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SERUM CALCIUM AND MAGNESIUM ABNORMALITIES IN PATIENTS WITH STATUS EPILEPTICUS: A SINGLE CENTRE TERTIARY CARE EXPERIENCE

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ABSTRACT

Background: Electrolyte imbalances frequently cause seizures, and these seizures may be the sole presenting symptom. Seizures are especially common in patients with sodium disorders, hypocalcemia, and hypomagnesemia. Successful management of patient seizures begins with the establishment of an accurate diagnosis of the underlying electrolyte disturbance, because rapid identification and correction of the disturbance is necessary to control seizures and prevent permanent brain damage. **Objectives:** To delineate the percentage of people with status epilepticus having calcium and magnesium deficiencies at admission. **Methods:** The study was carried out from April 2013 to October 2013 at Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan. Seventy patients diagnosed with status epilepticus were enrolled in the study and frequencies of serum calcium & magnesium abnormalities were measured and compared. **Results:** Calcium level was low in 29 (41.4%) patients. Magnesium level was low only in 7 (10%) patients. Both calcium & magnesium levels were low in 7 (10%) patients. Among the known epileptics, 16 (76.1%) were on regular antiepileptic treatment. Among those on antiepileptic drugs, 8 (50%) had low calcium levels while 6 (37.5%) had low magnesium levels. **Conclusion:** Serum calcium level was lower in nearly half while magnesium in nearly 2/5th of the previously diagnosed epileptics who presented in status. Among those on antiepileptic drugs, 50% had low calcium levels while 37.5% had low magnesium levels. It is suggested that all epileptic patients, especially those on long term AEDs, should at least be worked up once in detail for electrolyte abnormalities as timely identification and correction can help reduce the morbidity and mortality associated with future status epilepticus.

Key words: Calcium; magnesium; status epilepticus; antiepileptics; mechanism of seizures.

INTRODUCTION

The incidence of status epilepticus ranges from 10.3 to 61.0 per 100 000 people, with the highest incidence reported in populations with low socioeconomic standards of living and quality of health care. The incidence of status epilepticus is high in the young and the old. [1, 2] There are an estimated 3 million cases of status epilepticus worldwide each year; of which 70% are generalized convulsive status epilepticus (GCSE) and about 75% of these cases are overt GCSE. [2, 3] The other main category is that of non-convulsive status epilepticus (NCSE). GCSE is associated with substantial mortality and morbidity. [2, 3] Electrolyte disturbances in the ICU are most common. Low magnesium, phosphate, and both very low and very high calcium values can cause seizures. Critical care physicians must be vigilant to suspect and identify electrolyte disturbances in their patients, because they are potentially a cause, of poor prognosis. [4] The main causes of status epilepticus include low blood concentrations of antiepileptic drugs in patients with chronic epilepsy, cerebrovascular accidents, anoxia or hypoxia, metabolic causes, alcohol or illicit drug withdrawal and miscellaneous causes. [5, 6] Despite recent improvements in its diagnosis and treatment, status epilepticus is still associated with significant mortality. Patients presenting with seizures show that main laboratory abnormalities present are leukocytosis, metabolic acidosis, anemia and hypomagnesaemia. [5] It is now common practice to obtain a complete blood count and chemistry profiles routinely in patients presenting with status epilepticus as electrolytes (e.g. sodium, calcium) abnormalities or basic metabolic disorders (glucose). [5, 6] The correct diagnosis of seizures secondary to these electrolyte abnormalities warrants sharp thinking and meticulous search as seizures may be the sole presenting symptom of electrolyte imbalance. Identification and correction of electrolyte

imbalances is a potentially manageable ailment that can effectively reduce the proportion of morbidity and mortality associated with hypocalcemic and hypomagnesemic seizures. There is insufficient local data on evaluation of electrolyte imbalances in epilepsy in Pakistan and therefore, health care takers at primary and secondary care levels are unable to acknowledge a potentially treatable cause of epilepsy without long term use of antiepileptics. The objective of this article is to delineate the percentage of people with status epilepticus having calcium and magnesium deficiencies at admission in order to highlight the importance of early recognition and therefore prompt targeted treatment of electrolyte related seizures.

