Lamotrigine induced Steven Johnson syndrome: A case report in Al Batool teaching hospital in Diyala governorate

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Abstract

Background: Steven Johnson syndrome (SJS) is a rare disease that is characterized by acute cutaneous manifestation represented by eruptions of the skin and the mucosal membranes. SJS is an immune-mediated disease, a hypersensitive reaction, characterized by hyperpigmentation of the mucous membranes, rash on the skin and multiple bullae and erosions scattered all over the body especially the face, trunk, and the extremities. Many studies reported that the incidence rate of the SJS was about 1.2 – 6 cases/ million each year and it is more common among males while the toxic epidermal necrolysis (TEN) is more common among females. In addition to the cutaneous manifestations.SJS might show multiple systemic manifestations including the liver, lungs and kidneys. In this case we reported the development of Steven Johnson syndrome in relation to the use of lamotrigine antiepileptic drug.

Keywords: Lamotrigine; epidermal detachment; toxic epidermal necrosis ; Stevens johnson syndrome.

Introduction

Adverse reaction of drugs accounts about 6% of the entire hospital admissions which increases the economic burden on the health care system and results in drugs withdrawal from the market [1]. The adverse drug reactions may range from mild to severe reactions i.e. from a mild rash to serious conditions like Stevens Johnson's syndrome (SJS). SJS is regarded as a rare disease that is characterized by acute cutaneous manifestation represented by eruptions of the skin and the mucosal membranes. SJS is an

immune mediated disease, a hypersensitive reaction, characterized by hyperpigmentation of the mucous membranes, rash on the skin and multiple bullae and erosions scattered all over the body specially the face, trunk, and the extremities. Many studies reported that the incidence rate of the SJS was about 1.2 – 6 cases/ million each year and it is more common among males while the toxic epidermal necrolysis (TEN) is more common among females [2].

With regard to the epidermal detachment, the erosive skin diseases can be classified as follow: When the epidermal detachment < 10% of the body surface area it is said to be SJS, when it is > 30% ,then it is said to be TEN while when the epidermal detachment ranging between 10-30% then it is classified as SJS/TEN overlap [3]. Steven Johnson syndrome is regarded as one of the most serious systemic conditions which carry high rates of morbidity and mortality with a mortality rate reaching up to 5% [4]. SJS characterized by serious skin symptoms with multiple systemic manifestations including the liver, lungs and kidneys.

Patients with SJS might deteriorates and shows more than 30% epidermal detachment and develop TEN or even SJS – TEN overlap when epidermal detachment is 10 – 30%. The case can be diagnosed depending on the clinical and histopathological examinations of the lesion. The commonest cause of SJS was the drugs adverse reactions and they account for about 80% of cases. Among the famous drugs that cause SJS were lamotrigine, carbamazepine, valproic acid, phenytoin, allopurinol and sulfonamide [5]. In addition to the drugs viral infections like herpes simplex and mycoplasma pneumonia are among the common causes [6].

In SJS there will be activation of cytotoxic T – cells and natural killer cells which end in disseminated keratinocyte death and epidermal detachment. If the condition not treated there will be severe skin involvement which results in severe pain, massive fluid and protein loss. In addition, there will be heat loss and bleeding from the erosive lesions with subsequent secondary bacterial infections [7]. The necrotic keratinocyte characterized by either disseminated erosive skin lesions or full thickness necrosis of the epidermis. Sub-epidermal bleeding and vacuoles formation in the basal membrane is regarded as a feature of the necrosis keratinocyte while more superficially there is a perivascular lymphocytic infiltration in the upper dermis [8]. The earlier the diagnosis, removal of the causative agent and initiation of treatment the better the outcome and the more the success rate in the treatment of SJS patients. In spite of the use of many therapeutic regimes in the treatment of SJS including immunoglobulin, immunosuppressive and anti-inflammatory drugs still no single agent has clear efficacy in the clinical trials [9].

