

SEIZURE OCCURRENCE IN PATIENTS WITH CHRONIC RENAL INSUFFICIENCY IN REGULAR HEMODIALYSIS PROGRAM

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ABSTRACT - Hemodialysis-associated seizure is a complication of hemodialysis. This report describes the occurrence of seizures in patients with end stage renal disease on dialysis therapy at the Nephrology Institute of Mogi das Cruzes, São Paulo State, Brazil. A retrospective medical history of 189 patients was reviewed to investigate the occurrence of convulsive seizures during dialytic program. Seven patients with history of seizures were selected but five of them were included in our study. Three patients presented generalized tonic-clonic seizures, one had partial seizure with secondary generalization, and one presented unclassified seizure. Three patients presented seizure just during the dialysis (unique seizure) and one of them presented convulsive status epilepticus. The two other patients had already presented seizures prior the beginning of dialysis. We conclude that seizures in renal failure could be considered as occasional events that do not usually become chronic.

KEY WORDS: seizures, epilepsy, dialysis, renal failure.

Ocorrência de crises epiléticas em pacientes com insuficiência renal crônica em programa dialítico regular

RESUMO - Convulsões durante o tratamento dialítico podem constituir uma complicação da hemodiálise. Esse artigo descreve a ocorrência de crises em pacientes em estágio final de insuficiência renal crônica sob tratamento dialítico no Instituto de Nefrologia de Mogi das Cruzes, São Paulo, Brasil. Foram revistos os prontuários de 189 pacientes, com o objetivo de investigar a ocorrência de crises convulsivas durante o tratamento dialítico. Dos sete pacientes selecionados com história de crises, cinco concordaram em participar de nosso estudo. Três pacientes apresentaram crises generalizadas tônico-clônicas, um apresentou crise parcial com generalização subsequente e um apresentou crise inclassificada. Três pacientes apresentaram crises apenas durante o processo dialítico (crise única) sendo que um deles apresentou status epilepticus convulsivo. Os outros dois pacientes já haviam apresentado crises antes do início do tratamento dialítico. Nós concluímos que as crises convulsivas que ocorrem em pacientes com falência renal podem ser consideradas como eventos ocasionais e que usualmente não se tornam crônicas.

PALAVRAS-CHAVE: crises epiléticas, epilepsia, diálise, falência renal.

Epilepsy is characterized by chronic recurrent paroxysmal changes in neurological functions caused by abnormalities in the electrical activity of the brain¹. As epilepsy is considered to involve hyperexcitable neurons, a basic assumption in epilepsy research links the pathogenesis of epilepsy and the generation of synchronized neuronal activity with an imbalance between inhibitory [g-aminobutyric acid (GABA)-mediated] and excitatory (glutamate-mediated)

neurotransmission in favor at the latter². Approximately 2 million persons in the United States have epilepsy^{3,4} and each year, 100,000 new cases of epilepsy are diagnosed in the United States^{3,5}. The most commonly reported etiological factors are stroke, tumors, alcohol, head injuries, congenital factors and neuroinfections⁶. In Brazil, neurocysticercosis is the most frequently identified cause of epilepsy⁷. Bergen and colleagues⁹ reported an estima-

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ted incidence of seizure of approximately 10% in patients with chronic renal failure. Moreover, Plum and Posner⁹ also noted that convulsions occurred in one third of patients with end-stage renal disease (ESRD) and was frequently a preterminal event. The seizures in these series usually were generalized tonic-clonic type, however, the mechanism of reduced seizure threshold in renal failure is still unknown.

Hemodialysis-associated seizure (HAS) is a common complication of hemodialysis¹⁰. HAS occurs in 7% to 50% of children with ESRD, and their seizures are usually reported as generalized tonic-clonic seizures¹¹. On the other hand, non-convulsive seizures appear to be rare^{12,13}. Risk factors for HAS include young age, prior history of seizures, malignant hypertension, microvascular diseases, uremic encephalopathy and cardiomyopathy. Moreover, induced brain water disequilibrium, hypocalcaemia, uremic toxins, the use of acetate in the dialysate, intracranial hemorrhage due to systemic heparinization, treatment with recombinant erythropoietin, hemodynamic and metabolic defects, and drugs such as penicillin and theophylline are also considered responsible for HAS^{11,14,15}. The efficacy of anti-convulsant drugs in treating or preventing HAS is not well defined^{10,16}. Diazepam is a non-dialyzable anticonvulsant drug¹⁷ and the administration of oral diazepam (0.3-0.5 mg/kg per dose) 30 minutes before each hemodialysis session may help to prevent recurrence of HAS¹⁰. On the other hand, readily dialyzable antiepileptic drugs such as phenobarbital may increase the risk of HAS^{16,18}. Despite these observations, several lines of evidence support the idea that anaemia is one of the major limitations to rehabilitation in patients with ESRD. The efficacy of recombinant human erythropoietin in the treatment of renal anaemia is well established. However, this therapeutic approach has been associated with serious untoward effects: increased risk of hypertension, not infrequently accompanied by hypertensive encephalopathy and seizures^{19,20}.

Based on these facts, the aim of our study was to investigate the occurrence of seizures in patients with ESRD under regular hemodialysis program.

METHOD

A retrospective medical history of 189 patients was reviewed to investigate the occurrence of convulsive seizures in dialysis patients at the Nephrology Institute of Mogi das Cruzes. From 189 patients under dialytic treatment, 7 had suffered some type of convulsive seizure and were invited to participate in the study, but only 5 patients had agreed to participate. They were 4 males and 1 fe-

male, with a mean age of 42 years (range 20 to 72 years old). The five patients have severe systemic arterial hypertension and were using antihypertensive drugs. In our clinic, all patients have monthly evaluation of total calcium and were receiving aluminum hydroxide. The solution for the dialytic treatment contains 0.89 gr. of NaCl/5 L, with a calcium concentration of 3.5 mEq/L.

