Clinical commentary

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aPTT prolongation and skin eruption possibly associated with lamotrigine monotherapy in a paediatric patient

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ABSTRACT – We report the case of a six-year-old female with childhood absence epilepsy who developed combined aPTT prolongation, not corrected by normal plasma, and atypical skin eruption six months after initiating lamotrigine treatment with dose increment. Two weeks after lamotrigine withdrawal, the skin eruption disappeared and aPTT normalised. To our knowledge, this is the first report of aPTT prolongation possibly due to factor inhibitors associated with lamotrigine monotherapy.

Key words: lamotrigine, blood coagulation disorder, drug eruption

Coagulation factor-related coagulopathies (*i.e.* deficiency of vitamin K-dependent coagulation factors) have previously been reported during valproate treatment (Gerstner *et al.*, 2006; Serdaroglu *et al.*, 2002; Teich *et al.*, 2004) and some authors have suggested that valproate induces coagulopathies frequently in children (Gerstner *et al.*, 2006). However, there is no report of coagulation factor-related coagulopathies during lamotrigine monotherapy, although thrombocytopenia and disseminated intravascular coagulation (DIC) during lamotrigine monotherapy (Mackay *et al.*, 1997) and lupus anticoagulant induced by the combination of valproate and lamotrigine have been described (Echaniz-Laguna *et al.*, 1999). To the best of our knowledge, this is the first report of partial thromboplastin time (aPTT) prolongation accompanied by atypical eruption shortly after lamotrigine increment in a patient with childhood absence epilepsy.

Case study

A six-year-old female presented with short episodes of loss of contact or staring since the age of five years. She appeared otherwise healthy and her parents did not specify any other medical history. She was diagnosed with childhood absence epilepsy based on electroencephalography (EEG) with 3 Hz spike-and-wave complexes upon hyperventilation. Lamotrigine was initiated at 0.5 mg/kg per day which

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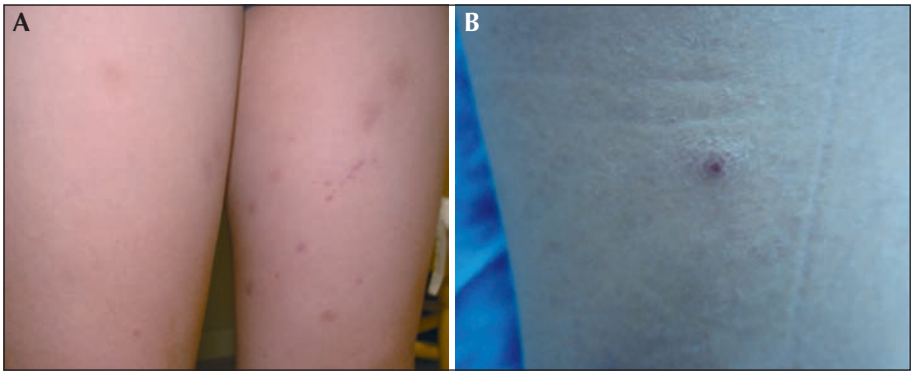

Figure 1. Skin eruption of the patient at three days following onset.
A) Fixed erythematous macular rash with central papular lesion which progressed to bruising with black discolouration.
B) Firm, elevated papular or nodular lesions were seen.

was maintained for two weeks and subsequently increased to 2 mg/kg for five months. Her parents did not notice any seizures shortly after lamotrigine medication or any adverse reactions such as skin rash. However, the dose was increased to 2.5 mg/kg after six months lamotrigine medication owing to 3 Hz spike-and-wave complexes which were still induced by hyperventilation on EEG. Three days after dose increment, the patient developed maculopapular skin eruptions with significantly firm and raised bumps, which subsequently appeared as bruise marks in the four extremities (mainly on the lower extremities) *(figure 1)*. The face and the trunk were spared. She had no systemic symptoms such as fever or arthralgia. There were no symptoms or signs of infection. Her parents reported no recent co-medication, unusual diets, or environmental changes. A complete blood count revealed platelets of 278,000 cells/mm^3, a haematocrit of 43%, and a peripheral white blood cell count of 5,300 cells/mm^3 with an absolute neutrophil count of 2,980 and 2.2% eosinophils. Erythrocyte sedimentation rate was within normal range (3 mm/hour). Blood chemistry showed normal aspartate aminotransferase (AST) at 29 U/L, alanine aminotransferase (ALT) at 20 U/L, and total bilirubin at 0.38 mg/dL. A urine analysis was negative for blood or protein. However, aPTT was prolonged at 85.3 seconds (range: 29.1-43.5) while the prothrombin time (PT) was within normal range; 12.9 seconds (range: 11.9-14.3 seconds). Bleeding time was normal. To exclude technical laboratory error, we re-tested aPTT, however, it remained prolonged at 88.8 seconds. We judged that coagulopathy and skin eruption was related to the lamotrigine dose increment; lamotrigine treatment was therefore discontinued immediately and the patient was evaluated for coagulopathies at the same time. Factors VIII, IX, XI, and von Willebrand factor were within normal range. In mixing studies with normal and patient plasma, aPTT prolongation persisted suggesting the presence of inhibitors rather than coagulation factor deficiency. However, reactivity to antinuclear antibody (Ab), anti-double stranded DNA Ab, lupus anticoagulant, anti-phospholipid Ab, anti-cardiolipin Ab, ssA/Ro Ab, ssB/La Ab, histone Ab, and factor VIII, IX Ab were all negative. Laboratory findings of the patient are summarised in *table* 1. Two weeks after lamotrigine withdrawal, the skin eruption disappeared and aPTT was normalised to 45.0 seconds.

