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Acute Symptomatic Seizures Caused by Electrolyte Disturbances

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In this narrative review we focus on acute symptomatic seizures occurring in subjects with electrolyte disturbances. Quite surprisingly, despite its clinical relevance, this issue has received very little attention in the scientific literature. Electrolyte abnormalities are commonly encountered in clinical daily practice, and their diagnosis relies on routine laboratory findings. Acute and severe electrolyte imbalances can manifest with seizures, which may be the sole presenting symptom. Seizures are more frequently observed in patients with sodium disorders (especially hyponatremia), hypocalcemia, and hypomagnesemia. They do not entail a diagnosis of epilepsy, but are classified as acute symptomatic seizures. EEG has little specificity in differentiating between various electrolyte disturbances. The prominent EEG feature is slowing of the normal background activity, although other EEG findings, including various epileptiform abnormalities may occur. An accurate and prompt diagnosis should be established for a successful management of seizures, as rapid identification and correction of the underlying electrolyte disturbance (rather than an antiepileptic treatment) are of crucial importance in the control of seizures and prevention of permanent brain damage.

Key Words EEG, electrolyte, epilepsy, seizures, hyponatremia, hypernatremia, hypocalcemia.

INTRODUCTION

Electrolyte abnormalities are commonly encountered in clinical daily practice, and their diagnosis relies on routine laboratory findings. Electrolyte disturbances may affect the brain among many other organs and tissues and need to be promptly recognized as they may lead to severe and life-threatening complications when overlooked or not appropriately treated. The neurological manifestations reflect the severity of acute neuronal derangement and therefore require emergency treatment.[1-3] Acute and/or severe electrolyte imbalances can manifest with rapidly progressive neurologic symptoms or seizures, which may be the sole presenting symptom. Seizures are more frequently observed in patients with sodium disorders (especially hyponatremia), hypocalcemia, and hypomagnesaemia.[3] Table 1 shows the different degrees of the electrolyte disturbances discussed in this review. An accurate and prompt diagnosis should be established for successful management of seizures, as rapid identification and correction of the underlying electrolyte disturbance are of crucial importance in the control of seizures and prevention of permanent brain damage.[2-4]

In this narrative review we focus on acute epileptic seizures occurring in subjects with electrolyte disturbances. Quite surprisingly, despite its clinical relevance, this issue has received very little attention in the scientific literature, with only a very few reviews specifically dealing with electrolytes disturbances and seizures published so far.[3,4]

To conduct this review we selected the most relevant data from the available literature on this topic identified by searching PubMed using the search terms "seizures" or "epilepsy"

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Table 1. Different degrees of the electrolyte disturbances that most frequently cause seizures

Electrolyte disturbance	Mild	Moderate	Severe
Hyponatremia	130–134 mEq/L	125–129 mEq/L	<125 mEq/L
Hypernatremia	145–149 mEq/L	150–169 mEq/L	≥170 mEq/L
Hypocalcemia	1.9–2.2 mEq/L		<1.9 mEq/L
Hypercalcemia	2.5–3 mEq/L	3–3.5 mEq/L	3.5–4 mEq/L
Hypomgnesemia	0.8–1.6 mEq/L		<0.8 mEq/L

combined with "electrolyte", "hyponatremia", "hypernatremia", "hypocalcemia", "hypercalcemia", "hypomagnesemia", "hypokalemia", and "hyperkalemia". Publications were chosen based on the quality of data and their relevance to the present review.

After an initial overview of this topic, which serves as general introduction, we discuss the risk of seizures according to each type of electrolyte disturbance.

A GENERAL OVERVIEW

The orderly function of the nervous system depends on its electrical excitability, which is maintained through a voltage gradient across neuronal and glial membranes by means of metabolically driven ion pumps. Alterations of electrolyte gradients across cellular membranes exert both direct and indirect effects on neuronal excitability and synchronization, and the consequent abnormal neuronal discharge may facilitate epileptiform activities.[5] Specifically, there are several clinical conditions, such as dehydration or renal failure, which can be associated with substantial modifications of plasma osmolality and electrolyte balance, determining marked alterations in brain metabolism and function leading to increased risk of seizures.

In a recent proposal by the International League Against Epilepsy (ILAE) acute seizures were defined as "a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult."[6] Suggestions were made to specify the brain insult as "events occurring within 1 week of stroke, traumatic brain injury, anoxic encephalopathy, or intracranial surgery; at first identification of subdural hematoma; at the presence of an active central nervous system (CNS) infection; or during an active phase of multiple sclerosis or other autoimmune diseases." In addition the ILAE suggest to make a diagnosis diagnosis of an acute symptomatic seizure "in the presence of severe metabolic derangements (documented within 24 h by specific biochemical or hematologic abnormalities), drug or alcohol intoxication and withdrawal, or exposure to well-defined epileptogenic drugs."[6]

Since electrolyte disturbances are, at least in the early stages, generally not associated with morphologic changes in CNS, the neurologic manifestations are typically reversible.[2-4,7]

However, seizures and the electrolyte disturbance itself can lead to structural alterations, so that the underlying electrolyte disturbances should be recognized and treated before the brain tissue injury becomes permanent.