All patients were evaluated for initial disease, duration, type and frequency of HAS and then submitted to clinical and neurological examination. The mean time of dialysis treatment and the electroencephalography (EEG) was analysed in all patients. The seizures were classified according the Commission on Classification and Terminology of International League Against Epilepsy²¹. The possible seizure triggering factors, such as the use or withdrawal of medications, sleep deprivation, arterial hypertension, infections, and electrolytic imbalance, especially hypocalcaemia, were also investigated.

RESULTS

In our study we analyzed the data of 5 out of 189 patients recruited under dialytic treatment at the Nephrology Institute of Mogi das Cruzes. All 5 patients had severe systemic arterial hypertension and were using antihypertensive drugs. These patients were also using antiepileptic drug (phenytoin 200 mg/daily) and CaCO₃ (1500 mg/daily). The mean age of beginning of dialysis was 25 years. The mean duration of dialytic treatment was 5.8 years (range 2 to 12 years). The causes of renal failure were diabetic nephropathy (4 patients) and chronic glomerulonephritis (1 patient) (Table 1). All patients had normal aluminum plasma levels and were not affected by other clinical pictures that could be led to possible aluminum intoxication. The signs of Chvostek and Trousseau were absent in all patients and the neurological examination was normal in 4 patients, but one presented pyramidal syndrome (left hemiparesia with pyramidal signs), with abnormal CT scan (hipodensity on right temporal lobe).

The seizure history of the five patients is listed on Table 2. Briefly, three patients presented generalized tonic-clonic seizures, one presented partial

Table 1. Causes of renal failure.

Case	Age	Sex	Causes
1	23	Female	Chronic glomerulonephritis
2	20	Male	Diabetic nephropathy
3	45	Male	Diabetic nephropathy
4	44	Male	Diabetic nephropathy
5	72	Male	Diabetic nephropathy

Table 2. Seizure history.

Case	Seizures during dialysis procedure	Seizures at home	Type of seizure	Frequency of seizures
1	Yes	Yes	Unclassified	Five
2	Yes	Yes	Generalized tonic-clonic	Twice
3	No	Yes	Generalized tonic-clonic	Unique
4	No	Yes	Generalized tonic-clonic	Unique
5	No	Yes	Partial with secondary generalization	Unique (SE)

seizure. with secondary generalization, and one presented unclassified seizure. All patients had seizures at home, two patients had seizures during dialysis procedure and one of them had presented convulsive status epilepticus. Two patients had already presented seizures prior the beginning of dialysis treatment; one of them without detectable structural central nervous system lesion, and the other showed hipodensity on right temporal lobe (vascular cerebral disease). All patients presented normal interictal EEG. At time of seizure, none of them presented infection, electrolytic misbalance (hypocalcemia), sleep deprivation or were using theophyllin. All patients had anemia and were using erithropoetin.

DISCUSSION

Our study evaluated the occurrence of seizures in patients with ESRD under hemodialysis program. It has long been believed that seizures are relatively common events among patients with systemic diseases. HAS are commonly caused by metabolic encephalopathy, hypertensive crisis, infection, and dialysis disequilibrium¹³. We observed the occurrence of HAS in only 2% of our patients. In this way, our data are not in agreement with previous studies, which related an estimated incidence of seizure of approximately 10% in patients with chronic renal failure⁸.

The mechanism of reduced seizure threshold in renal failure is unknown. One possibility is the presence of proconvulsive metabolites, including guanidosuccinic acid, creatinine, and creatine in human subjects²². Moreover, the epileptogenic potency of these compounds was further supported by animal studies²³.

In spite of reports that prior history of seizure did influence the risk of seizures among patients receiving hemodialysis¹¹, we did not observe higher risk in our patients who had prior history of epi-

lepsy. It is difficult to make comparisons between our with other studies since different factors may influence the analysis, such as the age of the subjects, type of seizures and risk factors for HAS as previously mentioned.

It has long been believed that in the absence of prior clinically detected stroke, hypertension, particularly severe and uncontrolled; increase the risk of unprovoked seizures in older individuals²⁴. Conversely, some studies did not find an association between hypertension and seizures in the absence of clinically detected stroke^{25,26}. In addition, hypertension per se can induce alterations in the human brain morphology²⁷, increasing the risk for clinically apparent brain dysfunction (e.g. epilepsy). In this way, despite a high prevalence of hypertensive diseases in patients with ESRD and the stroke been one of the commonly reported etiological factors, just one of our patients that presented seizures had preceding cerebrovascular stroke.

It has also been observed that anaemia is one of the major limitations to rehabilitation in patients with ESRD and the efficacy of recombinant human erithropoetin in the treatment of this condition is well established. All our patients presented anaemia and were using erithropoetin. This therapeutic approach has been associated with seizures and could justify the seizures in our patients that were using erithropoetin^{19,20}.

At the present moment, the efficacy of antiepileptic drugs in treating or preventing HAS is not well defined. However, the administration of oral diazepam, a non-dialyzable drug, (0.3 - 0.5 mg/kg per dose) 30 minutes before each hemodialysis session has been shown to prevent the recurrence of HAS¹⁶. In our study, all patients were using phenitoin (200 mg/daily) which is in agreement with Rust and Chun¹⁶, who demonstrated that the use of phenobarbital, a dialyzable drug, did not prevent the HAS.

We conclude that seizures in renal failure can be considered as an occasional events that do not usually become chronic and information on the management of seizures in renal failure should be disseminated among professionals treating systemic diseases.

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