Discussion

The aetiology of aPTT prolongation in this patient was not identified, however we suggest that it is related to lamotrigine based on the following: first, the episode showed a cause and effect relationship since it developed shortly after dose increment and disappeared after withdrawal of lamotrigine; second, coagulopathy was accompanied by skin eruption which is one of the most common adverse effects of lamotrigine (Guberman *et al*., 1999). To the best of our knowledge, this is the first case of aPTT prolongation without hepatic dysfunction possibly related to lamotrigine monotherapy. Moreover, the patient presented unusual skin eruption at the same time without evidence of hypersensitivity syndrome.

Haematological adverse effects related to lamotrigine, including thrombocytopenia and disseminated intravascular coagulation (DIC) during lamotrigine monotherapy (Mackay *et al*., 1997) and lupus anticoagulant associated with aPTT prolongation during co-medication with valproate, have been previously described (Echaniz-Laguna *et al*., 1999). Mechanisms responsible for lamotrigine-related haematological complications are unknown; immune-mediated responses have been suggested by some

Table 1. Laboratory findings of the patient.

Parameter	Normal range	Value	
		Immediately after skin rash	2 weeks after lamotrigine withdrawal
Haematocrit (%)	35-45	43	40
White blood cell (/mm^3)	3,400-8,800	5,300	6,070
Absolute neutrophil count (/mm^3)	1,500-7,500	2,980	3,380
Eosinophil (%)	0.0-6.6	2.2	2.0
Erythrocyte sedimentation rate (mm/hr)	0-20	3.0	
Aspartate aminotransferase (U/L)	0-37	29	23
Alanine aminotransferase (U/L)	0-41	20	11
Total bilirubin (mg/dL)	0-1.2	0.38	0.22
Prothrombin time (sec)	11.9-14.3	12.9	12.5
Partial thromboplastin time (sec)	29.1-43.5	85.3	45.0
After normal plasma mixing (sec)*	29.1-43.5	65.8	37.1
Factors VIII (%)	60-150	70	
Factors IX (%)	60-150	75	
Factors XI (%)	120-140	121	
Von Willebrand factor (%)	44-158	60.9	
Factor VIII antibody		Negative	
Factor IX antibody		Negative	
Antinuclear antibody		Negative	
Anti-double stranded DNA (IU/mL)	0-5.3	3.56	
Anti-histone antibody		Negative	
ssA/Ro antibody		Negative	
ssB/La antibody		Negative	
Lupus anticoagulant		Negative	
Anti-cardiolipin IgG/ IgM (U/mL)	0-23/0-11	7.0/5.0	
Anti-phospholipid IgG/ IgM (U/mL)	0-10/0-10	0.5/0.7	

*The patient's plasma is mixed with an equal volume of normal plasma.

authors (Echaniz-Laguna *et al*., 1999; Zaccara *et al*., 2007; Ural *et al*., 2005). In this patient, immune-mediated mechanisms were also suggested since aPTT prolongation was not corrected by normal plasma indicating the possible presence of inhibitors of coagulation factors. Drugs may induce the interaction between antigens and antibodies (Zaccara *et al*., 2007), which was reported to be the main mechanism for coagulation factor inhibitor-induced coagulopathy (Cohen and Kessler, 1996). However, in our patient, specific inhibitors of coagulation factors were not detected.

Lamotrigine-induced skin eruption has the typical characteristics of an allergic drug rash (Matsuo and Riaz, 2009) and usually occurs within six weeks of initiation of therapy (Guberman *et al*., 1999) which is associated with a T cell-medicated delayed hypersensitivity reaction (Zaccara *et al*., 2007). However, the

eruption in this patient presented vasculitic features of fixed erythematous macules with prominently elevated and firm central lesions which were different features from the most common forms of skin reaction reported with lamotrigine (*i.e.* simple mobiliform rash and urticaria) (Guberman *et al*., 1999). In addition, the skin eruption developed after six months of lamotrigine monotherapy which is considerably different from the typical onset time. We cannot explain the mechanism of skin eruption, however, a different pathophysiology to that of delayed hypersensitivity reaction may be related in this patient. A pathophysiological relationship between coagulopathy and skin eruption was therefore not indicated in spite of simultaneous occurrence.

Conclusion

There have been a few sporadic reports of coagulopathies including thrombocytopenia or DIC associated with the use of lamotrigine, however, this is the first report of transient aPTT prolongation with drug eruption associated with lamotrigine monotherapy. Further attention to lamotrigine-related coagulopathies is needed to better evaluate the incidence and aetiology of lamotrigine-induced skin eruption. □

Disclosure.
None of the authors has any conflict of interest to disclose.

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