Case Series

Drug Induced Encephalopathy in Patients with Chronic Kidney Disease: A Case Series

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Abstract:

Drug induced encephalopathy is an established side effect of many drugs when used in a higher dose. Though we do not encounter this side effect frequently in our day to day practice, yet with renal impairment this is not uncommon. Even with a reduced dose many of these can precipitate encephalopathy in this special group of patients. We are presenting here a series of seven such cases of drug induced encephalopathy in patients with renal impairment.

Key words: *Chronic kidney disease, Drug induced encephalopahty, encephalopathy.*

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Introduction

Altered level of consciousness in a patient of chronic kidney disease (CKD) is commonly attributed to the advanced stage of uremia. However there are several other causes which can alter central nervous system (CNS) functions. Electrolytes disturbances, hypoglycemia, sepsis, liver dysfunction, thiamin deficiency and last but not the least drug toxicity can lead the metabolic encephalopathy in patients with CKD[1]. In these group of patients not only the accumulation of the drug due to lower clearance but also alteration of blood brain barrier permeability, alteration of protein binding of drug and several other mechanisms can lead to the brain toxicity[2]. There are different classes of drugs having the potential to precipitate encephalopathy in higher dose, however in patient with compromised renal function these drugs even in lower dose can lead to profound encephalopathy. We had encountered seven such cases of drug induced encephalopathy in CKD patient from July 2015 to June 2016 in nephrology department of BIRDEM General Hospital, Here we are presenting those cases of encephalopathy caused by commonly used drugs that are not usually associated with CNS side effects in our day to day practice.

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Case 1a

A 48-year-old diabetic (DM) and hypertensive Bangladeshi female with end stage renal disease (ESRD) on maintenance hemodialysis (MHD), got admitted with fever and a tender, fluctuant swelling of about 7 cm in diameter around left sternal head of clavicle.

It was diagnosed as tubercular abscess on the basis of typical histopathological findings (Figure 1).

We initiated anti-tubercular treatment with renal dose adjustment and with higher dose of pyridoxine

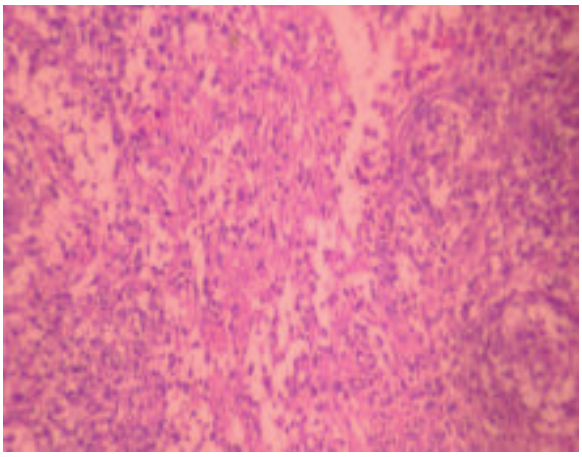

Figure 1. *Histopathology showing epithelioid granuloma with caseation necrosis.*

(50 mg daily). On 7th day the patient became drowsy with irrelevant talk, forgetfulness and involuntary movements of both upper limbs. She had bilateral flexor plantar responses. There was no new change in fundus and no signs of meningeal irritation. There was no interruption of hemodialysis schedule either. Clinical examination and investigations did not reveal any clue to this neurological manifestations. Therefore suspecting the possibility of isoniazid (INH) induced encephalopathy INH was stopped and dose of pyridoxine was increased. Alternate anti-TB drugs were prescribed. Patient's consciousness level was improved after 3 days of discontinuing the drug.

Case 2

A 55-year-old Bangladeshi diabetic kidney transplant recipient was admitted in our hospital for the management of septic arthritis of left knee joint. Synovial fluid culture revealed profuse growth of *Pseudomonas* and Injection ceftazidime 500 mg bid was initiated according to sensitivity. He was on immunosuppressive drugs (cyclosporine, mycophenolatemofetil, and prednisolone) since transplantation in 2008 and his serum creatinine level was 3.3 mg/dl. On 5th day of starting antibiotic, the patient became drowsy and disoriented. He also had myoclonic jerks on face and upper limbs. MRI of brain revealed no abnormality. Cyclosporine level was also within target range. Despite initiation of anticonvulsant, his neurological status was worsening and myoclonus persisted. No other identifiable factors were evident in clinical examination as well as in investigations. Therefore considering possibility of ceftazidime induce encephalopathy, the drug was discontinued and on second day, his involuntary movements reduced and sensorium improved. By fifthday he was fully conscious and myoclonic movement resolved completely.

Case 3a

A 40-year-old Bangladeshi diabetic hypertensive female with CKD (Stage 5) was admitted with deteriorating level of consciousness for last 1 day. She was in her usual state of health with a stable serum creatinine of around 5 mg/dl for last few years. Four days back she was prescribed tablet baclofen 10 mg bid and capsule tramadol hydrochloride 100 mg bid for low back pain. Following that she developed vomiting and tramadol was discontinued on second day. However her consciousness level gradually deteriorated and she became unresponsive on the day of admission. We found her deeply comatose, pupil were reacting to light and neck rigidity was absent. She was hemodynamically stable. Oxygen saturation in room air was 98%. Her serum creatinine was 5.6 mg/dl, RBS-8.9mmol/L. S Na-134 mmol/L, S K-3.5, mmol/L, S Cl-111 mmol/L and T CO2 was 19 mmol/L. CT scan of brain, CSF analysis revealed no abnormality. Baclofen encephalopathy was suspected .and the drug was discontinued. Haemodialysis was advised, but patient's attendant refused. Her consciousness level gradually improved on conservative management. She was discharged with full consciousness on fifth day. Exclusion of other causes of unconsciousness and spontaneous recovery on discontinuation of suspected offender, made the diagnosis of baclofen encephalopathy obvious.

