Korean Journal of Pediatrics Vol. 52, No. 3, 2009
DOI : 10.3345/kjp.2009.52.3.389
Case report

A case of antiepileptic drug hypersensitivity syndrome by lamotrigine mimicking infectious mononucleosis and atypical Kawasaki disease

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= Abstract =

Antiepileptic drug hypersensitivity syndrome (AHS), a delayed immunological reaction, is a relatively rare side effect of antiepileptic drugs and is usually overlooked. An array of symptoms can occur one to eight weeks after treatment with an antiepileptic drug. Symptoms may be as simple as a fever, skin rash, or lymphadenopathy, but may eventually involve internal organs and cause fatal outcomes. Additionally, because the symptoms resemble the features of various arrays of diseases and the reported mortality rate is approximately 10%, the importance of early diagnosis and ability to differentiate AHS from other diseases cannot be overemphasized. We report a case of a 14-year-old girl with AHS caused by lamotrigine, which mimicked atypical Kawasaki disease and infectious mononucleosis. (Korean J Pediatr 2009;52:389-391)

Key Words : Lamotrigine, Antiepileptic hypersensitivity syndrome

Introduction

Antiepileptic drug hypersensitivity syndrome (AHS) is a rare adverse effect of anti-convulsants that is potentially fatal[1]. It is a delayed immunological reaction that occurs usually one to eight weeks after taking aromatic antiepileptic medications such as phenytoin, phenobarbital, or carbamazepine[2, 3]. Recently, however, similar adverse events are being reported with non-aromatic anticonvulsant drug such as lamotrigine and valproic acid[4, 5]. The physical manifestation include symptoms like fever, skin rash, and lymphadenopathy which are very similar to those of Kawasaki disease[6] and infectious mononucleosis. However, AHS can also invade internal organs such as the liver, kidneys, and lungs[7]. When the liver is involved, the prognosis is poor and the condition is often fatal[4]. Because the reported mortality rate is approximately 10%, it is important to recognize adverse effects early and start an early mitigating treatment[5]. In this report, we describe a case of AHS of a 14-year-old girl who was on monotherapy with lamotrigine and showed symptoms mimicking atypical Kawasaki disease and infectious mononucleosis.

Received : 25 August 2008, Revised : 17 October 2008,
Accepted : 30 October 2008
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Case report

A 14-year-old female patient was admitted to our hospital via emergency center with fever and lymph node enlargement that had occurred over the prior one week. Her vital signs at admission were: body temperature, 38.8℃, pulse rate, 98/min; and respiratory rate, 24/min. She did not look acutely ill and her mental state was alert. On physical examination the mass (size: 2×1 cm) was palpated along the sternocleidomastoid muscle and it had warmth, erythema, and tenderness with no adhesion to surrounding tissues. At the time of admission, there was no rash or hepatosplenomegaly observed. Upon admission, In the blood test white blood cell was 1,600/μL and absolute neutrophil count was decreased to 1,088/μL; the patient's C-reactive protein (CRP) was raised to 1.9 mg/dL and ertythrocyte sedimentation rate (ESR) was 32 mm/hr, within normal range; biochemical reslts were AST: 42 IU/L and ALT: 20 IU/L. Atypical lymphocytosis were observed on the peripheral blood smear at the time of admission. We suspected infectious mononucleosis. The heterophil antibodies, EBV VCA IgM and EA IgM were all

negative, and the mycoplasma antibody titer was 1:20. After few days, the staff were informed by the patient's parents that one month previous, she had been diagnosed with generalized tonic-clonic seizure in the neurology department and was prescribed with lamotrigine for one week. After seventh admission day lamotrigine was discontinued because an erythematous maculopapular rash had spread to the whole body. When the medication was discontinued, the symptoms of fever, rash, and cervical lymphadenopathy showed marked improvement. On the 10th day, the fever and rash reappeared. We started administering prednisolone (1 mg/kg/day), but the symptoms persisted. With the remaining symptoms such as fever, cervical lymphadenopathy, and rash, even though the patient was 14-years-old, atypical Kawasaki disease couldn't be ruled out. Therefore, echocardiography and abdominal ultrasonography was done and intravenous immunoglobulin 2 g/kg/day was administered. There were no evidence of coronary vessel dilatation and no abnormalities in abdominal ultrasonography. With immunoglobulin administration all the symptoms subsided. On the 16th day, the patient was discharged with an improved general condition.

Discussion

Antiepileptic drug hypersensitivity syndrome (AHS) is a relatively rare adverse effect of antiepileptic drug, that is potentially fatal[1]. It is a delayed immunological reaction with triad of fever, rash, and internal organ involvement occurring one to eight weeks after exposure to an aromatic antiepileptic medications such as phenytoin, phenobarbital, or carbamazepine[2, 8]. Chaiken et al.[9] first described AHS as "Dilantin sensitivity" in 1955, reporting three cases in adult patients who were on multitherapy with several antiepileptic drugs. Recently, with similar symptoms appearing in non-aromatic (e.g. Lamotrigine) as well as aromatic antiepileptic drugs (e.g. phenobartital, phenytoin, carbamazepine), it is now well known as AHS. Lamotrigine is a relatively new antiepileptic drug that could cause potentially life threatening side effects with frequency of 1:1,000-10,000[2-4, 10].