MATERIALS AND METHODS

The study was carried out on inpatient of department of Neurology, Pakistan Institute of Medical Sciences (PIMS), Islamabad from April 2013 to October 2013. Seventy patients diagnosed with status epilepticus aged more than 12 years were included. The study was approved by hospital ethical committee and carried out according to international ethical standards of the responsible committee on human experimentation and with the latest version of Helsinki Declaration of 1975. Patients fulfilling the inclusion criteria were enrolled after taking informed written consent from the patients or relatives. Following information was collected: demographic data (age, gender), history of pre-existing epilepsy and use of antiepileptic drugs (AED), drug withdrawal, noncompliance to medication, clinical presentation (to ascertain/ define status epilepticus), routine laboratory tests, toxicology screen and brain imaging to ascertain the likely cause of status epilepticus. Routine laboratory investigations done in all patients at admission included complete blood counts, ESR, liver function tests, renal function tests, blood sugar random, serum electrolytes (sodium, potassium, calcium, phosphate and magnesium), urine routine examination, urine culture, blood cultures, arterial blood gases, serum albumin and AED drug levels. Corrected calcium was calculated for those with hypoalbuminemia. EEG was done in all patients within 24 to 48 hours of admission to monitor progress of management, to diagnose non-convulsive status epilepticus and to rule out other related abnormalities (e.g., encephalitis). Lumbar puncture (for CSF routine examination) and brain imaging (CT scan or MRI brain) was done in selected patients as per indications. All patients were managed according to the standard protocol for status epilepticus, along with full supportive care and cause specific treatment. Causes of status epilepticus were identified on the basis of history, physical examination, laboratory investigations, and/or neuroimaging studies. Factors precipitating status epilepticus were classified as: non compliance to antiepileptic drug, AED discontinuation within 48 hours (drug withdrawal), CNS infection, cerebrovascular disease, CNS structural lesions, systemic infections, metabolic/ electrolyte disturbances, illicit drugs/alcohol abuse, poisoning or idiopathic. The diagnosis of idiopathic status epilepticus was made if no apparent etiology was identified. The data was analyzed using SPSS version 16.0 (USA Inc.). Mean, Median, Mode, range and standard deviation were calculated for numerical variables i.e. age, serum calcium and magnesium. Frequency and percentages were presented for categorical variables i.e. gender, serum calcium and magnesium (normal, low, high), known epileptics, epileptics on AEDs and drug withdrawal.

RESULTS

Mean age was 32.8 ± 5.4 years, median was 27.5 years and mode was 22 years; with an age range of 77 (13-90) years. Among the 70 patients, 46 (46 out of 70; 65.7%) were females and 24 (24 out of 70; 34.3%) were males (Figure 1). 21 (21 out of 70; 30%) were known epileptics out of which 16 (16 out of 21; 76.1%) were on regular antiepileptic treatment. In those patients who were on antiepileptic drugs, there was history of antiepileptic drug withdrawal in 8 (8 out of 16; 50%) patients when they presented in status. Calcium level was low in 29 (29 out of 70; 41.4%) patients while it was normal in 41 (41 out of 70; 58.6%) patients. Range of calcium values was 1.24-2.50 mmol/ l with mean of 2.13 ± 0.24 mmol/l. Previously undiagnosed epileptics had low calcium in 19 (19 out of 49; 38.7%) patients. Previously diagnosed epileptics had low calcium in 10 (10 out of 21; 47.6%) patients. Those who were on antiepileptic drugs, 8 (8 out of 16; 50%) had low calcium levels. Overall, 9 (9 out of 24; 37.5%) male patients and 20 (20 out of 46; 43.4%) females had low calcium values. Magnesium level was low only in 7 (7 out of 70; 10%) patients and it was normal in 63 (63 out of 70; 90%) patients. Range of Magnesium values was 0.25-1.00 mmol/l with mean value of 0.81 ± 0.15 mmol/l. Previously undiagnosed epileptics had low magnesium in 4 (4 out of 49; 8.1%) patients. Previously diagnosed epileptics had low magnesium in 3 (3 out of 21; 14.2%) patients. Those who were on antiepileptic drugs, 6 (6 out of 16; 37.5%) had low magnesium levels. Overall, 2 (2 out of 24; 8.3%) male patients and 5 (5 out of 46; 10.8%) females had low magnesium values. Both calcium & magnesium levels were low in 7 (7 out of 70; 10%) patients (Figure 1). Comparison of

gender showed that proportion of status was almost double in females (female:male 1.9:1). All those with hypomagnesaemia invariably had hypocalcaemia.