Disorders of sodium and osmolality can be responsible for an encephalopathy characterized by depression of neuronal activity, with confusion, headache, psychomotor slowing and lethargy as the major clinical manifestations, usually associated with signs of irritability. Hypercalcemia and hypermagnesemia may also produce both a neuronal depression with encephalopathy and neuronal irritability. Hypocalcemia and hypomagnesemia lead almost exclusively to CNS irritability clinically manifesting with seizures, whereas disorders of potassium rarely produce symptoms in the CNS, with muscle weakness being their major clinical manifestation.[2,3,7]

The main causes of electrolyte disturbances leading to acute seizures are reported in Table 2.

Seizures occurring in patients with sodium disorders, hypocalcemia, and hypomagnesemia,[2,3,7] are usually generalized tonic-clonic, but also focal (partial) seizures or other seizure types may be present. Rapidly evolving electrolyte disturbances are more likely to cause seizures than those developing more gradually. It is therefore difficult to define absolute levels of electrolyte above or below which seizures are likely to occur.[3,7]

To identify the electrolyte disturbances leading to seizures, a complete serum chemistry evaluation, including measurements of sodium, calcium, and magnesium should be performed, in particular in subjects with a first-time seizures.[3,8,9] Since between 15 and 30% of acute symptomatic seizures among elderly patients occur in the setting of toxic-metabolic causes,[10] this diagnostic workup is particularly important in the elderly.

In a review of 375 adult cases of status epilepticus, 10% had a metabolic disorder as the primary etiology and mortality in this subset of patients was as high as 40%.[11]

Acute seizures due to electrolyte disorders may occur at any age, including infancy. When evaluating a first nonfebrile seizure occurring in children, the American Academy of Neurology has recommended that laboratory screening tests should be ordered based on individual clinical circum-

Table 2. Main causes of electrolyte disturbances

Electrolyte disturbances	Main causes
Hyponatremia	Depletion of circulating volume
	Congestive heart failure
	Cirrhosis
	Diarrhea
	Disorders leading to increased antidiuretic hormone (ADH) levels
	Syndrome of inappropriate ADH secretion
	Adrenal insufficiency
	Hypothyroidism
	Pregnancy
	Recent surgery
	Excessive water intake
	Polydipsia
	Drugs
	Thiazide diuretics, desmopressin, mannitol, sorbitol, glycine, carbamazepine, oxcarbazepine, eslicarbazepine
Hypernatremia	Excessive water loss
	Impairment in access to water (infants, elderly)
	Diarrhea
	Central of nephrogenic diabetes insipidus
	Drugs (mannitol)
	Overload of sodium
	Hypertonic sodium solutions
	Water moving into cells
	Convulsive seizures
	Severe physical exercise
Hypocalcemia	Hypoparathyroidism
	Post-surgical (thyroidectomy, parathyroidectomy)
	Idiopathic
	Secondary hyperparathyroidism in response to hypocalcemia (renal failure)
	Drugs
	Bisphosphonates
	Calcitonin
	Severe vitamin D deficiency
	Insufficient calcium intake (malnutrition)
	Infants of mothers with vitamin D deficiency
Hypercalcemia	Malignancy
	Drugs
	Thiazide diuretics
	Vitamin D intoxication
	Lithium
	Primary hyperparathyroidism
Hypomagnesemia	Loss of magnesium
	Diarrhea
	Abuse of laxatives
	Drugs (loop and thiazide diuretics, cyclosporines, aminoglycoside antibiotics)

stances.[12] More specifically, an electrolyte disturbance should be suspected (and laboratory tests ordered) in presence of vomiting, diarrhea, dehydration, or whenever the child has not returned to baseline alertness.[12] Despite these recommendations, the epidemiological data show that electrolyte disturbances (especially hyponatremia) represent a frequent cause of acute symptomatic nonfebrile seizures in patients of any age.[1-5] Consequently, we think that these relatively inexpensive and widely available laboratory tests should be systematically ordered in each patient presenting with a first

acute seizure.

Electrolyte disturbances may cause diffuse brain dysfunction that can be assessed by means of EEG recording. In general, the most prominent feature of the EEG record in metabolic encephalopathies is a slowing of the normal background frequency. If serial EEGs are performed, a gradually progressive disorganization of the EEG recordings over the course of the disease can usually be noted. Moreover, reactivity to photic or other types of external stimulation is frequently altered.[13] EEG evolution generally correlates well with the severity of encephalopathy; more specifically, the degree and severity of EEG abnormalities correlate with the rate of change of electrolyte balance rather than with the absolute level of a specific electrolyte or metabolite.[14]

However, EEG recordings have little specificity in differentiating between the various etiologies of encephalopathy. In fact, in metabolic encephalopathies, EEG patterns are usually unspecific, including various degrees of diffuse slowing, epileptiform discharges, intermittent rhythmic slow activity, and occurrence of triphasic waves, which are usually reversible after treatment of the underlying causes.[13,15]

HYPONATRIEMIA

Hyponatremia is defined as a serum sodium level of less than 135 mEq/L and is considered severe when the serum level is below 125 mEq/L.

