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Lamotrigine Induced Hypersensitivity Syndrome in Pregnancy

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DEAR EDITOR,

Medical management of epilepsy during pregnancy can be difficult because of the associated side effects of the antiepileptic drugs (AED) , most important being congenital malformations in the baby, but sometimes these drugs can cause severe cutaneous drug reactions which may be life threatening to the mother as well as baby. We present a case of lamotrigine induced severe adverse cutaneous reaction- hypersensitivity syndrome (ACHS) in the first trimester of pregnancy. To the best of our knowledge this is the first case reported of ACHS with LTG use in first trimester of pregnancy . We should adhere to the code of International Core Prescribing guidelines for LTG as add on therapy to Valproic acid to minimize complications. Patient with epilepsy should be advised appropriate contraceptive method if her seizures are not under control and preferably 9-12 months of seizure free interval is necessary before pregnancy is planned.

Lamotrigine (LTG) is the new antiepileptic drug which is being used commonly as a monotherapy or in combinations with other antiepileptic drugs(AEDs). Recent studies have shown its reproductive safety[1-3]. Anticonvulsant hypersensitivity syndrome (ACHS) is a specific and severe idiosyncratic reaction to aromatic ring containing AED such as phenytoin, carbamazepine, phenobarbital, and relatively new drug LTG with potentially life threatening consequences[4]. It is typically characterized by fever, rash, lymphadenopathy and multi-organ involvement. It can cause hepatitis, hematological abnormalities and even involve the kidneys, nervous system and lungs, resulting in a multitude of presentations, both clinically and in laboratory parameters. Multiorgan involvement in this condition differentiates it from other cutaneous reactions. ACHS was first described by Chaiken et al in 1950 as an adverse drug reaction to phenytoin[4]. Its incidence is estimated to be in 1 in 1000 to 1 in 10,000 exposures[5].

Lamotrigine is a newer antiepileptic which has been used since 1994 in the United States as an adjunctive treatment and as monotherapy since 1998[4]. The incidence of rash associated with hospitalization in clinical trials with lamotrigine is 0.3% in adults and the spectrum of serious rashes includes hypersensitivity syndrome, Steven Johnson syndrome (SJS), and toxic epidermal necrolysis[6]. These all are potentially fatal adverse reactions and early recognition is essential to proceed with the urgent management. We report a case of ACHS in first trimester of pregnancy with the concomitant use of LTG and valproic acid.

A 32year old primigravida of Hindu origin at 7 weeks period of gestation presented to the antenatal clinic of our hospital with chief complaints of fever and generalized body rash. The patient was a known epileptic for the last 10 – 12 years and was on irregular treatment. She had been on sodium valproate 750 mg twice a day since one year but because of recurrence of seizures lamotrigine 50 mg once a day was added to sodium valproate during early pregnancy. She developed a generalized body rash 3 weeks after the introduction of lamotrigine, which started from the upper trunk and face and then involved the whole body. Both the drugs lamotrigine and sodium valproate were stopped and she was given outpatient treatment in form of tablet prednisolone 30 mg once a day and tab diazepam 5 mg twice a day. However, the rash worsened over the next three days and led to edema of face and lips and difficulty in speaking and eating, necessitating hospitalization .There was no past history of skin or allergic reaction to antiepileptic drugs.

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On admission, patient was febrile, pulse was 92 /min, B.P was 130/80 mm Hg. Erythematous maculopapular rash was present all over the body with facial edema especially on the lips and erosions of the oral mucosa. There was no lymphadenopathy and icterus. Respiratorty, cardiovascular and nervous system examination were unremarkable.

Investigations revealed eosinophilia and markedly raised liver enzymes. The hemoglobin was 12.9gm%, total leucocyte count was 12.4x 10^9 with 62% neutrophils, 15% lymphocytes and 19% eosinophils. There were no circulating atypical lymphocytes. Liver function tests revealed serum bilirubin 0.6mg/dl, alkaline phosphatase 255 IU/L,aspartate aminotransferase 198 IU/L, alanine aminotransferase 85 IU/L. Platelet count, coagulation profile , blood sugar, urinalysis and renal function tests were normal. Blood and urine cultures were sterile. VDRL, HIV, HBsAg serology was negative. Obstetrical ultrasound showed intrauterine pregnancy corresponding to 8 weeks gestation with positive cardiac activity.

A diagnosis of hypersensitivity syndrome was made and the patient was aggressively managed with intravenous fluids, antihistaminic and injectable systemic steroids .She was shifted on to oral steroids when she started showing improvement and was discharged after 10 days when her rash improved and liver enzymes started decreasing .She was discharged on prednisolone 20 mg per day which was tapered and stopped subsequently and started on Clobazepam (AED). On follow up in antenatal OPD she was diagnosed to have missed abortion on ultrasound at 13 weeks period of gestation for which she underwent uterine evacuation. She required addition of Oxcarbazepine with Clobazepam for seizure control. Now she is well controlled on oxcrbazepine and clobazepam for the last 9 months and is trying for conception.

