Lamotrigine has been an important drug in the advancement of treatment of various conditions, including seizures, mood disorders and pain. It is preferred choice by many clinicians because it is usually very well tolerated and because of its limited interactions with other medications. It is commonly used for women of child bearing age, as it has less teratogenic effects than other anti-seizure medications. Lamotrigine can commonly cause adverse effects such as headache, nausea, dizziness and skin rash. Rarely, it can result in serious dermatological reactions, such as Stevens-Johnson syndrome (SJS) [1], toxic epidermal necrolysis (TEN) [2] and even more rarely drug reaction with eosinophilia and systemic symptoms (DRESS) [3] with a frequency of 0.001-0.0001% [4]. Clinical characteristics include fever, rash, multi-organ involvement, lymphadenopathy and blood dyscrasias [5]. Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state that results from the inability of the posterior cerebral circulation to autoregulate in response to acute changes in blood pressure. Hyperperfusion with resultant disruption of the blood brain barrier results in vasogenic edema, most commonly in the parieto-occipital regions [6-8]. The symptoms are usually reversible with supportive care. We present a case of a patient with absence epilepsy, who developed these two conditions within a few days of initiating the anti-seizure medication lamotrigine. The case exemplifies how the addition of anti-seizure medications is not always benign and can have severe unpredictable consequences.
Case History

The patient is a healthy 16 year old female with a diagnosis of childhood absence epilepsy since 4 years of age. She has an unremarkable past medical history and normal development. Her mother was diagnosed with multiple sclerosis, but there are no other pertinent findings in the family history. Her typical seizures consisted of brief episodes of staring and eye fluttering. Her EEG’s showed 3 Hz spike wave discharges consistent with absence epilepsy. Her seizures were initially difficult to control. Anti-epileptic medications tried include valproic acid, ethosuximide, clobazam, keppra, lamotrigine and sulthiame. She developed a rash with lamotrigine initially, but tolerated a repeat trial when she was younger. Her seizures were finally controlled with a combination of valproic acid and sulthiame. She finally became seizure free at 13 years of age and had normal EEG two and three years after becoming seizure free. Her primary neurologist recommended weaning off medications at that time. However, she did not agree as she wanted to obtain her driver’s license first. In Canada, a patient must be seizure free for 1 year after weaning medications before they can drive. Therefore, her neurologist recommended to replace valproic acid with lamotrigine, as this medication has less teratogenic effects and is often preferred in a young adolescent female. She was started on lamotrigine 12.5 mg daily and was provided with a slow titration schedule. She continued on valproic acid at 750mg twice daily and sulthiame 150mg/100mg.

Five days after initiation of lamotrigine, she developed nausea, vomiting and diarrhea. She had multiple non-bilious, non-bloody emesis per day. She also developed progressive generalized fatigue, diffuse maculopapular rash and fever. Her mother also noted that she was confused. She went to her local hospital and was treated empirically for sepsis with broad-spectrum antibiotics and fluids. Her initial blood pressure was 105/64 and she was febrile. The remainder of her vitals were stable. She was subsequently transferred to the pediatric tertiary center. Lamotrigine, valproic acid and sulthiame were discontinued. On arrival, her blood pressure was 92/52, pulse was 97 and respiratory rate was 16. Her oxygen saturation was 99% on room air. She was having intermittent fever up to 39 degrees. She had fluctuating confusion and was intermittently disoriented to time and place. She could not do serial sevens or spell “world” backwards. At times, she was answering questions inappropriately.

On physical exam, it was noted that she had small sub-centimeter lymph nodes in the anterior cervical chain, with no other lymphadenopathy. Erythematous non-blanching maculopapular rash was noted on her face, chest and back. She appeared dehydrated. Cardiac exam was normal. Chest was clear. On abdominal exam, she had no hepatomegaly, but had splenomegaly.

Her initial lab results showed thrombocytopenia, with a platelet count of 26. There was also neutropenia and mildly abnormal coagulation factors. No eosinophilia was evident. Her peripheral blood film demonstrated giant platelets with hypolobulated neutrophils. She also had acute kidney failure with a creatinine of 380. Her AST was minimally elevated at 44, with normal ALT and ALP. LDH was 1262 and CRP 45. Vasculitic work up, including anti-nuclear antibody and rheumatoid factor were negative. Valproic acid level was within normal limits.