Clinical features

The clinical manifestations of hypotonic hyponatremia are largely related to CNS dysfunction and are more conspicuous when the decrease in serum sodium concentrations is severe or occurs rapidly (within hours). The major clinical complications from acute hyponatremia are brain cell swelling and herniation with neurologic symptoms being evident when hyponatremia approaches 120 mEq/L. The risk of cerebral edema and neurologic manifestations is minimized if the decline in serum sodium occurs slowly and gradually (≥48 h), even in case of a marked absolute reduction of serum sodium values. Conversely, in case of a rapid decrease in serum sodium (acute hyponatremia), cerebral edema with neurologic symptoms are likely to occur.[16,17]

The neurological symptoms of hyponatremia therefore go in parallel with the severity of cerebral edema, and are less frequently induced by chronic than by acute hyponatremia: approximately half of the patients with chronic hyponatremia are asymptomatic, even with serum sodium concentration less than 125 mEq/L.[16,17] Symptoms in these patients rarely occur until the serum sodium is less than 120 mEq/L and are more usually associated with values around 110 mEq/L or lower.[3] Particularly the children are at high risk of developing symptomatic hyponatremia, because of their larger brain-to-skull size ratio. Severe and rapidly evolving hyponatremia may cause seizures, which are usually generalized tonic-clonic, and generally occur if the plasma sodium concentration rapidly decreases to <115 mEq/L.

Age and gender of the patient as well as other several factors influence the clinical outcome of neurological complications of hyponatremia. Children and women in childbearing age (rather than postmenopausal women) are the most susceptible subjects:[18,19] in a retrospective study hyponatremia was the only detectable cause of seizures in 70% of infants younger than 6 months.[19]

Women seem to be particularly prone to develop postoperative hyponatremia.[20] A case control study conducted in 65 adults with postoperative hyponatremic encephalopathy and 674 adult patients who had postoperative hyponatremia without encephalopathy showed a similar risk of developing hyponatremia and hyponatremic encephalopathy after surgery in women and men. Surprisingly, women in childbearing age had a 25-fold increased risk of death or permanent neurologic damage compared with either men or postmenopausal females.[20] Consequently, it is advisable to maintain a low threshold for hyponatremia and hyponatremic encephalopathy in the event of headache, vomiting, nausea or lethargy occurring after surgery, especially in women in childbearing age.[20]

Hyponatremia represents a frequent cause of epileptic seizures, as shown in a recent prospective observational multicenter study where acute epileptic seizures and focal neurological deficits were identified in 5% of patients with severe (<125 mEq/L) hyponatremia.[21]

Several etiologies may lead to hyponatremia, some of them affecting almost exclusively adults and some mostly children and infants.

In adults, generalized seizures have been reported as the first manifestation of multihormonal pituitary hormone deficiency causing normovolemic hyponatremia.[22]

Administration of some drugs, such as desmopressin[23,24] or thiazide diuretics,[25] may also lead to hyponatremia and seizures. To date, 54 cases of hyponatremia secondary to desmopressin treatment for enuresis presenting with altered mental status or seizures have been reported. In 47 of them an intranasal formulation had been used, while excess fluid intake was documented as a contributing factor in at least 22 cases. In most cases the neurological complications developed 14 days or less after starting desmopressin.[24]

Thiazide diuretics may cause hyponatremia in up to 14% of patients receiving these drugs (more commonly females, elderly subjects and subjects of low body weight), and may

cause confusion, falls and seizures.[25]

Although also tricyclic antidepressants cause frequently hyponatremia, seizures associated with hyponatremia are more frequently observed in subjects taking selective serotonin reuptake inhibitors.[26-28]

Several clinical conditions including fever (with true volume depletion) or polydipsia may also lead to hyponatremia. A study assessed the impact of fever on sodium values in children presenting with seizures during a gastroenteritis episode.[29] While the presence or absence of fever did not affect seizure characteristics or duration, mild hyponatremia (sodium levels between 126 mEq/L and 134 mEq/L) was found to affect some seizure features, particularly seizure duration, with increased risk of status epilepticus. In fact, children with hyponatremia had more prolonged seizures than patients with normal serum sodium levels (6.4 minutes vs. 1.9 minutes, respectively), irrespective of body temperature. In most cases, the seizures last less than 3 minutes (range: several seconds to 20 minutes).

