Bölüm 5

Review: Seizure and Epilepsy in Patients with Renal Diseases

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Abstract

More than 50 million individuals worldwide suffer from epilepsy, and concomitant conditions including decreased renal function can make managing the condition more difficult. It has been proven in many studies that the probability of convulsions is high in patients with kidney failure. Clinicians must understand how antiepileptic medications (AEDs) are influenced by decreased renal function and how epilepsy management strategies are affected by the kidneys in order to maximize epilepsy control in patients with kidney illness. On the otherhand, seizures are brought on in patient with renal failure by the buildup of toxins as well as by other conditions such as sepsis, hemorrhage, malignant hypertension, metabolic disturbances, and electrolyte abnormalities, acute dysequilibrium syndrome. Some antibiotics lower convulsive thresholds, putting patients at risk for status epilepticus. A thorough understanding of AED metabolism, their pharmacokinetic alterations in such disorders, careful use of concurrent drugs, and monitoring of AED serum levels are all necessary for effective seizure management in renal diseases. We wanted to remind the problems we face as clinicians and their solutions by reviewing the articles related to this review.

Introduction

Patient with chronic kidney disease are generally more prone to have seizure[1] due to their underlying kidney disease from different factors including uremia and it is toxins[2], electrolyte derangement such as hyponatremia, hypernatremia, hypomagnesemia, as well as metabolic derangement notably

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dysglycemia. On the other hand, patients with chronic kidney disease may have co-exsitıng epilepsy with their condition [3].

When the seizure is provoked due to the patient's underlying kidney dysfunction, the mainstay of management is to address and correct underlying metabolic derangement that caused the seizure such as uremic encephalopathy, electrolyte ımbalance. But sometimes due to the severity of the seizure it may be necessary to use anti epileptic drugs for a short time period. However, the type of antiepileptic medication should be carefully chosen, nevertheless, due to the fact that people with renal impairment will have altered drug pharmacokinetics.

Seizure in patient with renal impairment

Patients with renal impairment are generally prone to have seizures due to uremia which increases neuronal excitability provoking seizure. However, there is no single uremic compound that solely causes seizure but rather a combination of toxins. Uremic compounds cause encephalopathy, myoclonus and eventually generalized tonic clonic seizure[5]. The metabolites of creatine, guanidine compounds, are believed to be proconvulsant by inhibiting gamma-aminobutyric acid (GABA) receptors and stimulation of N-methyl-D-aspartate (NMDA) excitatory receptors which leads influx of calcium through voltage calcium channels and further activation of glutamate release and neuronal excitability[4].

Further, other factors that provoke seizure in patients with renal impairment are electrolyte imbalance, hyponatremia, hypernatremia, dysglycemia, hypomagnesemia, hypocalcemia, hypercalcemia, and acid base disturbance[6]. Sepsis in patients with renal impairment can provoke seizure due to disruption and increased permeability of blood brain barrier[7]. Dialysis disequilibrium disorder which is believed due to rapid dialysis or missing dialysis sessions may cause encephalopathy,seizure and cerebral edema[8,9].

As vascular events are more common in patients with renal impairment, acute stroke may result in symptomatic seizures. Subdural hematoma is another vascular factor which patients with renal impairment are more prone to due to following reasons: (1) uremic platelet dysfunction (2) coagulopathy during hemodialysis (3) decreased subdural cavity pressure[10].

Additionally, posterior reversible encephalopathy syndrome (PRES) is one of the causes of symptomatic seizures in patients with renal impairment. The syndrome is also characterized by other symptoms like headache, altered mental status, and visual disturbance because of a failure of cerebral

vascular autoregulation and extravasatıon and vasogenic edema in parietal and occipital area which can be seen on MRI[11]. This can occur due to: (1) uncontrolled hypertension (2) immunosuppressant use in patients with renal impairment who undergo renal transplantation, the culprit drugs are tacrolimus and cyclosporine. The seizure usually resolves by controlling blood pressure and stopping the offending drug but long term management of seizure may be needed.

Certain antibiotics such as penicillin, cephalosporins, carbapenems, and quinolones may cause cortical irritability and therefore cause seizure[12]. Cefepime is implicated particularly to cause seizure even when used within the renal dosage range[13]. Lastly, patients with renal impairment are more prone to have status epilepticus, convulsive or non-convulsive. Non-convulsive is more challenging to be diagnosed clinically, Clinicians must have a low threshold for ordering bedside electroencephalograms (EEG) for patients with persistent encephalopathy.