Case presentation

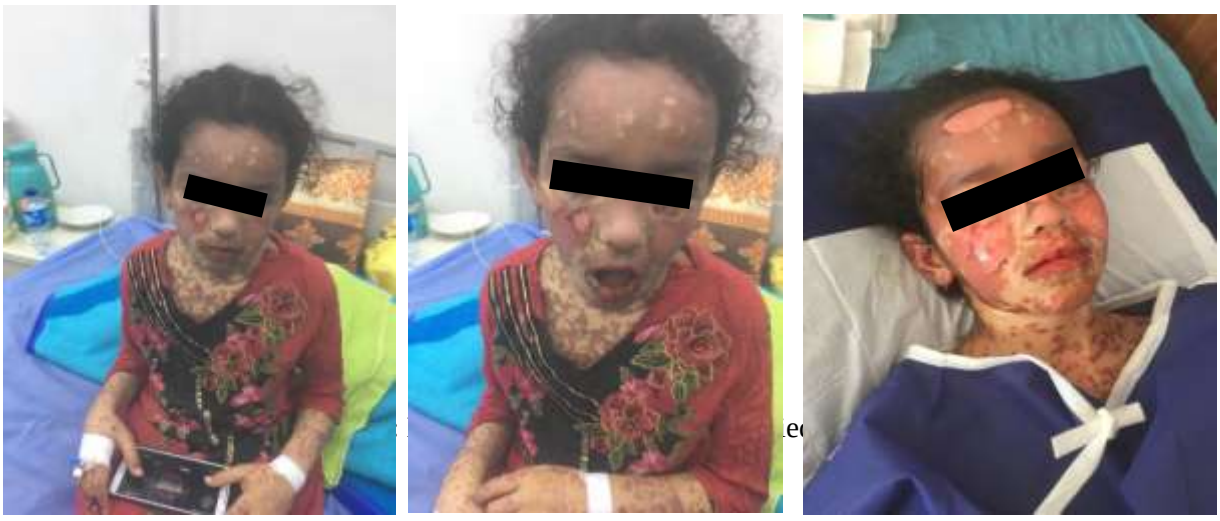
Lamotrigine is an anticonvulsant drug that is prescribed in psychiatric practices. It is found to be associated with Steven Johnson syndrome. In this case report, we studied a case of lamotrigine-induced Stevens Johnson syndrome. An eight year old female child was admitted from 27th of Dec. 2020 till 17th of Jan. 2021 into the pediatric department at Al-Batool teaching hospital in Diyala governorate complaining from diffused

maculopapular rash and mucosal ulcerations of the mouth and bullous lesions on the face and neck with high grade fever of five days duration. She is a known case of epilepsy since 2016 and she was on valproate and levetiracetam (kepra). Couple of weeks ago her physician increased the dose of valproate to be 300mg twice daily and added lamotrigine 100 mg twice daily to control her seizures. After-that, the patient experienced abdominal pain, fever and skin rash which started on the posterior aspect of the neck and then the rash spread all over the body including the face and the oral mucus membrane. A few days later the patient developed bullous cutaneous lesions on the face and the neck and ulcerations in the mucous membrane of the mouth and lips which started to erupt gradually. In addition the child developed vomiting, diarrhea and poor oral intake. On examination the patient was toxic; the temperature was 39˚C, with multiple erosions and blisters over the lips and face. In addition, there was diffused maculopapular rash all over the body sparing the genital region. The degree of epidermal detachment was found to be < 10% of body surface area. Laboratory tests and blood culture had been conducted. The complete blood picture revealed that: Hemoglobin 13g/dl, WBC 7260 cells/mm^3, platelet count 495000/mm^3. C- reactive protein was about 18 mg/dl. The liver function test was normal apart from alkaline phosphatase which was 253U/L. We sent for dermatological consultation that confirmed the diagnosis of Stevens Johnson syndrome.