Polydipsia, commonly seen in patients with psychiatric disturbances, is another cause of hyponatremia with increased risk of seizures. A retrospective cross-sectional study was carried out to study the association between different levels of hyponatremia and the occurrence of epileptic seizures in patients without a prior epilepsy diagnosis.[30] The authors identified from the database of a Swedish County hospital 363 in patients who were had serum sodium levels <125 mEq/L. Medical records were reviewed and 11 patients with seizures secondary to hyponatremia were identified. Seizures were the only neurologic manifestation of hyponatremia in the subjects with serum sodium levels >115 mEq/L. Marked increases in the frequency of their complex partial seizures due to hyponatremia was observed in five patients with epilepsy and polydipsia-hyponatremia with a decrease in the serum sodium level to 118−127 mEq/L.[31] In all cases, patients had received antipsychotic drugs, and the serum sodium levels returned to normal through restriction of fluids with consequent decrease in seizure frequency. As this study shows, hyponatremia caused by polydipsia is a risk factor for aggravation of habitual seizures in patients with epilepsy and psychiatric disorders.

Other conditions reported to be associated with hyponatremia and seizures are the ingestion of sodium phosphate or sodium picosulfates/magnesium citrate combination, which are commonly used to evacuate the colon and rectum before colonoscopy or colorectal surgery,[32] or polyethylene glycol preparation.[33]

Children and especially infants are particularly at risk of developing hyponatremia. A retrospective review reported 130 infants with hyponatremia (<136 mEq/L) associated with respiratory syncytial virus bronchiolitis in infants requiring intensive care. Four infants (4%) had seizures at admission (sodium 114−123 mEq/L), and were successfully managed with hypertonic saline infusions followed by fluid restriction, resulting in immediate termination of seizure activity and normalization of serum sodium values over 48 hours.[34]

Two infants had water intoxication associated with hyponatremic seizures (sodium levels 116 mEq/L and 121 mEq/L) after consumption of commercial bottled drinking water for infants.[35]

Hyponatremia should therefore be suspected in any infant less than 6 months old presenting with acute seizures and a body temperature of ≤36.5 degrees C.[36] In these patients, hyponatremia needs to be promptly recognized and treated to avoid complications, although improvement in neurologic function after correction of hyponatremia is usually more rapid in children than elderly patients.[37]

Although the American Academy of Neurology recommends that laboratory screening tests for electrolytes should be ordered based on individual clinical circumstances such as vomiting, diarrhea or dehydratation,[12] the epidemiological data show that hyponatremia is a frequent cause of acute symptomatic nonfebrile seizures in children. Consequently, laboratory tests should be systematically ordered in each child presenting with acute seizures.

Finally, it is noteworthy to mention that the antiepileptic drugs (AED) carbamazepine (CBZ), oxcarbazepine (OXC), and eslicarbazepine (ESL) may themselves represent a cause of hyponatremia due to syndrome of inappropriate antidiuretic hormone.[37] Possible mechanisms for this effect are an altered sensitivity to serum osmolality by the hypothalamic osmoreceptors and an increased sensitivity of the renal tubules to antidiuretic hormone.[37]

AED-induced hyponatremia is usually asymptomatic, although in some cases it may result in headache, confusion, general malaise, somnolence and in exacerbation of seizures.[38-41]

CBZ, OXC, and ESL may lead to hyponatremia in a relevant number of patients. One comparative study showed a much higher incidence of hyponatremia (defined as sodium levels ≤134 mEq/L) in patients treated with OXC compared to those receiving CBZ (29.9% vs. 13.5%; $p<0.0001$). Of note, sodium levels ≤128 mEq/L were found in 12.4% of patients treated with OXC and in 2.8% of those receiving CBZ ($p<0.001$).[42] Hyponatremia during CBZ therapy seems to be particularly common in patients with intellectual disability,[43] which therefore should be considered a subset of subjects particularly at risk. A subsequent study found an incidence of severe (sodium levels ≤128 mEq/L) and symptomatic hyponatremia of 11.1% and 6.8%, respectively, in patients

treated with OXC.[44] Age, AED polytherapy, and the concomitant use of diuretics were found to be independent risk factors for sever hyponatremia following OXC treatment.[44] Recently, also ESL (the most recent AED structurally similar to CBZ to be marketed) has been shown to be associated with hyponatremia (sodium values ≤134 mEq/L) in 12.5% of patients affected by post-stroke seizures; in 10% of these patients, hyponatremia was symptomatic and in 3% it was asymptomatic.[45]

The frequency of AED-induced hyponatremia is therefore particularly common after OXC administration, especially in the elderly or in patients taking diuretics. Incidence of hyponatremia following OXC appears to be dose dependent (in one study an increase of 1 mg in the dosage of OXC was shown to increase the risk of hyponatremia by 0.2% and may be prevented by a slower and lower titration-initiation schedule.[46] Routine plasma sodium monitoring for patients receiving OXC is not usually necessary, except for patients receiving AED polytherapy or sodium depleting drugs (e.g., thiazide diuretics), affected by sodium-depleting disorders, or in the elderly.[44,47] Conversely, monitoring of sodium serum levels are mandatory in patients under OXV therapy developing symptoms suggestive of hyponatremia (headache, confusion, general malaise, somnolence) and in those with unexplained worsening of seizures.[46,47] Although no specific guidelines are available, these recommendations can be reasonably extended to patients receiving CBZ, ESL and other sodium depleting drugs.