The most common adverse reactive events associated with adjunctive lamotrigine use are primarily neurologic, gastrointestinal and dermatologic.[7] Analysis of pooled clinical data indicates that adverse events necessitate withdrawal of adjunctive lamotrigine therapy in 10.2% patients. Of these, dermatological complication was responsible for discontinuation in 3.8 % of patients.[7,8] Only 0.1% of adult patients had cutaneous reactions reported as possible SJS and others were assumed to be hypersensitivity syndrome. Rash especially serious usually occurrs within 6 weeks of initiation of therapy with LTG, occasionally up to 12 weeks and only rarely after that.[6,9] The normal elimination life of lamotrigine (25-30hrs) may be more than doubled when used with valproate, a microsomal enzyme inhibitor, thus increasing the risk of adverse reaction. Also excessive initial dose may increase the risk of adverse reaction as was seen in our case.[10]

Adverse cutaneous reactions to drugs may be due to a variety of hypersensitivity responses. ACHS is one such specific type of idiosyncratic reaction which is potentially fatal; with cutaneous and systemic reaction. In the case of aromatic antiepileptics (phenytoin, carbamazepine, phenobarbital), it is the genetically determined inability to detoxiofy the toxic arene oxide metabolites of antiepileptics which leads to ACHS .These reactive metabolites may irreversibly modify cellular proteins which initiate an auto immune attack on specific drug modified proteins in target organs. Mechanics of idiosyncratic toxicity with LTG may appear distinct but actually involves the same processes of bioactivation, detoxification, covalent adduct formation, processing and presentation of antigen to the immune system and consequent formation of antibodies and T cell immune effectors.[11]

ACHS is characterized by a triad of fever, cutaneous reaction and internal organ involvement. Fever and rash (90%) are the most frequently presenting symptoms as was in our case, followed by lymphadenopathy (70%) and hematologic abnormalities especially eosinophilia (30%) and presence of mononucleosis like atypical lymphocytes.[12] Fever usually precedes onset of rash by several days but may appear concurrently and may persist even weeks after drug has been discontinued. Hematologic abnormalities usually consist of leucocytosis with atypical lymphocytes, and eosinophilia. An absolute eosinophil count of > 1.5 x 10^9 / L is toxic to endothelial cells and leads to involvement of other systems causing interstitial nephritis, pulmonary infilterates,eosinophilic myocarditis, pericarditis, and thyroid and brain involvement as well. Hepatitis is the most common type of visceral involvement as was seen in our case. It is usually anicteric and characterized by mild hepatomegaly and elevated liver function tests. However it can lead to liver failure and is the most common cause of death in this condition.[13]

Onset of fever, rash, lymphadenopathy along with visceral involvement in a person on an AED is presumptive evidence of ACHS and warrants discontinuation of drug and simultaneous exclusion of other causes.[13] Collagen vascular diseases, viral infections (hepatitis, CMV, HIV), lymphoma, porphyria, syphilis, hypereosinophilic syndromes and drug reaction to other drugs should all be excluded. Rash and hepatitis may persist for several weeks. Alternative anticonvulsants should be considered for control of epilepsy. Benzodiazepines are the best choice. Because of the cross sensitivity between other anticonvulsants especially arene oxide producing compounds, these should not be used in the acute or convalescent phase. Similarly, drugs like sodium valproate should also be avoided due to their potential hepatotoxicity.

Supportive care, vitals monitoring, maintenance of hydration and electrolyte balance is essential and monitoring of hematologic, hepatic, and renal function should be done as was done in our case. Care of cutaneous manifestation is best taken with topical steroids, wet wraps, and antihistaminics. Role of systemic steroids has not been studied in any randomized placebo controlled

trial although steroids have been found to be more useful for cutaneous rather than systemic manifestations.

In our case, according to the criteria for operational assessment of adverse drug reaction LTG was the most probable cause of adverse drug reaction.[14] There was a distinct temporal correlation between the onsets of rash occurring 3 weeks after the institution of LTG therapy and there was an improvement after drug withdrawal. Also, the code of International Core Prescribing guidelines for LTG as add on therapy to Valoroic acid, an enzyme inhibitor drug was not adhered to. LTG should have been given in the dose of 25mg on alternate day in first and second week then 25 mg per day in the third and the fourth week and to achieve maintenance dose further increased by 25-50 mg every one to two weeks.[6] Both these factors that are inappropriate initial dose and concomitant use with sodium valproate increased the risk of adverse reaction. So, it is important to emphasize the need to follow these guidelines. To have optimum maternal and fetal outcome in pregnancy Harden et al have recommended that the use of valproate and polytherapy with any AED combinations should be avoided, if clinically appropriate, before or during pregnancy to decrease the incidence of congenital malformation and seizure freedom of 9-12 months before pregnancy should be a goal.[1] This paper also highlights the importance of use of contraception to avoid pregnancy especially when the disease is not fully controlled The exact cause of missed abortion is difficult to ascertain in our patient but the antiepileptic drug or adverse reaction to it, may have contributed.

Antiepileptic drugs can sometime cause life threatening drug reactions which can even jeopardize the fetus if women is pregnant. It is mandatory to stress the use of contraception in women of child bearing age by the treating physician if epilepsy is not controlled. The code of International Core Prescribing guidelines for LTG as add on therapy to Valproic acid should be followed.ACHS should be aggressively treated.

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