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Editorial

Cephalosporin neurotoxicity: An overlooked cause of toxic-metabolic encephalopathy

Consider the following case: A 75-year-old woman with a history of chronic renal failure is admitted to the hospital for shortness of breath. She is diagnosed with pneumonia and started on ceftriaxone. Three days later, she is disoriented, speaking "ragtime," and has intermittent myoclonus. The on-call neurologist is asked to evaluate the patient for the cause of her "altered mental status."

Encephalopathy is one of the most common reasons that neurologists are consulted in the inpatient setting, and "toxic-metabolic" is one of the most common etiologies invoked for the cause of a patient's encephalopathy. In the vignette above, simply being elderly and hospitalized – let alone infected and uremic– would certainly be sufficient to cause delirium. But recent research has shown us that there is another "toxin" to be considered amongst the causes of toxic-metabolic encephalopathy: antibiotics.

The association of antibiotics and encephalopathy was first described the 1940s, when case reports emerged of penicillin causing seizures, and *in vitro* models demonstrated that penicillin provoked epileptic discharges when applied directly to neuronal cultures. A recent review demonstrates that nearly all commonly used antibiotics are associated with encephalopathy, with different classes of antibiotics associated with different clinical phenotypes [1]. But increased recognition of antibiotic-associated encephalopathy leads to a dilemma: in a routine case of encephalopathy in a hospitalized patient with an infection, which is the culprit – the infection or the antibiotic? The stakes are high, as some patients may need specific antibiotics for their specific infections, and so modifying the antibiotic regimen in such cases may not be without risk. Are particular antibiotics more commonly associated with encephalopathy? Are there any clinical features that help the neurologist to feel more confident in invoking a specific antibiotic as the particular 'toxin' amongst many potential causes of toxic-metabolic encephalopathy?

In this issue, Lacroix and colleagues[2] provide answers to some of these questions through their analysis of serious adverse drug reactions from cephalosporin antibiotics affecting the central nervous system (CNS) from the French Pharmacovigilance database. The authors report on adverse effects from 511 patients. Most of the adverse effects resulted in hospitalization or prolongation of hospitalization, and in 31 patients, the drug was thought to contribute to the patient's death. Many different cephalosporins were implicated in patient deaths with most reports found for ceftriaxone, one of the most commonly used cephalosporins. When analyzing all CNS adverse effects, cefepime had the most associated reports though twenty different cephalosporins were implicated. Most of the adverse effects occurred in patients whose cephalosporin dosing was within the recommended range. In contrast to prior reports that cephalosporins cause encephalopathy mostly in patients with renal impairment [1], few patients in the present study had renal impairment, although the data on renal function is incomplete –only 195 of 511 patients in the study had known renal clearance at the time of the adverse event.

The authors should be congratulated for their significant contribution to understanding the epidemiology of an under-recognized etiology of one of the most common reasons for neurologic consultation. The French Pharmacovigilance Database is remarkable because each reported adverse effect report is vetted individually to ensure likely causality. Also, the authors helpfully report toxicity from individual cephalosporin antibiotics rather than considering them in aggregate.

The study is not without its limitations, mostly related to the database itself rather than the authors' impressive analysis. With respect to clinical phenotype, it is not clear how "encephalopathy" differs from "confusional state" (the third most reported outcome) or from "disorientation" and "agitation." Convulsion and epilepsy are also related clinically but reported separately. Analysis of plasma levels shows that the majority of patients with CNS adverse effects had plasma levels of cephalosporins above the stated upper limit of therapeutic range, but it is not reported whether the plasma levels are peak or trough levels. In the patients with EEG data available, 28% had epileptic activity, but it is not specified whether this activity represented seizures or merely epileptiform discharges; the latter can sometimes be difficult to distinguish from the pattern of triphasic waves, which has a different clinical significance.

As for the vignette we presented in the opening, how can the findings of this paper guide us in determining what role –if any- antibiotics may be playing in the patient's encephalopathy? We learned from this report that most cephalosporins can cause neurotoxicity even when prescribed within the recommended dosing range and that the adverse effects can be severe enough to lead to death. The clinical features of the neurotoxicity include seizures and encephalopathy. The patient's renal failure may make her more susceptible, but uremia itself may also cause or contribute to development of encephalopathy. Because the majority of patients with neurotoxicity had elevated plasma levels of antibiotics, more widespread ability to measure plasma antibiotic levels may allow more effective diagnosis of antibiotic neurotoxicity in patients like the one we presented. Until then, whether – and to what degree – antibiotics may be contributing to encephalopathy in patients with systemic infections remains a vexing question requiring careful consideration in each patient who develops encephalopathy while being treated with cephalosporins.

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