EEG abnormalities

Hyponatremia usually produces nonspecific EEG slowing. A very severe hyponatremia may initially cause posterior slowing followed by diffuse delta activity. However, a variety of other EEG abnormalities have been described, such as triphasic waves, burst of high-voltage rhythmic delta activity, and central high voltage 6-Hz to 7-Hz activity with stimulation-induced paroxysms of delta waves. Periodic lateralized epileptiform discharges may also occur, while full seizure activity is very rare.[13,48]

A case of polydipsia-induced hyponatremia causing *de novo* nonconvulsive status epilepticus was associated with focal EEG discharges.[49] After recovery from status epilepticus, EEG showed some spikes in the left frontal area. In this case it is reasonable to hypothesize that hyponatremia induced by polydipsia precipitated epileptogenicity in the left frontal area, and then focal activity secondarily generalized and led to status epilepticus.

Treatment

Hyponatremic seizures represent an ominous sign and hence a medical emergency, as they are associated with high mortality.[2] Thus, a prompt recognition and treatment of acute symptomatic hyponatremia is of utmost importance as secondary brain damage may be rapid and irreversible, even in subjects with mild clinical symptoms.[13] Since a small increase in the serum sodium concentration can substantially reduce cerebral edema, seizures induced by hyponatremia can be controlled by increasing the serum sodium concentration.[14] However, improvement in neurologic function may occur several days after correction of the electrolyte abnormality, particularly in elderly patients.[50]

The most common treatment for hyponatremia consists of hypertonic saline (3%), which produces a rapid reduction in brain volume and intracranial pressure. An increase in serum sodium to values of 120 mEq/L to 125 mEq/L should be the target of therapy. Of note, more aggressive treatment of hyponatremia with hypertonic saline solution carries the risk of shrinkage of the brain leading to osmotic demyelination syndrome manifesting with severe neurologic symptoms such as quadriplegia, pseudobulbar palsy, coma, and even death.[2,3,13]

The sodium concentration should therefore be corrected at a rate of 0.5 mEq/L/h. Higher correction rates (a rate of 1 mEq/L to 2 mEq/L/h) have been used young patients at a risk for respiratory arrest, severe neurologic sequelae, and death[14,51] and appear to be well tolerated in children.[52]

Hyponatremia induced by AED or other sodium-depleting drugs may be managed through water restriction, reduction of the dose and, if necessary, discontinuation.[47]

HYPERNATREMIA

Hypernatremia is defined as a serum sodium concentration in plasma >145 mEq/L.

Clinical features

While hyponatremia is often the cause of seizures or status epilepticus, hypernatremia is more likely to be the consequence of convulsive seizure activity (especially generalized tonic-clonic seizures). In fact, during seizures intracellular glycogen is metabolized in the muscle to lactate. Since intracellular osmolality of muscle fibers increases (lactate is more osmotically active than glycogen), water moves into cells, causing hypernatremia. A few minutes after the onset of hypernatremia, loss of water from brain cells determines an increased intracellular brain cell osmolality and shrinkage of the brain.

The degree of CNS disturbance in hypernatremia is therefore related mainly to the rate at which the serum sodium increases.[53] In acute hypernatremia, the combination of hy-

perosmolality and shrinkage in brain volume (especially in infants) results in an encephalopathy due altered synaptic structure and function of CNS cells.[3,7] Conversely, in chronic hypernatremic states, the risk of brain shrinkage with subsequent neurological symptoms is minimized. A slow, gradual increase in sodium values to levels as high as 170 mEq/L is often well tolerated. Severe symptoms of hypernatremia are primarily neurologic and usually result from an acute (i.e., within hours) elevation in the plasma sodium concentration to >158−160 mEq/L. Values >180 mEq/L are associated with a high mortality rate, in adults more frequently than in children.[53] In infants with hypernatremia seizures are typically absent, but can occur in case of inadvertent sodium loading or aggressive rehydration.[3,53]

In patients with hypernatremia the rupture of cerebral veins, as well as the intracerebral and subarachnoid hemorrhages, which are induced by brain shrinkage, can in turn provoke seizures.[3] Although rapid sodium loading can cause seizures, convulsions are more frequently seen during rapid correction of hypernatremia, and in ≤40% of patients treated for severe hypernatremia by rapid infusion of hypotonic solutions.[3,6]

Treatment

The treatment of hypernatremia consists of replenishing body water, thus restoring osmotic homeostasis and cell volume at a rate that avoids significant complications. The speed of correction depends on the speed of development of hypernatremia and accompanying symptoms.[53,54] In subjects with prolonged hypernatremia, cerebral edema may occur when the osmolality is abruptly normalized; this correction may therefore lead to convulsive seizures, coma, and death. The targeted correction of chronic hypernatremia should not exceed 0.5−0.7 mEq/L/h and 10 mEq/L/day to avoid complications.