The management of provoked seizure in renal impairment involves addressing and reversing the underlying cause that provoked seizure. For Example, in uremic seizure the management would often be hemodialysis, in PRES, the management would be to control blood pressure and stop the culprit drug. However, this would not be enough in case of convulsive status epilepticus or non-convulsive status epilepticus, where it would be necessary to start antiepileptic drugs (AED). The choice of AED drug in this context will depend on the underlying cause of the acute symptomatic seizure and the comorbid conditions the patient has. But generally levetiracetam, phenytoin, carbamazepine and valproic acid will be a good choice with the appropriate renal adjustment needed.

Epilepsy and renal impairment

Epilepsy is a common neurological disorder which affects nearly more than 1% of the world papulation. As per the most recent definition by International League Against Epilepsy (ILAE) in 2014, epilepsy is occurrence of **(1)** at least 2 unprovoked seizure more than 24 hour apart or **(2)** one unprovoked seizure with having a high risk of additional seizure similar to the general recurrence risk after 2 unprovoked seizure (≥60%), this can be a due to remote structural lesion such as stroke, CNS infection. **(3)** lastly diagnosis of epilepsy syndrome[14].

Epilepsy can be classified as generalized or focal in origin. Generalized types can be further classified into tonic-clonic, tonic, a tonic, absence, myoclonic. Focal types can be classified into focal aware seizure(previously

known as simple partial seizure), focal impaired awareness(previously known as complex partial awareness), focal motor,non motor seizure and focal tonic to bilateral tonic clonic seizure[15].

One of the main goals for managing epilepsy is to optimize the quality of patients with epilepsy with anti epileptic drugs-AED- while balancing the side effects of this drug and controlling seizure adequately.

However,if the patient has comorbid conditions such as renal impairment this will pose a challenge to adequately control seizure given some AED are eliminated through the kidney altering the pharmacokinetics of this medication.So, in order to be able to select the appropriate AED in patients with epilepsy and renal impairment, one must be familiar with the pharmacokinetics of each drug and its metabolites since most of the new AED drugs undergo renal clearance.

Generally, in patients with renal dysfunction dose reduction is required when the drug or its metabolite is excreted at least 30% unchanged in the urine. On the other hand, dialysis patients may need post-dialysis dose replacement if the drug is dialyzable depending on its protein binding properties and molecular size[16].

Although it is rare, typically less than 1%, some AED may cause nephrotoxicity, this could be through idiosyncratic hypersensitivity reactions of some AED drugs or direct kidney injury.

Carbamazepine, phenytoin, primidone, and phenobarbital are examples of the AED drugs that can cause idiosyncratic hypersensitivity reaction, they cause systemic symptoms with eosinophilia (DRESS syndrome) which occasionally involves the kidney causing injury. On the other hand, valproic acid may cause direct renal dysfunction leading to fanconi syndrome by affecting mitochondria in the renal proximal tubular cells.

Some AED is reported to cause nephrolithiasis such as topiramate, acetazolamide, zonisamide, this side effect is increased in patients with reduced renal function, elderly people, diabetic patients, so close monitoring is needed in these patients

Renaly cleared AED such as levetiracetam, gabapentin, pregabalin, topiramate, eslicarbazepine, lacosamide and vigabatrin. Without a dose change, their elimination half life will be extended and their side effect profile will increase. Levetiracetam and gabapentin are great examples which could cause encephalopathy and excessive sedation respectively if dose adjustment is not done.

Non-renally cleared AED are also being altered their pharmacokinetics in renal impairment. This is because the accumulation of uremic toxins and hypoalbuminemia leads to reduced protein binding properties of highly bound AED which increases their free active part in the plasma and subsequent high adverse reaction[17].

This has its great significance when starting new AED in a renal impaired patient because in chronic administration, the high free active part will decrease with time due to increased drugs volume distribution and plasma clearance.Therefore, it will be necessary to monitor carefully in this patient if they are taking AED with high protein binding properties such as valproic acid and phenytoin. Unfortunately, free AED levels monitoring are not available widely, so physicians will need to interpret total AED levels cautiously. Additionally, there is new emerging evidence that renal impairment will also affect non renal cleared AED by affecting drug transporters and cytochrome P450 expressions throughout the body[18].

Patients with epilepsy and renal impairment undergo dialysis which may lead to partial or complete removal of some AED from the bloodstream which necessitates total or partial dose supplementation of AED. Several factors influence drug removal during dialysis, drug molecular size and the protein bound properties.

Since most AED have low molecular size which allows them to diffuse through dialysis filters easily, Drug protein bound properties are what determines which drug will be removed through dialysis and those who will not. protein drug complex will hinder diffusion through the dialysis membrane.thus drugs which are highly protein pound will be less likely to be removed such as valproic acid, phenytoin and carbamazepine and will not need dose supplementation post dialysis. On the other hand, drugs with low protein binding properties such as levetiracetam will more likely cleared by dialysis needing post dialysis supplementation.

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