Antimicrobial Neurotoxicity: an under-recognised cause of delirium

D. Moynan, N. Reidy, E. Maqbool, C. Curran, E. de Barra
Department of Infectious Diseases, Beaumont Hospital, Dublin
Department of Geriatric and Stroke Medicine, Beaumont Hospital, Dublin

Background

- Antimicrobial associated encephalopathy (AAE) is a well-documented, though under-recognised, adverse event associated with antimicrobial use [1]
- Clinical manifestations of AAE are varied, ranging from myoclonus and seizure to an encephalopathy with cerebellar signs 1, the overall presentation governed by the antimicrobial in question
- Awareness of this adverse event is important for all antimicrobial prescribers
- We describe a reversible encephalopathy characterised by confusion, myoclonus and stupor in a 76 year old gentleman on antimicrobial therapy for the recurrence of a peri-rectal abscess
- Consent was obtained from the patient for presentation and discussion

Case

- A 76 year-old gentleman presented unwell to hospital with a fever, tachycardia and hypotension
- The patient's background was significant for a rectal abscess related to stump dehiscence from a previous subtotal colectomy for colorectal carcinoma
- The patient was deemed an unsuitable surgical candidate and the abscess had previously been managed through interventional radiology and subsequent antimicrobial therapy
- Comorbidities included CKD (Stage 3A), type 2 diabetes mellitus and benign prostatic hypertrophy with a long term catheter in situ. The patient had no history of liver disease or previously diagnosed cognitive impairment
- Bloods at presentation and during the first seven days admission are seen in *table 1,* noting an acute on chronic kidney injury
- Previous culture and sensitivities informed the empiric start of intravenous cefuroxime (750mg TDS), oral metronidazole (400mg TDS) and intravenous daptomycin (600mg OD). Two days into admission, the dose of intravenous cefuroxime was increased to 1.5mg TDS

- The patient demonstrated a clinical and biochemical recovery
- Fifteen days into treatment the patient demonstrated new confusion and was disorientated to time and place, requiring prompting to carry out one-stage commands
- Glasgow Coma Scale (GCS) was 14/15 (E4, V4, M6). Mild, peripheral myoclonus was noted in the arms with normal tone throughout, normal reflexes and bilateral down-going plantar reflexes. Power, sensation and coordination were difficult to assess given the patient's confusion
- Over the following 24 hour period, the patient deteriorated in a step-wise manner. Confusion increased and the patient was no longer following commands with evidence of swallow failure. GCS dropped to 10/15 (E4V1M5). Myoclonus had progressed proximally and become more marked. Plantar reflexes at this time were up-going bilaterally
- Neuroimaging, guided by neurology consultation, including a contrast-enhanced CT brain and intracranial angiogram and subsequent MRI brain failed to identify an acute pathology

- A working diagnosis of metabolic encephalopathy was established, likely driven by antimicrobial therapy
- Antimicrobials were stopped and the patient's condition improved dramatically with resolution of neurological function over the subsequent days, although a sustained delirium remained for two weeks following withdrawal of the drugs. Vivid hallucinations were described by the patient with a specific reference to Richard Attenborough greeting the patient in the evenings
- Given the reluctance to restart antimicrobials, a urinary catheter was inserted into the rectum (see; *image 1*) to facilitate drainage and obtain source control, with interval imaging noting resolution
- The patient's delirium settled and was discharged home following a period of ward based rehabilitation

