To the Editor

Levetiracetam Induced Acute Pancreatitis Case in Pregnancy

It is reported that at least 25% of people with epilepsy are women of child-bearing age. Levetiracetam, a second generation antiepileptic drug, has been preferred in pregnancy and lactation due to promising safety in pregnancy[1,2]. Herein, we report a pregnant case of levetiracetam induced pancreatitis. Twenty-five year old pregnant woman at 27 weeks gestation was consulted to gastroenterology department due to abdominal pain, nausea and hyperamilasemia of 396 U/L (normal range in our laboratory: 28-128). Her lipase level was also high 264 U/L (N: <60 U/L). Ultrasound showed enlarged, edematous pancreas but no gallstones. Serological analysis was normal. Blood count disclosed anemia (Hb: 9.1 g/dl). Serum calcium and lipid levels were within normal limits. Her past medical history was unremarkable except levetiracetam monotherapy start due to epileptic seizure at 12 weeks gestation. Levetiracetam was discontinued. Supportive measures such as fluid-electrolyte therapy was given. Her amylase level declined to normal level in a week. Abdominal pain was over. Antiepileptic drug was not recommended by the neurology department until the delivery. Pancreatitis in pregnancy had been associated in the past with a high maternal and fetal morbidity rate or preterm labor[3]. Earlier diagnosis and greater treatment options improve the prognosis of pancreatitis in pregnancy. Pancreatitis in pregnancy is mostly related with gallstones. Although levetiracetam has been known to be a safe drug in pregnancy, pancreatitis should be considered in patients with epilepsy on levetiracetam.

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To the Editor

Pulmonary Edema and Simultaneous Cardiac Dysfunction After Epileptic Seizures

Severe pulmonary and/or cardiovascular dysfunctions may be the result of acute insults of the central nervous system (CNS). Acute pulmonary edema occurring shortly after a significant CNS injury was termed neurogenic pulmonary edema (NPE). It was described mainly as a rapid consequence of subarachnoid bleeding or intracranial hemorrhage, but many injurious CNS events can be associated with this pathology[1]. The pathogenesis of NPE is not entirely clear yet, but the pathophysiological mechanism is thought to be an increase of intracranial pressure with an increased central sympathetic nerve activity transmitted via peripheral α- or β- adrenergic receptors. Clinically, these patients may demonstrate a broad spectrum of presentations from an asymptomatic clinical picture to acute and severe pulmonary edema[1,2].

On the other hand, clinical studies have shown that acute cerebral lesions (in particular stroke, haemorrhage and seizures) may induce changes in cardiovascular functions including hypertension, arrhythmias and myocardial necrosis. Moreover, it is demonstrated that damage to the insular cortex, the amygdala, lateral hypothalamus and brain stem is likely to cause disturbances in either sympathetic or parasympathetic autonomic system with subsequent cardiac dysfunction[1-4].

It is well known that commonly during seizures both transient changes in the respiratory function (e.g. dyspnea, apnea, cyanosis) and cardiac symptoms (e.g. tachycardia, bradycardia) can occur[1,3].

We report an interesting case of acute bilateral pulmonary edema and concomitant left ventricular dysfunction occurring after epileptic seizures.

Case Report

A 61-year-old woman, with previous acute myocardial infarction in chronic therapy with acetyl salicylic acid and in current good cardiovascular condition, was admitted to the Emergency Department due to two generalized tonic-clonic seizures within short distance of each other. As reported by witnesses, the seizures were associated with prolonged apnoea and cyanosis. During the first medical observation, she was not responsive and showed respiratory failure with evidence of large amounts of blood-stained secretions. There was no evidence of gastric acid aspiration or acute lung infection. Metabolic blood tests were not altered.

Her electrocardiogram (ECG) showed tachysystole, heart rate was 110 beats/minute (min) and cardiac enzyme levels were no significantly above the normal range. The chest auscultation revealed widespread fine crackles, arterial blood gas tensions suggested alveolar hypoventilation and respiratory acidosis (pH: 6.7; pCO_2: 84 mmHg; pO_2 52 mmHg). A chest X-ray showed widespread bilateral pulmonary edema (Figure). Moreover, echocardiography demonstrated depression of left ventricular function with a shortening fraction of 30%. The EEG revealed diffuse slowing as post-critical state. Brain computed tomography (CT) scan and magnetic resonance imaging (MRI) were both normal. The patient was sedated, intubated and ventilated. She was treated with antiepileptic therapy (levetiracetam 2000 mg/day).

https://doi.org/10.1017/S0317167100022630 Published online by Cambridge University Press

