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LAMOTRIGINE-INDUCED HYPERSENSITIVITY SYNDROME: CASE REPORT

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ABSTRACT:
Anticonvulsant hypersensitivity syndrome (AHS) is a life-threatening, idiosyncratic, non-dose related adverse reaction reported to occur with aromatic antiepileptic drugs. We present an 11-year-old girl diagnosed with hypersensitivity syndrome with a fever, rash, lymphadenopathy, and hepatic and pulmonary involvement. Although timely recognition of the signs and symptoms, discontinuation of the drug, supportive care, and close observation are crucial in the management of AHS, the use of systemic corticosteroids and intravenous immunoglobulin seems to be a good option for severe cases with multiorgan involvement as in our patient. We present our case to emphasize once more the importance of close laboratory monitoring and clinical follow-up after starting antiepileptic drugs and also informing the families about the adverse effects of drugs.
Key words: Anticonvulsant Hypersensitivity Syndrome, Lamotrigine

LAMOTRIJİNLE İNDÜKLENEN HİPERSENSİTİVİTE SENDROMU: OLGU SUNUMU
ÖZ:
Antikonvülzan hipersensitivite sendromu (AHS); aromatik antiepileptik ilaçlarla olduğu bildirilen, hayatı tehdit eden, idiosenkratik, doza bağımlı olmayan bir ilaç reaksiyonudur. Ateş, döküntü, lenfadenopati, karaciğer ve akciğer tutulumuyla hipersensitivite sendromu tanısı alan 11 yaşında kız hastayı sunuyoruz. Belirti ve bulguların zamanında fark edilmesi, ilacın kesilmesi, destek tedaviler ve yakın izlem AHS'un tedavisinde çok önemli olmakla beraber hastamızda olduğu gibi multiorgan tutulumu olan ciddi vakalarda sistemik kortikosteroidlerin ve intravenöz immunglobulinin kullanılması iyi bir tedavi seçeneği olarak görülmektedir. Antiepileptik tedavi baslandıktan sonra yakın laboratuar ve klinik izlemin ve ilaçların yan etkileri hakkında ailelerin bilgilendirilmesinin önemini bir kez daha vurgulamak için olgumuzu sunuyoruz.
Anahtar Kelimeler: Antikonvülzan Hipersensitivite Sendromu, Lamotrijin

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INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunction. The syndrome develops 2 to 6 weeks after the initiation of a specific drug including carbamazepine, phenytoin, phenobarbital, dapsone, mexiletine, salazosulfapyridine, allopurinol, and minocycline[1-2]. The diagnostic criteria for DIHS/DRESS are shown in Table 1. There is usually no mucocutaneous involvement, which helps distinguish DIHS/DRESS from other forms of severe drug eruptions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

DIHS/DRESS has no age or sex predilection. The delayed onset in relation to introduction of the causative drug is an important feature of DIHS/DRESS that can be used to distinguish it from other types of drug eruptions. An intimate relationship is suggested between human herpes-virus 6 (HHV-6) and DIHS[3].

Table 1. Diagnostic criteria for DIHS/DRESS.

1. Maculopapular rash developing > 3 weeks after starting therapy with a limited number of drugs
2. Lymphadenopathy
3. Fever (> 38 °C)
4. Leukocytosis (>10×10^9/L)
   a. Atypical lymphocytosis
   b. Eosinophilia
5. Hepatitis (ALT>100 U/L)
6. HHV-6 reactivation

The diagnosis is confirmed by the presence of five of the six criteria above

Anticonvulsant hypersensitivity syndrome (AHSS) is a specific severe idiosyncratic reaction to aromatic antiepileptic drugs (AEDs) such as phenytoin, carbamazepine, phenobarbital, primidone, and lamotrigin[4]. The risks for AHSS range from 1 to 10 per 10,000. AHSS is not reported during monotherapy treatment with topiramate, gabapentin, or levetiracetam, and is reported rarely with valproic acid[5].

We report an 11-year-old girl hospitalized with rash and fever for 1 week and re-admitted to the emergency department 2 days after discharge with serious clinical findings including lymphadenopathy, coagulopathy, and hepatic and pulmonary involvement and diagnosed with hypersensitivity syndrome due to lamotrigine.

CASE REPORT

An 11-year-old girl with the diagnosis of epilepsy followed up for 5 years was admitted to our hospital with the complaints of

fever and rash. She had been taking sodium valproate (40 mg/kg/day) for 5 years and lamotrigine (1 mg/kg/day) had been added to her therapy 15 days before hospitalization because of recurrent epileptic seizures. Drug allergy due to the lamotrigine was surmised, the lamotrigine was discontinued, and she was treated with antihistamines. The rash disappeared and the fever decreased to normal levels. After 1 week she was discharged on valproate therapy.