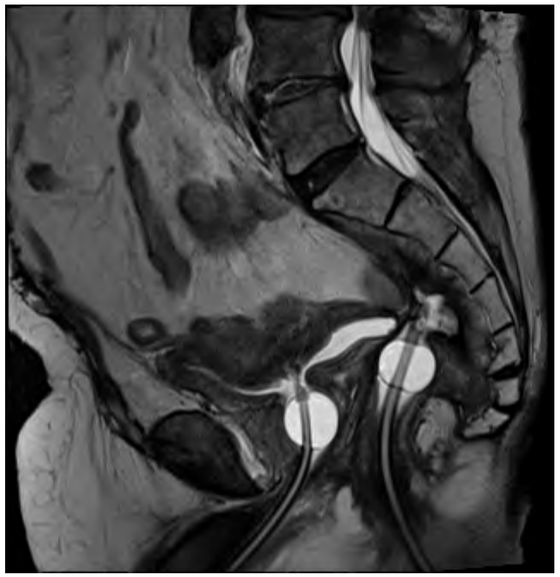

Image 1: MRI noting urinary catheter in rectum to facilitate abscess drainage

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
UREA	19.5	25.4	24.3	22.3	18.2	15.2	14.4
CREATININE	292	338	326	281	224	168	161
CRCL	24	21	22	25	32	42	44
WCC	17.5	16	10.5	7.5	9.75	10	6
CRP	186	159	132	125	163	100	53

WCC; White Cell Count x10^9/L, CRP; C-Reactive Protein mg/L, CrCl; Creatinine Clearance mL/minute; Urea mmol/L; Creatinine umol/L

Table 1: Laboratory results

Discussion

- This patient's neurological presentation, characterised by marked myoclonus and stupor, is in keeping with a cephalosporin induced antimicrobial-encephalopathy which is frequently seen in the context of renal impairment [1,2,3]. While a lower dose of intravenous cefuroxime was commenced at presentation, the subsequent increase in dose may have been premature in the setting of ongoing renal injury and resulted in an undesired build-up of the antimicrobial
- While the exact mechanism behind AAE is not fully understood, the myoclonus which develops from beta-lactam antimicrobials is believed to arise from a disruption of inhibitory synaptic transmission leading to excitotoxicity [1]
- The pathophysiology rests with the beta-lactam ring itself, which has the capacity to bind to the ligand-gated ion channel γ-aminobutyric acid class A receptor ($GABA_AR$), ultimately impeding the inhibitory neurotransmission with subsequent excitotoxicity [3,4]
- Ultimately a clinical diagnosis of exclusion, diagnostic aids have been reported to facilitate the identification of AAE cases, most notably electroencephalography (EEG) [1,3,5]. While this investigation was not performed on our patient, the literature suggests that AAE is associated with an abnormal EEG in 70-100% of cases, more commonly when cephalosporin-induced [1], with periodic discharges and triphasic morphologies notable on recordings [3,5]
- Treatment is conservative and depends on a timely diagnosis and withdrawal of the offending antimicrobials

- This case highlights the importance of first principles in medication prescribing, notably is this the right dose for the right patient [6], particularly in the setting of renal impairment. Furthermore, it serves as a reminder to physicians to broaden the differential in the setting of a delirium

References

1. Bhattacharyya, S., Darby, R. R., Raibagkar, P., Gonzalez Castro, L. N. & Berkowitz, A. L. Antimicrobial-associated encephalopathy. *Neurology* **86**, 963–971 (2016).
2. Herishanu, Y. O. *et al.* Cefuroxime-induced encephalopathy. *Neurology* **50**, 1873–5 (1998).
3. Grill, M. F. & Maganti, R. Cephalosporin-Induced Neurotoxicity: Clinical Manifestations, Potential Pathogenic Mechanisms, and the Role of Electroencephalographic Monitoring. *Ann. Pharmacother.* **42**, 1843–1850 (2008).
4. Akahane, K., Tsutomi, Y., Kimura, Y. & Kitano, Y. Levofloxacin, an Optical Isomer of Ofloxacin, Has Attenuated Epileptogenic Activity in Mice and Inhibitory Potency in GABA Receptor Binding. *Chemotherapy* **40**, 412–417 (1994).
5. Triplett, J. D., Lawn, N. D., Chan, J. & Dunne, J. W. Cephalosporin-related neurotoxicity: Metabolic encephalopathy or non-convulsive status epilepticus? *J. Clin. Neurosci.* **67**, 163–166 (2019).
6. Sullivan, G. H. Five 'rights' equal 0 errors. *RN* **54**, 65–6, 68 (1991).