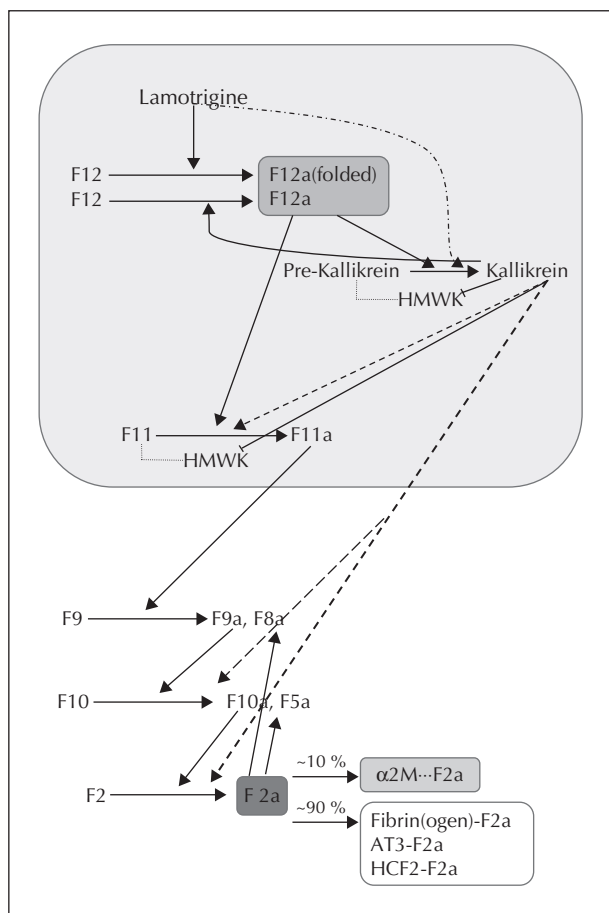


# Lamotrigine triggers the contact phase of coagulation

Comment on: "aPTT prolongation and skin eruption possibly associated with lamotrigine monotherapy in a paediatric patient" by Yeom *et al.* (*Epileptic Disord* 2011; 13: 425-5)

## To the editor,

Lamotrigine has been described to be able to prolong activated partial thromboplastin time (aPTT) and produce skin eruption (Yeom *et al.*, 2011). Lamotrigine



**Figure 1.** Lamotrigine-induced contact activation of coagulation. Lamotrigine folds factor 12 (F12) into activated factor 12 (F12a). In the F12a-kallikrein loop, high plasmatic activities of kallikrein are generated that are highly pro-inflammatory. F11a, F9a, and F10a are generated. If the hepatocytes are insufficient, high activities of circulating thrombin are generated (picture drawn by Christel Müller, Photodepartment of the University Hospital of Marburg and reproduced with the kind permission of Nova Science Publishers [Stief *et al.*, 2011]).

is a trigger of the contact phase of coagulation, the intrinsic system of coagulation (Stief, 2012); plasma concentrations of about 2 mg/L lamotrigine, via folding of factor 12 into activated factor 12 (figure 1), enhance the recalcified intrinsic thrombin generation two-fold. This is of particular pathophysiological importance if the respective patient suffers from liver insufficiency, because the hepatocytes normally clear activated factors of the contact phase out of the circulation (Loureiro-Silva *et al.*, 1993). Prolongation of aPTT together with skin eruptions is typical of massive activation of the contact phase, characterised by consumption of contact factors and systemically circulating kallikrein, an important pro-inflammatory compound (Tomita *et al.*, 2012) that could cause the observed skin eruptions. Patients who are susceptible to lamotrigine-induced contact activation could be identified by performing an ultra-specific, ultra-sensitive thrombin generation assay, such as the RECA (recalcified coagulation activity assay) and by checking liver sufficiency (bilirubin, ALT, and  $\gamma$ GT) before exposure to the drug. Lamotrigine in such susceptible patients should be combined with prophylactic concentrations of low-molecular-weight heparin (Stief, 2011).

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doi:10.1684/epd.2012.0503

## Response from Yeom et al.

### To the editor,

We read with great interest the above comments of Stief, in response to our recent case report regarding lamotrigine-induced aPTT prolongation and skin eruption (Yeom et al., 2011). Stief commented that the contact phase, the initiating step of the intrinsic pathway of coagulation, is activated by binding of factor XII to lamotrigine. Contact-phase activation by lamotrigine itself may be considered as an aspect of the pathophysiology of lamotrigine-induced coagulopathy. Comments of Stief were very impressive because a concept of coagulation pathway activation by drug itself is not familiar to clinicians. However, the patient previously described in our case report cannot be explained by lamotrigine-induced contact-phase activation for the following reasons:

- 1) Contact factors, factors XI and XII, are consumed in contact-phase activation. However, the level of factor XI was normal in our patient (Yeom et al., 2011);
- 2) aPTT prolongation by consumption of coagulation factors, including contact factors, can be corrected by normal plasma mixing. However, aPTT prolongation persisted in mixing studies in our patient, suggesting that aPTT prolongation was less likely to be due to coagulation factor deficiency as a result of the consumption of factors;
- 3) Stief documented that plasma concentrations of about 2 mg/L lamotrigine enhanced recalcified

intrinsic thrombin generation two-fold (Stief, 2012). However, that study was performed *in vitro*. Normally, hepatocytes clear activated factors from the contact phase from the circulation (Loureiro-Silva et al., 1993) and hepatocyte function was normal in our patient. Blood flow also influences the coagulation pathway (Campbell et al., 2010) and it is unclear which factors were missing in the *in vitro* study.

For these several reasons, we concluded that contact-phase activation by lamotrigine did not contribute to the aPTT prolongation in our patient. However, Stief's point should be considered when the drugs in question are possibly associated with coagulopathy or thrombin generation. In particular, neurologists should exercise great caution when administering combination therapy of antiepileptic drugs with ethosuximide and/or valproic acid, which have strong tendencies to trigger thrombin generation *via* contact-phase activation (Stief, 2012).

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