Other cases of drug induced encephalopathy are listed in Table I.

Table I. Summary of seven cases of drug induced encephalopathy in CKD patients

Trait	Case 1a	Case 1b	Case 1c	Case 2	Case 3a	Case 3b	Case 3c
Age (yrs)	48	36	42	55	40	50	52
Gender	F	M	M	M	F	F	M
CKD	Stage 5	stage 3	Stage 3	Chronic allograft nephropathy	Stage 5	Stage 3	Stage 5
RRT	MHD	IPD	NA	NA	NA	NA	MHD
Reason to use offending drug	EPTB	EPTB	PTB	sepsis	LBP	LBP	Hiccup
Offending drug dose	INH* 300mg daily	INH 300mg daily	INH 300mg daily	Ceftazidime 500mg bid	Baclofen 10mg bid	Baclofen 10mg tid	Baclofen 5mg bd
DM	+	+	+	+	+	+	+
Encephalopathy	7th day	10th day	2nd month	5th day	1st day	2nd day	1stday
Improvement (After discontinuation)	3 days	5 days	7 days	5 days	5 days	3 days	2 days

*Pyridoxine 50 mg was given with INH in all cases of tuberculosis

[CKD=Chronic kidney disease, AKI=Acute kidney disease, RRT=Renal replacement therapy, MHD=Maintenance hemodialysis, IPD=Intraperitoneal dialysis, EPTB=Extra pulmonary tuberculosis, PTB=Pulmonary tuberculosis, LBP=Low back pain, INH=Isoniazid, DM=Diabetes mellitus]

Discussion

IN induced encephalopathy is one of the earliest drug induced encephalopathy reported in in the literature[1]. Castaigne, P. et al in 1961 1st described a case of INH induced encephalopathy due to pyridoxine deficiency.[3] Patients on dialysis and in those with a slow acetylator phenotype conferred by NAT2 polymorphisms are at increased risk of INH encephalopathy.[4] In our 1st case the patient developed encephalopathy 7 days after initiation of INH. In Case 1c (Table-I) encephalopathy developed after 2 months of INH therapy. Timing of INH encephalopathy is variable, it could be developed any time between 1st few days to 5 months of INH therapy, however recovery is more or less predicted, usually within 1 week of cessation of INH with supplemental pyridoxine.[5-7] A Higher dose of pyridoxine is recommended to prevent INH encephalopathy in CKD patient with tuberculosis.[8,9]

Our second case was ceftazidime encephalopathy. Ceftazidime is a most frequently used 3rd generation cephalosporin for treatment of sepsis. CNS toxicity from cephalosporin is termed as cephalosporin encephalopathy. After cefepime, ceftazidime is the most commonly responsible agent for this disorder.[10] Renal impairment is the most important risk factor for cephalosporin encephalopathy. Grill, M.F. and R. Maganti in 2008 described 19 patients of cephalosporin neurotoxicity, within them 13 had renal impairmen.[11] Older age and preexisting CNS disorder are other important risk factors.[12] Myoclonus, asterixis, seizures, non-convulsive status epilepticus and even coma can be associated with this condition. Cephalosporin encephalopathy is associate with characteristic EEG findings which include diffuse slow-wave delta activity, semi periodic tri phasic sharp wave activity, or frank periodic discharges, paroxysmal myoclonic or convulsive bursts may also be observed.[13-15] Underlying mechanism of their toxicity is to inhibition of GABAA receptor.[16] Withdrawal of the drug is associated with reversal of encephalopathy.[11] For myoclonus and seizures benzodiazepines or other anticonvulsants are often needed. In patient with renal failure dialysis hasten recovery. To prevent this toxicity dose adjustment according to age and CCR is recommended.

One of the frequently encountered drug induced encephalopathy in our setup is baclofen encephalopathy. Baclofen is a GABA agonist. It is commonly used for spastic low back pain and it also very effective in

resistant hiccup.[17,18] Baclofen is readily absorbed after oral administration, most of the absorbed drug eliminate from the body through kidney, only a small portion cross blood brain barrier to produce the desired pharmacological effec.[19] In renal impairment serum level of baclofen increased significantly even in lower dose, a cumulative dose of as little as 15 mg can cause severe toxicity.[20] It produces global depression of cerebral function leading to fatigue, syncope, hypotension, ataxia, psychological disturbances, and cardiovascular and respiratory depression.[21] In severe case it produce a state of reversible unarousable comma.[22,23] However the drug is readily dialyzable and cleared up from the body quickly, usually one or two hemodialysis session completely reverse the condition.[23,24] In our index case dialysis was not possible and it took longer time to resolve.

Conclusion

Not everyone develops an encephalopathy after taking a certain drug but it should be kept as a differential diagnosis when a disturbance of the consciousness is unclear especially in CKD patients.

Conflict of interest: Nothing to declare.

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