Infectious workup including blood culture, urine culture, lumbar puncture and stool studies, was all negative. CMV IgM was positive and IgG and PCR were both negative. She was empirically treated for sepsis with cefotaxime and acyclovir, which were discontinued when the studies were normal. Abdominal ultrasound showed no hepatomegaly, but splenomegaly of 12.8cm. Cardiac echo was normal.

Due to her thrombocytopenia, she required a platelet transfusion and was followed by Hematology, no other causes for her abnormal blood work was found. She received vitamin K for 3 days. Her platelets normalized to 197 within a few days. She was investigated by numerous specialists. Rheumatology did not feel she had vasculitis. Nephrology confirmed her kidney injury could be secondary to severe dehydration in addition to a hypersensitivity reaction. With IV fluid replacement, her creatinine gradually normalized. Infectious Disease did not think her symptoms were secondary...
to infection, even though she was empirically treated with antibiotics. Dermatology felt the rash was consistent with a hypersensitivity reaction, but no biopsy was performed. The rash resolved within 3 days. She continued to have mild encephalopathy that was fluctuating, but improving.

Her brain MRI was normal. Initial EEG showed diffuse slowing consistent with a mild encephalopathy of non-specific etiology. No epileptiform discharges were noted. By day seven of admission, her encephalopathy improved and her mother thought she was returning to baseline. Overall, her diagnosis was most consistent with probable DRESS syndrome. She was not treated with steroid, as she was clinically improving.

10 days after admission to hospital, the plan was to discharge her home, as she had recovered from her symptoms. However, the night before discharge, she was noted to have elevated blood pressure of 130-140/80. The next day, she developed blurred vision and headaches. She then had a new type of seizure, where she was seeing coloured lines lasting for a few minutes.

24 hour continuous EEG monitoring showed bilateral occipital periodic lateralized epileptiform discharges (PLEDS). An urgent MRI showed evidence of vasogenic edema within the occipital and parietal regions that was most consistent with PRES. Leviteracetam was started to treat her seizures. Her elevated blood pressure was treated with amlodipine. Nephrology could not find any underlying cause for her elevated blood pressure, except for the aggressive fluid replacement she received initially. Her renal function had normalized and she was no longer on any medications at the time of her elevated blood pressure. She did not have any further seizures and returned to baseline in a few days. She was discharged from hospital 3 days later in improved stable condition.

Discussion

Lamotrigine is a commonly used medication to treat seizures, mood disorders and pain. It is effective and overall well tolerated, with little interaction with other medications. It has relatively few adverse effects on mood, cognition or weight. It is also preferred in young females, as it has a better safety profile than other seizure medications with regards to teratogenicity. Lamotrigine is an aromatic phenyltriazine with two benzene rings, and displays linear pharmacokinetic characteristics. Its mechanism of action involves stabilizing the synaptic membrane through glutamate release and calcium channel control. It blocks the voltage dependent sodium channel and suppresses secretion of excitatory neurotransmitter that are involved with the N-methyl-D-aspartate receptor [9, 10].

Common adverse effects include drowsiness, headache, nausea, dizziness and diplopia. The overall rate of rash for patients taking lamotrigine is 13% [11]. Serious dermatological reactions, such as Stevens-Johnson syndrome (SJS) [2], and toxic epidermal necrolysis (TEN) [2] are reported. Development of hypersensitivity reaction to aromatic anticonvulsants, such as lamotrigine, is very rare with a frequency of 0.001-0.0001% [4].

DRESS syndrome was first described by Bocquet as a hypersensitivity reaction occurring within the first 2 months of initiation of drug treatment [12]. The constellation of symptoms include dermatologic rashes, fever and evidence of systemic organ involvement, which is distinct from SJS or TEN, which usually involve erythema of skin and mucosa followed by extensive cutaneous and mucosal exfoliation particularly oral and conjunctival surfaces [13,14]. DRESS is most commonly associated with sulfonamides, allopurinol, and aromatic antiepileptic medications [15]. Of the anti-seizure medications, most cases involve carbamazepine, phenobarbital, primidone and lamotrigine [16].

