Anticonvulsant Hypersensitivity Syndrome after Carbamazepine Administration in a Young Girl

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Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare, life-threatening clinical condition that occurs secondary to drug reaction and typically associated with antiepileptic medications. The clinical findings of AHS include a classical triad of fever, cutaneous eruption and multi-organ impairment.

We report a nine-year-old girl who presented with high-grade of fever, maculopapular skin rash and liver enzymes impairment two weeks after receiving carbamazepine for her first episode of seizure activity.

The diagnosis of AHS was made based on the patient clinical triad and after excluding other differential diagnoses. The patient's clinical condition was completely resolved and her liver function tests returned to normal two weeks after discontinuation of carbamazepine which was replaced by levetiracetam.

The aim of reporting this case was to provide insight into the symptomology and early diagnosis of AHS to prevent mortality and long-term serious complications.

INTRODUCTION

Anticonvulsant hypersensitivity syndrome (AHS) is an uncommon medical condition which can lead to lethal serious complications if not diagnosed and managed early[1]. AHS is classically associated with antiepileptic medications which include carbamazepine, phenobarbital and phenytoin[1].

Patient with AHS typically present with triad of fever, dermatological skin rash and internal organs damage, which usually occur within 1-8 weeks after exposure to an anticonvulsant medications[2,3].

The main management of AHS is by supportive care and discontinuation of antiepileptic medications, AHS has a favorable prognosis if diagnosed and treated early[4,5].

The aim of this case was to provide insight into the symptomology and early diagnosis of AHS to prevent mortality and long-term serious complications.

THE CASE

A ten-year-old girl who was newly diagnosed with epilepsy started on carbamazepine one month ago. She presented with two-weeks history of fever and generalized body rash two weeks after starting carbamazepine for her epilepsy. Her fever was continuous and of high-grade and relived temporarily relieved by antipyretic. She was seen initially in a private hospital and managed only by IV fluid and paracetamol. The patient had two episodes of generalized tonic–clonic seizure followed by post-ictal phase for which she was started on carbamazepine one month ago. Her initial EEG was abnormal in the form of generalized epileptiform spike and wave discharges. There were no history of vomiting, diarrhea, cough, headache or joint pain and no documented history of sick contact or recent travel.

Physical examination showed oriented cooperative child and her vital signs showed a temperature of 39 °C. ENT and oral mucosal membrane examination were normal, with no signs of conjunctivitis and no lymphadenopathy. There was a generalized erythematous maculopapular skin rash involving the face, abdomen, upper and lower extremities, see figures 1-3. Her neurological function was intact, and the rest of her physical examination was normal. The initial investigations revealed white cell counts 18.04x109/L, neutrophils 11.7%, lymphocytes 81.9% and eosinophil 0.3%. Hemoglobin and platelet counts were normal. Her liver function tests showed G-glutamyltransferase (Ggt) 1323 IU/L (normal range 5-36 IU/L), Aspartate aminotransferase (Ast) 201 IU/L (normal range 0-36 IU/L), Alanine aminotransferase 293 IU/L (normal range 0-32 IU/L). Her electrolytes and renal function tests were normal. Her viral profiles which include Anti–CMV /IgM, Anti–HBC ll, Anti–HBC IgM, Anti–HBe, Anti-HCV, Anti-HSV-2 IgG, Anti-Rubella–IgM, Anti-toxoplasmosis IgM, HAV Ab-IgM, EBV IgM, HIV AB/AG COMBO, Measles–IgG, Measles IgM and mono spot were all negative.

Vasculitis work-up which include ANA screen and dsDNA Abs were negative. C3, C4 and ESR were within normal values. Carbamazepine level was 21.64 umol/L (normal range 17-50 umol/L). Her CXR and echocardiogram were normal.

The final diagnosis of anticonvulsant hypersensitivity syndrome was confirmed based on the patient clinical history, laboratory findings and recent introduction of carbamazepine for her epilepsy treatment.

The patient was mainly managed by supportive care with antipyretic and IV fluids.

Her carbamazepine was discontinued and replaced with levetiracetam. The patient's clinical condition improved significantly after ten days of her hospital admission. Her skin rash completely disappeared and her

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liver function tests returned to normal two weeks after discontinuation of carbamazepine.