DISCUSSION

Electrolyte abnormalities affect many organs and tissues, including the brain. Most of the clinical manifestations of electrolyte abnormalities are predominantly neurologic and parallel the severity of neuronal damage.[7, 8] Acute and severe electrolyte abnormalities may appear with seizures, or with rapidly progressive neurologic symptoms and signs, which needs emergency treatment. Seizures are especially common in patients with hypocalcemia and hypomagnesemia. Seizures occur in 20–25% of patients with acute hypocalcemia as a medical emergency, and in 30–70% of patients with symptomatic hypoparathyroidism. [9, 10] Successful management of seizures starts with the establishment of an accurate diagnosis of the underlying electrolyte abnormalities, because rapid identification and correction of the disturbance is important to control seizures and prevent permanent brain damage. [11, 12] Electrolyte (e.g., sodium, calcium) abnormalities or basic metabolic disorders (glucose) are reported in some patients with status. [13, 14] Generalized tonic-clonic, focal motor, and (less frequently) atypical absence or akinetic seizures may be the sole presenting symptom in hypocalcemia. [10] Generalized tonic–clonic seizures can occur in neonates and adults in association with severe hypomagnesemia as well. [15, 16] According to one study, 10% of patients had a metabolic disorder as the primary underlying etiology of status epilepticus. [13] According to our study, 41.4% of patients presenting as status had low calcium level which is higher percentage than the percentage reported in previous studies. [13] According to our study, magnesium level was low in 10% patients who presented in status epilepticus. Our results are comparable to that of Aguset al. who showed that hypomagnesemia occurs in nearly 12 % of hospitalized patients. [14] According to Singhiet al., magnesium disturbances in critically ill children admitted to pediatric intensive care unit show that hypocalcemia and hypermagnesaemia occurs in 60% and 4% of patients, respectively. The incidence of low RBC-Mg (magnesium) in their study was 17.3 episodes per 100 patient days. Mortality was nine-fold higher in hypomagnesemic (30%) compared with normomagna-esemic (3.3%) patients. If magnesium and calcium both were low, the mortality rate was 33% in contrast to nil if both were normal. [17] According to our study, both calcium & magnesium levels were low in 10% of patients who presented in status. Reportedly, most patients with acute symptomatic convulsive status epilepticus have either acute metabolic derangement (electrolyte imbalance, hypoglycemia, hypocalcemia, or hypomagnesemia) or an acute CNS infection. [17, 18] A study from Pakistan by Khalid et al. showed high male to female ratio i-e-, 2.4 to 3:1 for these electrolyte abnormalities while our study showed that 65.7% were females and 34.3% were males (1.9:1) i-e-, high female to male ratio (Figure 1). [5]

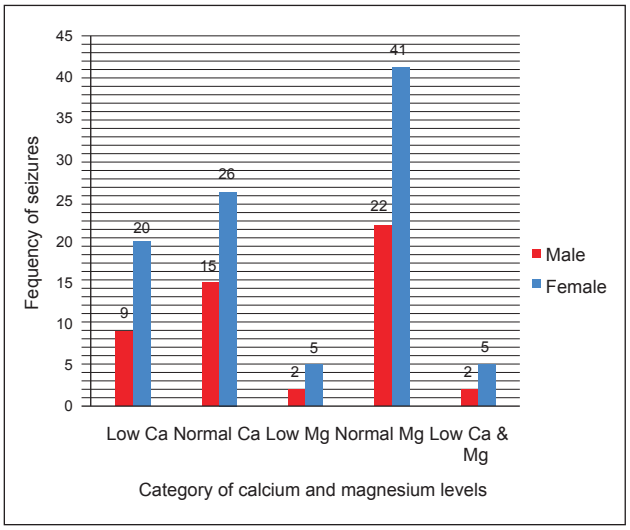

Figure 1: Frequency of normal and abnormal calcium and magnesium levels among males & females. According to our study, 30% were known epileptics out of which 76% were on antiepileptic treatment. Among these, there was history of antiepileptic drug withdrawal in 50% when they presented in status. In a study by Aminoffet al., the etiology, clinical features and outcome of status epilepticus in 98 patients over the age of 14 years have been reviewed. The most common single cause of the status was noncompliance with anticonvulsants and this accounted for status in 53% of patients which is almost similar to our findings. [19] Non-convulsive status epilepticus secondary to hypocalcemia has also been reported. Seizures can occur without muscular tetany in patients with hypocalcemia. EEG changes associated with hypocalcemia include evolution from alpha through theta and delta dominance. Other EEG findings are generalized spikes, sharp-waves burst of delta activity with sharp components. [2,20] Because neurologic symptoms of electrolyte disorders are functional rather than structural, the neurologic manifestations of electrolyte disturbances are typically reversible. [11, 12] Electrolyte homeostasis in the central nervous system is very essential for brain function. [13, 18] Regulation of ionic balance is an essential process involving a complex array of molecules for moving ions into and out of the

brain and involving blood–brain barrier function as well as mechanisms in the membranes of both neurons and glia. Alterations in ion gradients across cellular membranes have direct and indirect effects on neuronal discharge and may facilitate epileptiform activities. [21, 22] Hypocalcemia and hypomagnesemia cause mainly CNS neuronal irritability with seizures. When the extracellular concentration of calcium ions falls below normal, the nervous system becomes progressively more excitable, because this causes neuronal membrane permeability to sodium ions, allowing easy initiation of action potentials. At plasma calcium ion concentrations about 50 percent below normal, the peripheral nerve fibers become so excitable that they begin to discharge spontaneously, initiating trains of nerve impulses that passes to the peripheral skeletal muscles to elicit tetanic muscle contraction. Consequently, hypocalcemia causes tetany and seizures because of its action of increasing excitability in the brain. As mechanics of calcium at cellular level are dependent on serum magnesium levels, hypomagnesemia via causing hypocalcemia causes the same (Figure 2). [18, 22]