Two days later the child returned to the emergency department because of high fever, nausea, vomiting, and spread of the rash. Her physical examination revealed a toxic appearance with a generalized erythematous eruption composed of multiple, deeply blanchable macules, papules, and urticarial plaques. Tender, firm, and enlarged lymph nodes were found in the cervical region. Severe facial edema and erythema were present. Cefotaxim therapy was empirically initiated to treat a potential bacterial infection. The hematologic parameters were within the normal ranges except leucocytosis and liver enzymes were elevated (AST: 82 IU/L, AST: 114 IU/L). The peripheral smear revealed lymphocytosis (88% lymphocyte, no eosinophilia).On day 5, she had periorbital and pretibial edema, tachypnea, crepitant rales, and hepatomegaly. The results of laboratory studies included leucocytosis, 30,000 cells/mm^3 (N: 4000-10,000 cells/mm^3); anemia, 7.8 g/dl (N: 11-14 g/dl); thrombocytopenia, 49,000 cells/mm^3 (N: 150,000-400,000 cells/mm^3); elevated liver enzymes: aspartate transaminases (AST) 1170 IU/L (N: 20-40 IU/L), alanine aminotransferase (ALT) 340 IU/L (N: 20-40 IU/L), hypoalbuminemia, 1.9 g/dl (N: 3.5-5.5 g/dl), coagulopathy: prothrombin time 21.3 s (N: 13-16), partial thromboplastin time 59 s (N: 26-32). Toxic hepatitis was thought to be present and the valproate therapy was withdrawn and the patient was referred to the Pediatric Allergy Department. Treatment with intravenous (IV) methylprednisolone for 3 days and IV immunoglobulin (400 mg/kg/day) for 5 days was started with the diagnosis of drug-induced hypersensitivity syndrome. On the third day of therapy, thrombocyte level increased to 71,000, and the levels of ALT and AST decreased to 123 and 223 IU/L, respectively. On the sixth day of therapy, thrombocyte level was 257,000 cells/mm^3, ALT 42 IU/L, and AST 49 IU/L. The serology for Epstein-Barr virus, cytomegalovirus, hepatitis virus, and mycoplasma pneumonia was negative. Urine, blood, and stool cultures were sterile. Abdominal ultrasonography revealed hepatomegaly, ascites, grade I nephropathy, and pleural effusion. The search for collagen diseases and malignancies revealed nothing. On the third day of IVIG therapy, the patient became afebrile and the cutaneous rash disappeared. On day 15, she was discharged with topiramate in good health.

DISCUSSION

Hypersensitivity syndrome (HSS) reactions are one of the most feared idiosyncratic drug reactions and are most common after exposure to antiepileptic drugs, sulfonamides, nonsteroidal anti-inflammatory drugs, corticosteroids, and allopurinol.

HSS is associated with chemotoxic and T-cell-mediated inflammatory injuries in barrier tissue systems that contain cytochrome oxidases (e.g. skin, mucosa, liver, and lungs) and can be seen as a derangement in the defense system against xenobiotics-bioactive foreign molecules. The mechanism for anticonvulsant HSS is incompletely understood but involves genetic susceptibility with accumulation of AEDs and oxidized metabolites causing major histocompatibility complex (MHC) and non-MHC-dependent clonal activation of T cells and subsequent cytokine/chemokine production in T cells, keratinocytes, and other target cells[5]. In Han Chinese patients carbamazepine-induced SJS correlates strongly with an HLA marker: 100% (44 of 44 patients) had the human leucocyte antigen HLA-B 1502, while the same genetic marker was present in only 3% (3 of 101) of patients who tolerated carbamazepine and in 8.6% (8/93) of the general population[6]. This possibly explains the several-fold higher incidence of SJS resulting from carbamazepine compared to the incidence in Caucasians.

The pathogenesis of AHSS appears to be multifactorial. Factors involved include a balance between active metabolites and detoxification pathways. It was found that lymphocyte toxicity for the aromatic amines (i.e. phenytoin, carbamazepine, phenobarbital) depended on oxidation by cytochrome P-450 isozymes into reactive arene oxide metabolites[7-8]. Lymphocyte toxicity was increased when epoxide hydrolase, the detoxifying enzyme that removes the reactive intermediate, was inhibited or defective. This finding suggests that HSS was partially caused by loss of detoxification capacity, which resulted in an accumulation of reactive epoxide intermediates. There is considerable evidence supporting this hypothesis, including the fact that rapid accumulation of AEDs or their metabolites increases the risk for HSS in susceptible patients. Rapid infusion of phenytoin or rapid initiation of lamotrigin, for example, increases the risk for AHSS.