Lamotrigine, as mentioned previously, is a relatively new antiepileptic drug with broad spectrum of activity that has been approved for use in adults with either partial or generalized seizures. Lamotrigine is thought to act by blocking voltage-dependent sodium channels, thereby preventing excitatory neurotransmitter release and achieving an antiepileptic effect[1, 7]. It is also widely prescribed by pediatric neurologists, because it is effective in children with idiopathic, resistant, and generalized seizures, and it does not impair cognition[4]. With its more widespread use, more cases of AHS due to lamotrigine, along with other antiepileptic agents, are being reported[2].

The exact mechanism of AHS is unknown, but several possible hypotheses have been proposed. Allergic hypersensitivity is the first possible hypothesis, because the symptoms develop after a certain period of time and after exposure to similar medications, the same symptoms recur[11]. The fact that the development of the symptoms is seemingly irrelevant to the amount of medication taken supports this hypothesis[9]. Secondly, the toxic metabolite that appears in the process of metabolizing an antiepileptic drug may cause AHS[11]. In the process of metabolizing antiepileptic agents, hydroxylated aromatic compounds such as arene oxides are produced, and if these metabolites fail to be eliminated and bind with macromolecules then cell death or secondary immunological reactions may take place this chain of reactions causes clinical manifestations of AHS[9, 10]. Arene dioxide is known to be lysed by epoxide hydrolase, and further studies show that patients with AHS tend to lack these enzymes[12].

The skin lesions of AHS typically develops later than most other serious skin reactions in most of the cases, symptoms developed between seven and 23 days[10]. It varies from mere macular rash to more severe Stevens Johnson syndrome or toxic epidermal necrosis. Facial edema or periorbital edema may also accompany the rash[10]. Besides the major symptoms, mentions previously, leukocytosis, eosinophilia, hepatitis, and acute renal failure may occur[11, 13]. Other manifestations may involve internal organs such as the liver, kidneys, heart, lungs, and those of the central nervous system[4]. It is important to note that once internal organs like liver, for instance, are affected and sustains dysfunction, fatal results are often inevitable. The reported mortality rate is as high as 18-40%[14]. And also, because various symptoms of AHS may mimic those of Kawasaki disease and various infective, hematooncological, connective tissue, or cardiovascular diseases, early and accurate diagnosis may be difficult[4, 6].

As a diagnostic tool, a lymphocyte toxicity assay and patch test can be used. The former is not widely used, because it is expensive and complicated the results of the latter, meanwhile, are not consistent[5]. Therefore, correlation between clinical manifestations and medication dosage is very important in diagnosing AHS[5, 10].

In cases of AHS prompted by lamotrigine, it is important

to recognize symptoms of AHS as early as possible, discontinue lamotrigine use, and change the maintaining medication to another antiepileptic drug[4, 5]. When lamotrigine is stopped, AHS symptoms improve very rapidly however, in some severe cases, treatment with intravenous immunoglobulin and steroid may be necessary[4, 15]. It is known that the skin lesions and edema improve slowly and along with the symptoms found via laboratory findings[5, 14]. In our patient the symptoms showed marked improvement with the discontinuation of Lamotrigine. However, rash, fever, and cervical lymphadenopathy reappeared and persisted mimicking the symptoms of atypical Kawasaki disease. In 2000, Chinen and Piecuch[6] reported a case of Kawasaki disease, which was misdiagnosed as AHS. In this case report the authors stressed on the need to keep in mind that all the possible diseases that have similar clinical presentations, such as Kawasaki disease and infectious mononucleosis.

We report a case of 14-year-old girl whose clinical presentation of AHS mimicked that of atypical Kawasaki disease and infectious mononucleosis to emphasize the importance of early recognition and ability to differentiate these diseases.

한 글 요 약

전염성 단핵구증과 비전형적 가와사키병과 유사한 lamotrigine에 의한 항경련제 과민증후군 1예

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AHS는 항경련제에 의한 부작용으로 드물게 발생하지만 생명을 위협할 수 있는 지연형 면역반응이다. 보통 항경련제 복용 후 1-8주 사이에 고열, 피부발진, 림프절병증의 임상 증세를 나타내고, 혈액, 간, 신장, 또는 폐 등의 내부 장기를 침범한다. AHS는 항경련제에 의한 부작용으로 증상이 전신적으로 다양하게 나타날 수 있다. 그리고 전염성 단핵구증이나 가와사키병과 같은 전신적 질환들과도 유사한 임상증상들을 보이기 때문에 이런 질환들과 감별하는 것이 중요하고 사망률도 10%에서 보고되고 있어 조기에 발견하고 치료하는 것이 중요하다. 저자들은 임상증상과 초기 검사가 전염성 단핵구증과 비전형적 가와사키병과 매우 유사한 lamotigine에 의한 AHS 1예를 보고하는 바이다.

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