Inpatient medication

After collection and interpretation of data we decided to cease all the antiepileptic drugs and initiates the following inpatients medications: Thus the patient received luminal injection 15 mg/kg loading dose followed by 5 mg/kg twice daily, intravenous fluid for 10 day, intravenous immunoglobulin 0.5 g/kg /day as a single daily dose for three days, intravenous dexamethasone injections 0.4 mg/kg twice daily for 3 days followed by prednisolone tablet 10 mg three times daily, pheneramine malate syrup 5 ml twice daily, intravenous paracetamol injection 250 mg four times daily for 5 days, intravenous ceftriaxone injection 50 mg/kg twice daily for 10 days , intravenous acyclovir injection 10 mg/kg three times daily for 7 days, intravenous metronidazole injection 200 mg three times daily for 7 days, mebo and fucidin ointments after washing the skin with normal saline, mouth wash, nystatin drops 100000 IU four times daily, lidocaine spray for the mouth.

On day ten of hospitalization valproate tables 200 mg twice daily and kepra 500mg twice daily were added to the patient. Phenobarbital injection changed to tablet 5mg/kg twice daily for 2 days and tapered gradually over one week. Three days after commencement of the therapy the fever subsided and the patient started to take light diets orally and there was no evidence of new cutaneous or mucosal lesions and the skin started to heal gradually. Discharge medications include valproate 200 mg twice daily and kepra 500mg twice daily.



Figure(1): These Images were taken before initiation of intravenous immunoglobulin and systemic steroids

Figure(2): The image was taken after treating the patient with intravenous immunoglobulin and systemic steroid

Discussion

Side effects of drugs are an important topic to be discussed with parents of epileptic patients since many of the serious clinical conditions might be related to the medications used by the patients. NSAIDs, antibiotics, anti-epileptics, and antipyretics were commonly blamed to cause SJS and TEN as adverse drug reactions especially when there is a rapid increase in the dose which increases the risk of cutaneous adverse reactions. Steven Johnson syndrome is considered a rare unpredictable adverse reaction to the use of lamotrigine. Parveen, and Javed, (2013) mentioned in their case report that the increasing use of lamotrigine in the clinical practice as antiepileptic and mood stabilizer can be associated with the

development of SJS and TEN although not very commonly [10]. Hilas, and Charneski, , 2007 stated that SJS found to be associated with the use of lamotrigine in patients with epilepsy, despite the dose being used and the duration of the treatment [11]. Saha, 2000 and Abe, et al., 2003 stated that the exact pathophysiology of Steven Johnson syndrome and toxic epidermal necrolysis is still unclear but the reasonable explanation for these conditions might be the apoptotic mechanism in which there are involvement of cytotoxic T-cell, tumor necrosis factor-α (TNF-α) and Fas (CD 95), Fas ligand. Thus the activation of Fas through FasL is considered as an initial step that leads to diffuse apoptosis and death of epidermal cells [12,13]. Similarly, Khalili, and Bahna, (2006) wrote in their study that the epidermal cell apoptosis may be triggered by keratinocyte Fas – FasL interaction or it may be triggered by the secretions released from cytotoxic T – cells [14]. Zeng, et al., (2015) in their study reported that there is a significant statistical association between HLA-B*1502 and lamotrigine induced SJS and TEN in Chinese individuals [15]. Khalili, and Bahna, (2006) stated that the administration of intravenous immunoglobulin had promising results in contrary to the use of systemic corticosteroid therapy. Parenteral immunoglobulin can eliminate epidermal cell death as it is interacted with keratinocytes and improve the disease progression and reduce healing time of skin lesions [14]. Thus SJS is a very rare condition which is associated with lamotrigine and the physician must be aware of its side effect before prescribing it to epileptic patients. In addition to that the proper use of antibiotic and skin lesion care are important to reduce the complications that might occur secondary to the SJS which include septicemia, secondary bacterial infections, pneumonia acute renal failure.

Conclusions

The use of lamotrigine was associated with the development of Steven Johnson syndrome (SJS) in epileptic patients.

Recommendations

Specialists who want to prescribe antiepileptic drugs to their patients especially lamotrigine must take in considerations the possibility of SJS development.

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Ethical clearance: The ethics committee and the institutional review board of Diyala College of medicine approved the study in 2021.

Conflict of interest: There is no conflict of interest.

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