In subjects with acute hypernatremia the treatment may be more rapid, and a decrease in the serum sodium concentration by 1 mEq/L/h can be considered appropriate.[54]

Patients with hypernatremia may be treated with hypotonic fluids, such as hypotonic saline or dextrose solutions given orally or, if this approach is not feasible, intravenously.

Importantly, the volume should be restricted to that required to correct hyperosmolality to prevent the risk of cerebral edema, which increases with the volume of the infusate.[53]

HYPOCALCEMIA

Hypocalcemia is defined as a plasma calcium level of <8.5 mg/dL or an ionized calcium concentration <4.0 mg/dL.

Clinical features

The symptoms of hypocalcemia depend on the degree of hypocalcemia and the speed of the decrease in the serum calcium concentration.[55] Acute hypocalcemia primarily causes increased neuromuscular excitability and tetany.

The typical CNS manifestations of acute hypocalcemia are mental status changes and seizures.[2,3,7] Generalized tonic-clonic, focal motor, and (less frequently) atypical absence or even akinetic seizures may occur in patients with hypocalcemia even without muscular tetany.[2,3,7] Hence, seizures can represent the unique presenting symptom of hypercalcemia.[2,3,55] Nonconvulsive status epilepticus secondary to hypocalcemia has also been reported.[56] Seizures are a frequent complication of acute seizures: they have been reported in 20−25% of patients with acute hypocalcemia, and in 30−70% of patients with idiopathic hypoparathyroidism.[57,58]

The main etiologies of hypocalcemia are hypoparathyroidism, severe vitamin D deficiency (VDD) and drugs (Table 2).

Hypoparathyroidism, usually as a complication of thyroidectomy, is a common cause of hypocalcemia. Characteristics of seizures at presentation, occurrence of subclinical seizures during follow-up, and the effect of AED withdrawal has recently been assessed in 70 patients with IH.[59] Seizures were present in 64% of patients (87% of them being generalized tonic-clonic), and were treated with phenytoin (47%), valproate (40%), and CBZ (27%). Most (69/70) patients were seizure-free during the follow-up of 6.6±4.5 years. Ten of 14 (71.4%) patients were successfully withdrawn from AED and remained seizure free during the follow-up period of 13.5±2.4 months (range 9−18). In few patients AEDs were restarted because of the recurrence of seizures (n=3) and poor compliance with calcium/vitamin D intake (n=1). The mean serum total calcium increased from 1.9±0.19 to 2.1±0.14 mEq/L after AED withdrawal.

Two cases with generalized tonic-clonic seizures as the first manifestation of postoperative hypoparathyroidism, appearing months and years after thyroidectomy have been described.[60] Thus, iatrogenic (i.e., postoperative) hypoparathyroidism needs to be considered in the differential diagnosis of adult-onset, generalized, tonic-clonic seizures even if the thyroidectomy was performed years earlier.

Hypocalcemic seizures may also occur in subjects with severe VDD, frequently in children and during the neonatal period.[61-64] Overall, seizures during the neonatal period have a broad differential diagnosis.[61] Unlike in developing countries, where VDD and hypocalcemia constitutes a major cause of infantile seizures, the number of neonatal seizures attributed to hypocalcemia in developed countries has decreased dramatically due to the obligatory vitamin D supplementation. In developed countries, most infants presenting

with hypocalcemic seizures have underlying endocrinological etiologies rather than dietary insufficiencies.[61,62]

The incidence of hypocalcemic seizures secondary to VDD in children in the UK and Ireland have been investigated in one study.[62] Ninety one confirmed or probable cases were reported, equating to an overall annual incidence of 3.49 per million children aged 0−15 years. Incidence was significantly greater in males compared to females, in infants compared to older children, and in children of South Asian or Black ethnicity compared to children from white ethnic backgrounds. The authors concluded that current implementation of public health policy in the UK is not successful in preventing children from developing one of the severe manifestations of VDD.

