/L and ALT: 24 U/L. There were no bacterial growth in nasal, throat, blood, urine, and fecal culturs. Mycoplasma, herpes simplex virus, Ebstein-Barr virus, Cytomegalovirus, hepatitis virus (A, B, C, and E), and HIV serologies were all negative. Lamotrigine level was 3.8 mcg/ml and VA level was 27,6 mcg/ml in blood of the patient. The patient was diagnosed with lamotrigine-related SJS on the basis of history and physical findings, and according to the current consensus guidelines. The lamotrigine was stopped immediately and anticonvulsant therapy of the patient was changed as valproic acid and diazepam for any seizure risk. Additional treatment including fluid replacement, methylprednisolone (1mg/kg/day), oral antibiotic, bicarbonate and clorhexidine mouth wash for oral mucosal lesions, wet dressing for epidermal surfaces were applied. Following the treatment, lesions progressively resolved and the dose of prednisolone was reduced gradually. The patient showed a sufficient recovery and he was discharged after 20 days.

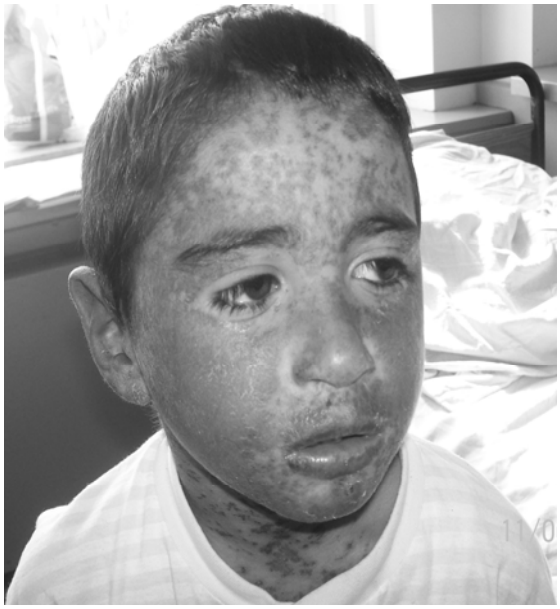

Figure 1. Erythematous papules on face /neck and hemorrhagic crust on lips of patient.

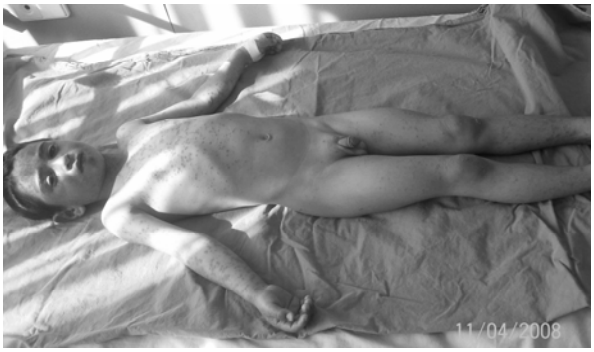

Figure 2. Purpuric lesions on the trunk, extremities, and genital region of patient.

DISCUSSION

Stevens-Johnson syndrome is a rare (1-2 cases per million population per year) but life-threatening mucocutaneous reaction characterized by detachment of epidermis, acute skin blisters, and mucous membrane erosions. Desipite many etiological factors, certain drugs such as antibiotics, antiepileptics, and analgesics are usually considered to be responsible for the disease (1). Among antiepileptics the mostly accused ones are phenytoin, carbamazepine, phenobarbital, and recently lamotrigine. The risk arises most frequently within the first 2-8 weeks of antiepileptic treatment (2-5, 6). Liver damage, heamatologic and central nervous system findings are the common side effects of valproic acid. Cutaneous side effects are quite rare and result twisting and thinning of hair and alopecia, rarely (7).

Although the exact mechanism(s) of LTG-related SJS remain to be elucidated yet, there are two hypotheses about this issue. In immunological hypothesis, drug metabolites have been claimed to assume the role of hapten and lead to particularly T-cell originated immunological reactions and cell-associated cytotoxicity. This hypothesis has been proved by demonstrating the infiltrations of CD8+ T cells into epidermis and CD4+ T cells into dermis with lymphocyte transformation test and immunohistological investgations (1,8). Other hypothesis claims that, VA probably interferes with metabolizing of LTG by glucuronide inhibition, thus leads to increased serum LTG levels, or alteration of LTG metabolism. This interference causes accumulation of toxic intermediate metabolites and severe skin reactions (9). Weintraub et al (10) reported that valproic acid decreases lamotrigine clearance by approximately 60% in a study with 570 patients.

Our patient had used only VA for three years, previously. Therefore, this drug was not considered as etiologic factor. However, we believe that the increment of LTG dose from 25 mg/day to 50 mg/day which metabolizes through glucuronidation, might have increased LTG blood level and caused skin reaction. Severe cutaneous reactions following LTG treatment may ocur even in case of low initial and gradually increasing doses (8, 11). According to Guberman et al (12), children have an approximately three-fold risk of developing serious rash with lamotrigine, moreover the risk may increase when one exceeds the advised initial doses for titration or when combined with valproate. Drugs are the most common factors for development of SJS whereas mycoplasma and herpes virus infections comprise less common causes (1). There was no bacterial growth in cultures of our patient. Additionally, the bacterial and viral serology were all negative. Therefore, no infection was considered as a cause in this case.

In conclusion, the side effects of drugs should be followed carefully in the patients requiring combined antiepileptic drugs. Severe skin reactions may be prevented by avoiding of concomitant use of drugs that are metabolized in the liver, slow dose escalation, and routine measurement of LTG blood levels. Clinicians should be aware of the fact that combination of of antiepileptic drugs increases the risk of SJS especially in children. Patients who undergo therapy with AEDs should be informed about possible cutaneous adverse effects and the therapy should be discontinued if any rash appears.

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