Although the incidence of rash with lamotrigine is greater in the pediatric population [17], the incidence of DRESS is not. The diagnosis is usually established by evaluating the time between drug intake and the onset of the cutaneous eruption and the resolution of the symptoms after drug withdrawal. Early recognition is important, as the mortality rate is up to 10% [18].
Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples (RegiSCAR) have created inclusion criteria to aid physicians in making a diagnosis of hypersensitivity reactions, such as DRESS. These criteria include fever >38°C, enlarged lymph nodes at a minimum of two sites, involvement of at least one internal organ, blood count abnormalities, hospitalization, a reaction suspected to be drug-related, acute rash, lymphocytes or eosinophils above the laboratory limits and platelets below the laboratory limits; at least three of the first four of these criteria are required to make the diagnosis [19]. Based on these criteria our patient had probable DRESS syndrome. Other infectious, rheumatological and malignant etiologies were ruled out. In addition, her symptoms developed within days of starting lamotrigine.

Potential risk factors for the development of rash in patients treated with lamotrigine include concurrent use of valproic acid, larger than recommended starting dose, rapid dose escalation, age younger than 12 years or a history of a skin or allergic reactions to other anticonvulsants [20, 21, 22]. Shiohara et al. indicated that adults are more likely to be affected than children [17].

The risk is higher for the combined treatment with valproic acid. This is likely to be due to the fact that valproate, a microsomal enzyme inhibitor, interacts with lamotrigine, leading to a reduced total clearance and a marked increase of the elimination half-life of lamotrigine [23]. Our patient stayed on both lamotrigine and valproic acid treatment for a few days, which may have increased the risk of DRESS syndrome. Several years ago, she developed a rash to lamotrigine, which resolved on subsequent trial. This could have increased her risk for a delayed hypersensitivity reaction. She was also on sulthiame, which is also known to rarely cause a rash. In addition, sulthiame, in combination with lamotrigine, can lead to an elevation of lamotrigine levels in the blood in individual cases.

Various internal organs can be affected in DRESS [24]. The most frequently involved internal organ is the liver, for which the rate of involvement varies from 34 to 94% [25]. The presentation of liver involvement can range from mild elevations in serum transaminase levels to fulminant hepatic failure. Liver failure is the most common cause of mortality associated with this syndrome. One study reviewed 57 patients with lamotrigine-induced DRESS that were published between 1999 to 2014 [26]. Demographic characteristics, latency periods, clinical features, results of laboratory tests, responses to treatment, and outcomes were evaluated in this study. They found an elevation in serum transaminase levels [57.89%] followed by hyperbilirubinemia [31.58%]; hepatic failure developed in 8/22 [23.68%] patients, and one patient needed a liver transplant. Renal dysfunction associated with DRESS has been reported to occur in 10% of cases and is attributable to acute interstitial nephritis (AIN). 23.68% patients suffered with renal dysfunction with DRESS secondary to lamotrigine, which was higher than other drugs. The result indicated that renal involvement may be the specific risk factor for lamotrigine induced DRESS [27]. A greater predominance of women with lamotrigine induced DRESS was noted, and 68.42% patients were >18 years of age.

Other studies showed that DRESS syndrome associated with lamotrigine has more severe rash, less eosinophilia, and less lymphadenopathy than symptoms resulting from other antiepileptic agents [28]. There is one other case report of a teenager with DRESS induced by lamotrigine. This patient also had severe rash, “influenza like symptoms” and multi-organ involvement [28].

Our patient was atypical, in that in addition to the rash, fevers, GI symptoms, fatigue, neutropenia and encephalopathy, she had predominant renal involvement. She had no liver involvement or eosinophilia, which is more commonly observed in DRESS secondary to lamotrigine, as described above.

The cause of DRESS has not been fully elucidated. The cytotoxicity is caused by the metabolites of aromatic anti-seizure medications, such as arene oxide. Although epoxide hydrolase degrades arene oxides, a deficit of the enzyme can cause anticonvulsant hypersensitivity syndromes [29, 30]. It is theorized that DRESS could be the result of an immune reaction, abnormal metabolism, or activation of human herpes virus 6 [12]. It is considered a delayed hypersensitivity, type IV, drug
reaction mediated by T cells [31].

One paper described an unusual case of DRESS syndrome due to lamotrigine with reactivation of Epstein-Barr virus, autoimmune limbic encephalitis and syndrome of inappropriate antidiuretic hormone secretion. Discontinuation of lamotrigine, administration of methylprednisolone and intravenous immunoglobulin led to improvement [32]. In the literature, there is only one reported case of lamotrigine-associated DRESS syndrome with the reactivation of herpes viruses [33].