Severely-malnourished children presenting with hypocalcaemia have an increased risk of death than those without hypocalcaemia.[63] In this subset of patients, the prevalence of hypocalcaemia has been reported to be as high as 26%.[62] Acute diarrhea, convulsive seizures, and lethargy on admission to hospital are the main clinical predictors of hypocalcemia in these children. The presence of these features in hospitalized children with severe acute malnutrition should alert clinicians about the possibility of hypocalcemia and may help undertake potential preventive measures, in particular calcium supplementation. Also infants with rickets may be particularly prone to acute convulsive seizures due to hypocalcemia.[64]

A possible link between acute neonatal seizures, hypocalcemia and subsequent severe intellectual disability has been assessed in 149 adults with 22q11.2 deletion syndrome.[65] A history of neonatal seizures and neonatal hypocalcemia were significant predictors of a more severe level of intellectual disability, suggesting that neonatal seizures may increase the risk for more severe intellectual deficits in 22q11.2 deletion syndrome, likely mediated by neonatal hypocalcemia.

A study conducted in UK among children presenting to the emergency department identified 89 patients with a low vitamin D level (total vitamin D levels less than 50 nmol/L), with 83% of those having very low vitamin D levels (less than 25 nmol/L).[66] Seizures were present in 17% of patients, whose most common ethnic origins were Pakistani (37%) and black African (11%). Thus, acute seizures following hypocalcemia due to severe VDD should be particularly suspected in children from developing countries or with specific ethnic origins.

Furthermore, it is important to remind that maternal VDD is commonly observed in nursing mothers of infants diagnosed with rickets and that mothers of infants presenting with hypocalcemic seizures invariably have severe VDD.[67,68] Hypocalcemic seizures in infants secondary to maternal VDD might be prevented by supplementation of vitamin D.[67]

Although rarely, hypocalcemic seizures may also follow the administration of zoledronic acid, an aminobisphosphonate that is administered annually against osteoporosis.[69]

Chvostek's and Trousseau's signs are two physical findings resulting from a neuromuscular hyperexcitability due to latent tetany associated with reduced serum ionized calcium may provide clues to a diagnosis of hypocalcemia, although they have no value in differentiating among the various etiologies leading to this electrolyte imbalance. Chvostek's sign is a contraction of the ipsilateral facial muscles, ranging from minimal twitching of the lip to spasm of all muscles, elicited by tapping the facial nerve just anterior to the ear. Conversely, Trousseau's sign refers to the occurrence of a carpopedal spasm (i.e., adduction of the thumb, flexion of the wrist and metacarpophalangeal joints, and extension of the interphalangeal joints) following inflation of a sphygmomanometer above systolic blood pressure for three minutes.

A study assessed the clinical utility of Chvostek's sign in 154 patients with seizures (epilepsy, n=91; non-epileptic event, n=41; febrile convulsion, n=19; hypocalcemic seizure, n=3).[70] While patients with febrile convulsions or non-epileptic seizures had either negative or mild Chvostek's sign, a marked Chvostek's sign was only found among those with the diagnosis of epilepsy or hypocalcemia. Normocalcemic patients had no other signs of neuromuscular hyperexcitability while those with hypocalcemia manifested positive Trousseau's sign and other signs of neuromuscular hyperexcitability.

EEG abnormalities

Early EEG abnormalities associated with hypocalcemia include slowing of background rhythm with evolution from alpha through theta and diffuse increase in slow wave activity in the theta and delta range. Generalized spikes, sharp-waves burst of delta activity with sharp components, have also been reported and associated with absence seizures.[13] Neonatal EEG recordings may show reversible 3- to 4-Hz spike-waves discharges.[71]

Treatment

The indication for urgent therapy for hypercalcemia usually reflects the severity of neurological symptoms and the degree of hypocalcemia. Acute hypocalcemia is an emergency that requires prompt attention, and patients with symptomatic hypocalcemia should be treated immediately because of the highly associated morbidity and mortality. Treatment with intravenous calcium is the most appropriate therapy. Doses of 100 mg to 300 mg of elemental calcium should be infused intravenously over a period of 10 min to 20 min. Calcium-infusion drips should be started at 0.5 mg/kg/h and continued for several hours, with close monitoring of calci-

um levels.[55] Hypocalcemic seizures should be treated with calcium replacement, while AEDs are typically not needed. Interestingly, AEDs may abolish both overt and latent tetany, whereas hypocalcemic seizures may remain refractory.[57,71,72] Obviously, the treatment of hypocalcemia should be directed at the underlying disorder, and oral calcium repletion is commonly prescribed for outpatient treatment.

HYPERCALCEMIA

Hypercalcemia is defined as serum calcium levels of ≥2.5 mmol/L.