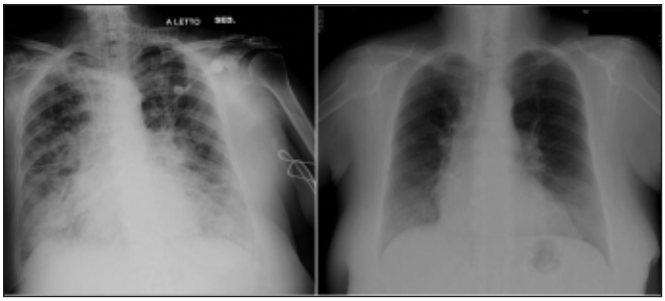

Figure: *Bilateral pulmonary oedema on chest radiography (left). Normal chest radiography after 72 hours (right).*

The cardio-circulatory failure was adequately treated, circulation sustained and organ-perfusion promoted. After continuing intensive care therapy, including positive pressure ventilation, the patient's clinical condition improved rapidly and she underwent a successful extubation 36 hours later. Left ventricular function had normalized with ejection fraction of 55%. Respiratory recovery was excellent and the patient was eupnoic with normal results of chest radiography 72 hours later (Figure). The most common medical conditions (e.g. myocardial infarction, myocarditis, toxic causes, electrolyte alterations) possibly causing left ventricular dysfunction were ruled out by adequate examinations. During the long-term follow-up (two years), the patient did not show any epileptic seizures, and left ventricular contractility was normal on echocardiography.

Discussion

Neurogenic pulmonary edema can follow any acute cerebral insult such as severe head injuries, subarachnoid haemorrhages or epileptic seizures. It may result from a sudden increase in intracranial pressure which mediates a massive increase in sympathetic drive and subsequent intense generalized vasoconstriction and increased systemic arterial and pulmonary vascular pressure. The increased pulmonary vascular pressure may induce an alteration of the Starling forces in the lungs with a shift of fluids into the pulmonary alveoli and the interstitial spaces. However, in explaining mechanisms of edema some authors advocate alterations in pulmonary endothelium rather than hemodynamic changes. The high mortality of NPE is attributable mainly to the underlying insult but if diagnosed early, recovery is usually rapid[1,2].

Nevertheless, it is reported that the centrally mediated α-adrenergic sympathetic discharge may provoke not only pulmonary edema, but also potentially malignant ventricular dysrhythmia increasing the associated risk of sudden death[3-5]. Finally, differently from the traditional view of considering NPE as a non cardiogenic form of pulmonary edema, in some cases it is described as the consequence of a direct myocardial injury with depressed cardiac contractility. Thus, the changes in pulmonary circulation may be associated with a cardiac insult, especially in patients with previous heart diseases. This pathological condition is very rare, but potentially ominous[4].

In our patient the acute brain injury provoked both respiratory and cardiac dysfunctions, and it is very difficult to make a clear distinction between primary cardiac failure followed by acute pulmonary edema or primary NPE with simultaneous cardiac insult. A unique pathophysiological mechanism involving cathecholamines may be hypothesized.

Moreover, despite pulmonary edema after epileptic seizures is a rare condition, its recognition is crucial. The importance of awareness of NPE needs to be emphasized because it is suspected to be related to unexpected sudden death in epileptic patients (SUDEP). In fact, it is found in the majority of SUDEP at autopsy. Growing interest in SUDEP in both the clinical and basic sciences, however, has provided insight into its possible underlying pathophysiological mechanisms. To date, it has been demonstrated that dysregulation in cardiac and respiratory physiology, dysfunction in systemic and cerebral circulation physiology, and seizure-induced hormonal and metabolic changes might all contribute to SUDEP[5].

Generally, the risk factors most consistently associated with SUDEP include poor seizure control, antiepileptic drugs polytherapy, and a long duration of epilepsy. Despite the poor available data, also the mechanisms of antiepileptic drugs probably involved in SUDEP are related to the cardiac system[5].

Thus, probably it is appropriate to consider an important risk factor the occurrence of cardiovascular or respiratory dysfunctions after seizures since patients with these dysfunctions might have an intrinsic susceptibility to SUDEP.

In conclusion, cardiac and respiratory complications of epileptic seizures could be a real clinical emergency. The collaboration of anaesthesiologists and neurologists is essential in the management of these complications to increase the possibility of a better outcome for the patient. Moreover, the strict relation between seizures and cardiovascular and/or pulmonary dysfunction needs to be considered mainly in view of its potential impact on the therapeutic and clinical management of patients.

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https://doi.org/10.1017/S0317167100022630 Published online by Cambridge University Press