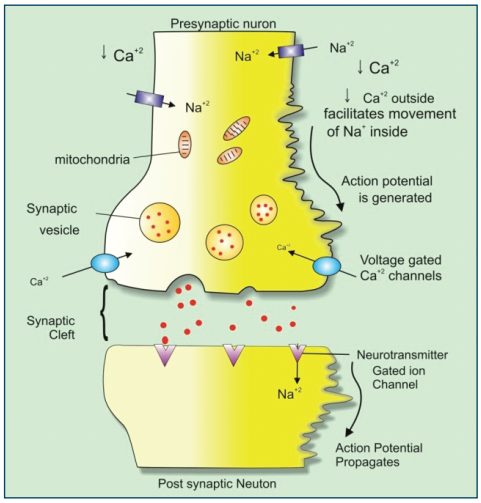

Figure 2: Molecular mechanisms behind seizures secondary to hypocalcaemia: Hypocalcaemia facilitates movement of sodium ions into the nerve, thus causing spontaneous discharge of electrical activity.

Main treatment for hypocalcemic seizures is calcium replacement; AEDs are typically not needed. AEDs may abolish both overt and latent tetany, whereas hypocalcemic seizures remain refractory. However, those in status may benefit from AEDs. The inhibition of N-methyl-d-aspartate (NMDA) glutamate receptors and the increased production of vasodilator prostaglandins in the brain is the anticonvulsant action of magnesium. Magnesium serves to stabilize neuronal membranes and the lack of it explains the tendency to have seizures in the first place. [23, 24] Also, mechanism of calcium regulation on neurons is coherent with magnesium levels and hypomagnesaemia in itself interferes with the action of calcium at cellular level. [12, 16] In the setting of seizures or symptomatic or severe (<1.2 mg/dl, <1 mEq/L) hypomagnesemia, it is advisable to inject 1-2 g of MgSO4 (magnesium sulfate) over a 5-min period, to be followed by an infusion of 1-2 g of MgSO4 per hour for the next few hours. If seizures persist, the bolus may be repeated. [17, 24] Serum calcium level is tightly regulated by parathyroid hormone (PTH) and 1, 25-dihydox -yvitamin D in humans. It is important that one should take a look at background factors that have significant effects on calcium and its' regulating hormones. Among these, vitamin D insufficiency, magnesium depletion and treatment with bisphosphonates, glucocorticoids and anticonvulsants are most important. A complete workup of epilepsy, therefore, should include workup for calcium, magnesium, phosphorus, albumin, vitamin D and PTH levels at least in addition to brain imaging and EEG (electro encephalogram). [11, 15] Status epilepticus is an under diagnosed entity in Pakistan. It is a potentially reversible condition but has a high mortality if not recognized and managed on time. [25] According to our study, among those on antiepileptic drugs, 50% had low calcium levels while 37.5% had low magnesium levels. Keeping the above statistics in mind, it is suggested that patients on long term AEDs should at least be worked up once in detail for electrolyte abnormalities as timely identification and correction can help reduce the morbidity and mortality associated with future status epilpeticus. As such, in the long run, being a potentially treatable cause, epilepsy secondary to electrolyte imbalances can be effectively treated without long term unnecessary use of antiepileptics and can help reduce both the burden of follow-up epilepsy in neurology clinics as well burden of cost on both the patients and the health care system.

CONCLUSION

Calcium level was abnormal in 41.4% of patients while magnesium was low in 10% of patients. Serum calcium level was lower in nearly half while magnesium in nearly 2/5th of the previously diagnosed epileptics who presented in status. Among those on antiepileptic drugs, 50% had low calcium levels while 37.5% had low magnesium levels. It is suggested that all epileptic patients, especially those on long term AEDs, should at least be worked up once in detail for electrolyte abnormalities as timely identification and correction can help reduce the morbidity and mortality associated with future status epilepticus.

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All authors contributed equally to this work. They performed the literature search, did data collection, analyzed the data and wrote the paper. All the authors meet the criteria for authorship as established by ICMJE.