In this syndrome, the onset of symptoms is highly variable; usually patients develop two or three features of symptoms followed by a step-wise development of other symptoms. In many severe cases, these symptoms continue to deteriorate or several flare-ups can be seen even for weeks after the offending drug is stopped. Interestingly, the more severe reactions often occur 3 days after withdrawal of the causative agent[3]. This important knowledge must be kept in mind by clinicians.

In this case, the patient developed a rash and fever 15 days after lamotrigine was added to VPA treatment. She was hospitalized for 1 week, lamotrigin was withdrawn, and she was discharged with clinical improvement. Unfortunately she was re-admitted to the emergency department with a serious clinical and laboratory deterioration. In addition to fever and rash, she had lymphadenopathy, hepatitis, hematologic disorders, and pulmonary involvement.

Lamotrigine is an antiepileptic drug in increasing use in the pediatric population and that is effective for a broad range of seizure types[9]. Lamotrigine acts through voltage-sensitive sodium channels and decreases the synaptic release of excitatory amino acids, such as glutamate. Lamotrigine has been associated with life-threatening rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Although risk factors for serious rash are thought to include the initial

6 weeks of therapy, concomitant valproic acid therapy, age younger than 13 years, high initial dose of the lamotrigine, and too rapid escalation of the lamotrigine dose, avoiding these factors is not always protective[10]. Most of these risk factors were present in our patient. Lamotrigine was added to our patient's therapy with an initiation dosage of 1 mg/kg/day, but starting the treatment with a low dose (0.15 mg/kg/day) and titration rate (0.3 mg/kg/day after 2 weeks) slower than currently recommended doses should be preferred, especially in children on valproate therapy.

Concomitant use of VPA with lamotrigine significantly increases the risk for development of adverse cutaneous reactions. It is known that VPA interacts with lamotrigine metabolism, leading to a reduced total clearance and therefore to an increased elimination half-life of lamotrigine and resulting in higher serum concentrations. The present case and previously published reports point out the risks caused by the concomitant use of lamotrigine and VPA.

Lack of knowledge amongst physicians and lack of access to a confirmatory laboratory test or genetic analysis are the reasons for the small number of published cases. There are several case reports of AHSS after lamotrigine use in children in the literature[11-13]. Karande et al. describes a child developing AHSS on exposure to lamotrigine and the drug reaction was confirmed by in vitro lymphocyte toxicity assay[14]. We are unable to perform this laboratory test in our hospital.

Patients with AHSS can suffer serious epidermal scarring, mucosal inflammation, hepatic failure, pneumonitis, and, with TEN, sepsis and shock. AHSS is a potentially lethal condition. The first and most important step in the management of AHSS is to identify the clinical syndrome and discontinue the offending agent immediately, followed by supportive care with hydration and skin care[5]. There have been no successful controlled trials for treatment of AHSS, and reports vary considerably as to whether patients benefit from treatment with corticosteroids. The use of steroids in this condition is controversial with positive and negative results being reported in the literature[15-16]. In Bessmertney's series[17], the clinical outcome was similar between children who received systemic steroid therapy and those who did not.

It has been suggested that IVIG blocks CD95 (fas), a cell surface receptor on keratinocytes that plays a role in triggering apoptosis. Antibodies present in IVIG have been shown to block CD95-mediated keratinocyte death and subsequent epidermal detachment in patients with toxic epidermal necrolysis and a similar mechanism could be responsible for the improvement seen in AHSS[3]. Several uncontrolled series suggested that treatment with high-dose IVIG hastens recovery from SJS and TEN in some patients[18-19]. Well-controlled, prospective, multicenter clinical trials are needed to determine the optimal dosage and duration of therapy guidelines and to compare the efficacy and safety of IVIG with other therapies.

Prais[20] describes four adolescents with AHSS who were treated with IVIG and systemic corticosteroids and recovered completely following an uncomplicated, short course and hospitalization. They suggest that this regimen might be a promising treatment option for this patient population. The role of steroids and IVIG in this condition is unresolved, but their use was associated with rapid clinical and laboratory improvement in our case.

Future treatments for AHSS may also involve reducing buildup of reactive intermediates and blocking target cell reactions, such as keratinocyte secretion of TNF-α. Hunger et al.[21] reported a patient with TEN that recovered immediately with anti-TNF-α treatment.

The present case and previously published reports highlight the risks caused by the concomitant use of lamotrigine and VPA. Clinicians must be aware of AHSS and cross-reactions between various aromatic antiepileptics. The use of corticosteroids and intravenous immunoglobulin in severe cases with multiple organ involvement seems to be a good option. Clinicians must be careful about the risks of concomitant use of valproate and lamotrigine reported several times in the literature until libraries of MHC and enzyme-subtypes associated with serious drug reactions are developed. We hope that it will be possible to show the individual genetic susceptibility to HSS and other serious drugs in the future.

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