Tang et al. performed the lymphocyte transformation test (LTT) in patients with SJS/TEN who reacted to lamotrigine, and found that low rates of positive LTT reactions were observed in patients with lamotrigine-induced SJS/TEN [34]. In the literature, only one paper contains information about LTT in lamotrigine induced DRESS. One 8-year-old boy has been reported, in whom a skin patch and a lymphocyte stimulation test for hypersensitivity to lamotrigine were performed after steroid therapy had been stopped for 2 months, and both tests were positive [35].

Current studies are investigating specific enzyme defects at the genomic level that contribute to the acute hypersensitivity reaction [5]. HLA-B*5801 has been described as a genetic risk factor. In addition, one study showed for the first time that HLA-B*1502 negativity does not prevent LTG-HSR in Han Chinese [36]. Our patient tested negative for all infections. Her serum IgM was positive, but IgG was negative and these were negative in the CSF.

There is no definitive treatment for DRESS. Early recognition and withdrawal of the suspected agent may avoid irreversible damage to organs and will be lifesaving. Although optimum treatment remains controversial, treatment with corticosteroids and intravenous immunoglobulin are reported to be effective, though no controlled trials of such therapies have been reported [3].

In a review of 57 patients with lamotrigine induced DRESS, corticosteroids were prescribed according to the severity of rash and associated systemic involvement. Treatments of pulse methylprednisolone at a dose of 30 mg/kg [max 1 g/day] and oral methylprednisolone at a dose of 1 mg/kg were successfully carried out in some cases, which expedited the recovery [26]. Rapid tapering of corticosteroids was associated with reactivation of the syndrome [27]. Our patient did not require treatment with steroids, as her symptoms gradually improved with supportive management.

Our patient subsequently developed PRES secondary to acute hypertension. The hypertension was thought to be due to aggressive fluid replacement at initial presentation. She did not have a history of elevated blood pressure in the past. Nephrology could not find any other causes for hypertension. Her kidney function had normalized by the time of presentation and she was no longer on any medications.

Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state that results from the inability of the posterior circulation to autoregulate in response to acute changes in blood pressure. Hyperperfusion with resultant disruption of the blood brain barrier causes vasogenic edema, most commonly in the parieto-occipital regions [6-8]. The symptoms are usually reversible with supportive care. The term PRES can be a misnomer as the syndrome can involve other regions of the brain, in addition to the posterior cerebrum. Furthermore, although most cases fully resolve with supportive treatment, some patients can have permanent injury and residual neurological defects.

High blood pressure can lead to loss of self-regulation, hyperperfusion with endothelial damage and vasogenic edema. Endothelial dysfunction can lead to vasoconstriction and hyperperfusion resulting in cerebral ischemia and subsequent vasogenic edema [6-8]. Hypertension is not present or does not reach the upper limits of self-regulation (150-160 mmHg) in 25% of patients. Etiology for PRES includes severe hypertension, often seen in the postpartum setting, eclampsia/preeclampsia, or acute glomerulonephritis. It is also seen in haemolytic-uraemic syndrome (HUS), thrombocytopaenic thrombotic purpura (TTP), systemic lupus erythematosus (SLE), drug toxicity (cisplatin, interferon, erythropoietin, tacrolimus, cyclosporine, azathioprine, and L-asparaginase), bone marrow or stem cell transplantation, sepsis and...
hyperammonemnia [8, 37-43]

Our patient presented with typical symptoms of headache and altered vision. Her seizures were also very characteristic of occipital lobe seizures, with visual hallucinations. Her EEG showed occipital PLEDS, a marker of involvement of the posterior head regions. She was treated symptomatically and gradually improved. There is another case report of a 21 month old patient with DRESS with simultaneous leukoencephalopathy [44]. However, this is different from our patient, who recovered from her symptoms of DRESS and had an initial normal MRI.

Conclusion

Caution should be used with prescribing medications, even with well tolerated, commonly used medications. Lamotrigine rarely can lead to serious skin reactions, including DRESS, which has a mortality rate of 10% [18]. Vigilence, early recognition and removal of the offending drug is extremely important. Our case exemplifies that with medical management and treatment, iatrogenic complications can inadvertently occur. In the future, it would be useful if there was a way of predicting risks for adverse reactions to medications via genetic testing or biomarkers. Our patient initially had a serious adverse reaction to lamotrigine. Subsequently, she developed PRES due to elevated blood pressure from aggressive fluid management. In hindsight, the patient may not have needed further anti-seizure medication because she was seizure free for three years with a normal EEG. However, a new medication was started due to her desire to drive. Pros and cons of decisions to start new medications should be addressed with patients and families, with the understanding that no medication is completely benign.

References


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