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Letter to the Editors

Cerebral angioedema associated with enalapril

Eric Decloedt,[1] Rob Freercks[2] & Gary Maartens[1]

[1]Division of Clinical Pharmacology, Groote Schuur Hospital and [2]Department of Internal Medicine, University of Cape Town, Cape Town, South Africa

The first case of angioedema associated with angiotensin converting enzyme (ACE) inhibitors was described nearly 30 years ago [1]. Since then various forms of ACE inhibitor-induced angioedema have been described including angioedema of the face, airway, viscera, and genitalia [2]. We present, to our knowledge, the first case of enalapril-induced angioedema of the brain.

A 28 year old woman from the Democratic Republic of the Congo presented to Groote Schuur Hospital, Cape Town, South Africa, with diffuse alveolar haemorrhage requiring ventilation. She was diagnosed with systemic lupus erythematosus (SLE) with renal and pulmonary manifestations. Antibodies to double-stranded DNA were markedly raised at 331 IU ml^{-1} (>15 is regarded as positive). She responded well with resolution of her alveolar haemorrhage and improvement of her nephritis on prednisone 1mg kg^{-1} day^{-1} and an intravenous infusion of cyclophosphamide. She was discharged on prednisone 60 mg daily, atenolol 50 mg daily, amlodipine 10 mg daily, enalapril 10 mg 12 hourly, furosemide 40 mg daily and simvastatin 10 mg daily as well as calcium and iron supplements. She had no known drug allergies.

She was reviewed 2 weeks after discharge. Her blood pressure remained uncontrolled at 170/110 mmHg and she had dependent oedema and ongoing severe proteinuria. The dose of enalapril was increased to 20 mg 12 hourly and she was given another intravenous infusion of cyclophosphamide. Three days later she presented to the emergency department with angioedema of the lower face and lip without airway involvement. The enalapril was discontinued and she was admitted for observation. Several hours later she developed generalized tonic-clonic seizures, which were terminated with intravenous diazepam and an intravenous loading dose of phenytoin. Her blood pressure was 170/110 mmHg. There was no evidence of hypertensive retinopathy and her serum creatinine remained normal. Computed tomography (CT) of the brain was performed, which showed extensive cerebral oedema involving the white matter. There were no features of obstructive hydrocephalus, no contrast enhancement, and the venous sinuses were patent. C3 complement was reduced (0.720 g l^{-1}, range 0.9–1.8), C4 was normal and C1 esterase inhibitor concentration was mildly elevated (0.45 g l^{-1}, range 0.21–0.40 g l^{-1}). The cerebrospinal fluid findings were: 1 polymorphonuclear cell and 1 lymphocyte per cu mm, protein 1.17 g l^{-1}, glucose 7.3 mmol l^{-1} and IgG index 0.8. Bacterial and mycobacterial cultures of cerebrospinal fluid were negative. Anti-double stranded DNA remained slightly elevated (23.2 IU ml^{-1}), but was much lower than at her initial presentation. Her lupus anticoagulant and anticardiolipin antibodies were negative.

After the seizures, she remained in a semi-comatose state with a Glasgow coma score of 9. She received supportive treatment, and 10 mg dexamethasone intravenously 12 hourly was added. Over the next 5 days, she made a full recovery to normal mental state and the facial angioedema resolved. Her hypertension was controlled (blood pressure on discharge 140/80 mmHg) with atenolol, doxazosin, amlodipine, and hydralazine. At follow up, 5 months later, she remained well on maintenance cyclophosphamide and reducing doses of prednisone.

We believe that our patient developed enalapril-associated angioedema of the brain due to the temporal association between the angioedema of the lip and face, and the exclusion of other causes, notably C1 esterase inhibitor deficiency. To our knowledge, no case of ACE inhibitor-induced cerebral angioedema has been described.

A definitive diagnosis of enalapril-associated angioedema of the brain would require a rechallenge with enalapril, but this would clearly be inappropriate in this case. The differential diagnosis of the cerebral oedema and seizures in this patient included other causes of angioedema affecting the brain, and alternative causes of the cerebral oedema, notably a neuropsychiatric manifestation of SLE.

Neurological manifestations of hereditary angioedema have been previously described [3]. The absence of a family history of angioedema and the absence of C1 esterase inhibitor deficiency rule this diagnosis out. Other drugs causing the angioedema are extremely unlikely. Although type 1 hypersensitivity reactions to glucocorticoids and

cyclophosphamide have been described [4, 5], the resolution of the angioedema despite ongoing administration of cyclophosphamide and prednisone makes this diagnosis very unlikely.

Infective causes of the cerebral oedema are effectively ruled out by the normal cerebrospinal fluid findings, the absence of a focal lesion on the CT scan, and the recovery without specific therapy. The neuro-imaging abnormalities of neuropsychiatric SLE include infarcts, high intensity lesions in periventricular or subcortical white matter, and cortical atrophy[6, 7]. To our knowledge, diffuse white matter brain involvement has not been described as a presentation of neuropsychiatric SLE.

Posterior reversible encephalopathy syndrome (PRES) is characterized by various neurological manifestations and transient changes on neuro-imaging consistent with cerebral oedema, which typically, but not exclusively, involves the posterior circulation [8]. Although the exact physiopathology remains incompletely understood, it is hypothesized that it is caused by a brain capillary leak syndrome secondary to the cytotoxic effect of, among other causes, immunosuppressive drugs and SLE. The CT of the brain in our patient demonstrated extensive cerebral oedema involving the white matter of the entire brain, thus steering the diagnosis away from PRES. Furthermore, PRES has not been associated with angioedema.

ACE inhibitor-induced angioedema occurs in 1 to 6.8 patients per 1000 treated [9, 10]. African-Americans are more than four times more likely to develop ACE inhibitor-induced angioedema than Caucasians [11, 12]. Ethnicity-related differences between the kallikrein-kinin system may underlie the increased rate of angioedoema among Black subjects [11]. Despite the fact that our patient presented with ACE inhibitor-induced angioedema after an increase in her ACE-I dose, there is no evidence that ACE inhibitor-induced angioedema is dose-related [13].

Although the pathophysiology of ACE inhibitor-induced angioedema is not well understood, various mechanisms have been proposed. Apart from acting on angiotensin I, ACE inhibitors also prevent inactivation of bradykinin. Bradykinin is a potent inflammatory autocoid causing vascular permeability and vasodilatation. However, bradykinin inactivation is blocked in all patients on ACE inhibitors, yet only a small fraction of patients develop angioedema. This suggests that factors other than bradykinin are involved in the development of angioedema. Further evidence against the bradykinin hypothesis is that angiotensin receptor blockers, which do not affect bradykinin, also cause angioedema, albeit at a lower frequency than ACE inhibitors [14]. Angioedema has also been described in patients receiving renin inhibitors [15].

In conclusion, we have presented a case of diffuse cerebral oedema temporally associated with angioedema of the lip and lower face. Alternative causes were excluded and the condition resolved on withdrawal of enalapril. We propose that enalapril-induced angioedema of the face and brain was responsible for this presentation.

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CORRESPONDENCE
Dr Eric Decloedt, Division of Clinical Pharmacology K45, Old Main Building, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa 7700. E-mail: eric.decloedt@uct.ac.za