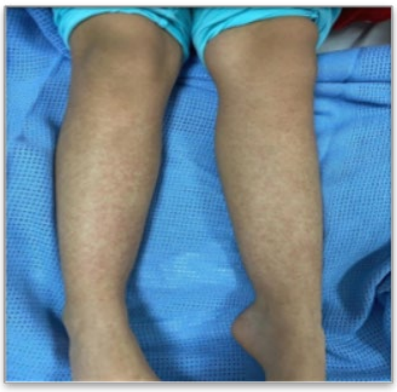

Figure 1: Generalized Erythematous Maculopapular Skin Rash Involving the Lower Extremities

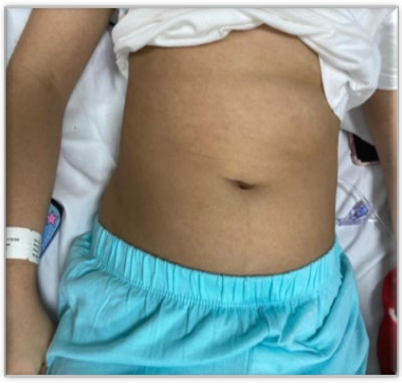

Figure 2: Generalized Erythematous Maculopapular Skin Rash Involving the Abdomen

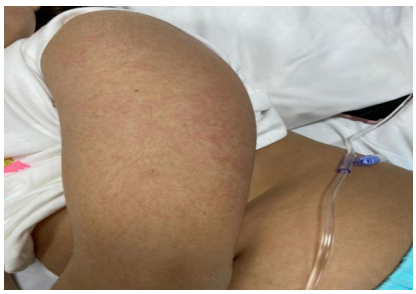

Figure 3: Generalized Erythematous Maculopapular Skin Rash Involving the Upper Extremities

DISCUSSION

AHS is a rare disease and potentially lethal, multi-system disease with an estimated incidence of one in 1,000 to one in 10,000 patients prescribed antiepileptic medications and carries a mortality rate of 10–20%[1,6].

AHS is typically associated with aromatic ring antiepileptic medications with carbamazepine and phenytoin being the most common agents causing AHS[6,7].

The complete pathogenesis of AHS remains unclear however, it has been proposed that aromatic ring antiepileptic drugs are metabolized by liver enzyme cytochrome p-450 to arene oxides which associated with immunological response and subsequent cell death. AHS has been also associated with viral agents such as human herpesvirus 6, human herpesvirus 7, EBV and CMV. Herpesvirus 6 reactivation leads to decreased level of CD 19B which contributes to the development of AHS. It has been also suggested that the presence of human leukocyte antigen HLA–A3101 is strongly associated with carbamazepine inducing AHS[6]. The diagnosis of AHS is made based on the patient's clinical triad[6].

AHS present with specific clinical manifestations occurring one week to two months after initiation of antiepileptic drugs which includes fever, rash and multi-organ involvement. With the liver being the most internal organ involved. Our patient typically presented with history of high-grade fever, generalized body rash and liver enzymes impairment two weeks after starting carbamazepine medication, which is similar to the clinical symptoms described by Maulin Mehta et al[8].

Skin eruptions is seen in approximately 3% of patients with carbamazepine treatment. This skin eruptions can be seen in the form of urticaria, skin petechiae, maculopapular rash or Steven Johnson syndrome which usually seen 1 to 2 weeks after drug administration[8]. The clinical symptoms of fever and skin rash must present in all patients with AHS as described by albert M Li et al[9].

The management of AHS is essentially by supportive care and withdrawal of antiepileptic medication[10]. Our patient completely responded to the supportive care and discontinuation of antiepileptic medication with no further complications in her clinical condition.

Early diagnosis of AHS and discontinuation of offending antiepileptic agent favour a good prognosis for the patient[11].

CONCLUSION

AHS is a rare life-threatening condition which needs to be considered in every patient who developed fever, skin manifestation and internal organ involvement within one week to two months after starting antiepileptic medications.

AHS is typically managed by termination of anticonvulsant drug to prevent further deterioration of the condition. AHS has an excellent prognosis with early diagnosis and discontinuation of anticonvulsant medication.

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