Clinical features

Hypercalcemia (especially that related to malignancy) is much more common than hypocalcemia,[2,3,55] but is less frequently associated with acute seizures. The most common symptoms of severe hypercalcemia (defined as calcium levels higher than 3.5 mmol/L) are related to disturbances of nervous system and gastrointestinal function.[2,3,60]

A rapid increase to moderate (12−13.9 mg/dL) hypercalcemia frequently results in marked neurologic dysfunction. On the contrary, chronic severe hypercalcemia (≥14 mg/dL) usually causes only minimal neurologic symptoms.[73]

The main neurologic manifestations of hypercalcemia are drowsiness, lethargy, weakness, and confusion. Hypercalcemia is associated with reduced neuronal membrane excitability, and thus only rarely causes seizures. However, hypercalcemia-induced hypertensive encephalopathy and vasoconstriction have been hypothesized to be responsible for seizures.[3,14,74]

EEG abnormalities

In subjects with hypercalcemia EEG abnormalities (fast activity and burst of delta and theta slowing) appear when calcium levels are higher than 13 mg/dL. At higher calcium levels, increased background slowing (mainly frontal), paroxysmal theta/delta bursts, and triphasic waves can be observed.[13,75] Diffuse and more occipital spike-slow-wave complexes may also appear, possibly due to a calcium-mediated vasospasm in the posterior cerebral circulation, which can be noted with very high calcium levels.[76] In most cases, normalization of calcium levels improves, even if gradually, the EEG pattern.

Treatment

The urgency of treatment depends on the presence of clinical manifestations and the underlying cause of the problem, rather than on the serum calcium levels. Severe hypercalcemia should be treated aggressively with hydration and administration of medications used to decrease calcium serum level such as intravenous bisphosphonate (e.g., pamidronate or zoledronate) or calcitonin.[55] First, vigorous rehydration with normal saline should be initiated at a rate of 200 to 500 mL/h, monitoring fluid overload. Then 20−40 mg furosemide may be administered intravenously, after rehydration has been achieved. If high calcium levels persist, the use of intravenous bisphosphonates (pamidronate or zoledronate), and in second line of glucocorticoids, calcitonin, mithramycin, gallium nitrate, may be considered.

In subjects with chronic or asymptomatic hypercalcemia the management can be limited to treatment of the underlying disorder with hypocalcemic diet, although oral bisphosphonates may also be administered.

HYPOMAGNESEMIA

Hypomagnesemia is defined as a plasma concentration of magnesium <1.6 mEq/L; magnesium values lower than 0.8 mEq/L represent severe hypomagnesemia.

Clinical features

Magnesium has membrane-stabilizing effects and interacts with N-methyl-D-aspartate glutamate receptors which, when activated, leads to a massive depolarization of neuronal networks and bursts of action potentials.[77] Magnesium also acts as a voltage-dependent calcium channel antagonist and prevents membrane depolarizations. Furthermore it leads to an increased production of vasodilatatory prostaglandins in the brain.[78] Symptoms of hypomagnesemia usually occur at serum ionized Mg^{2+} levels lower than 1.2 mg/dL, although they do not always correlate with Mg^{2+} concentrations. The most important clinical features of hypomagnesemia are neuromuscular irritability, CNS hyperexcitability, and cardiac arrhythmias. Seizures (usually generalized tonic-clonic) can occur in neonates and adults in association with severe hypomagnesemia, usually at levels <1 mEq/L.[2]

HIV-seropositive patients and children are particularly prone to develop acute seizures and statu epilepticus following hypomagnesemia, although the mechanisms leading to this propensity are unclear.[79] Hence, all HIV-seropositive patients with new-onset seizures should undergo metabolic screening including renal function and serum magnesium levels.[79]

Also children (especially infants) may experience seizures following severe (magnesium levels <0.8 mEq/L) hypomagnesemia. In a pediatric study conducted in West Indies, 3% of children aged 6 months to 8 years presenting with fever and seizures to the emergency department had hypomagnesaemia.[80] In these patients hypomagnesemia was consid-

ered to be the cause of seizures, as meningitis or an underlying bacterial infection were excluded, as well as hyponatremia, hypocalcaemia or hypoglycemia.

Hypomagnesemia has recently been recognized as an important side effect of proton pump inhibitors (PPIs), and also several cases of hypomagnesemia-induced seizures in subjects taking PPIs have been reported.[81,82]

Treatment

Mild (magnesium levels between 0.8 mEq/L and 1.6 mEq/L) and/or asymptomatic hypomagnesemia can be treated with oral administration of magnesium (e.g., magnesium gluconate), usually given in divided doses (total daily dose of 500 mg). Symptomatic or severe (<1.2 mg/dL, <1 mEq/L) hypomagnesemia, especially if seizures are present, requires an injection of 1 to 2 g of magnesium sulfate over a 5-min period, followed by an infusion of 1 to 2 g per hour for the next few hours, which may be repeated if seizures persist. In patients with renal insufficiency, these dosages should be reduced.[2,83] During treatment potassium and magnesium levels should be closely monitored. In women with eclampsia/preeclampsia, magnesium sulfate 4-g to 6-g loading dose diluted in 100 mL fluid should be given intravenously over 15 minutes, followed by continuous intravenous infusion at 1 to 2 g per hour, which can be discontinued 24 hours after delivery or last seizure.[77,84] Intravenous magnesium has also been administered in status epilepticus, even in the absence of evidence of magnesium deficiency.[85,86] The infusion should be given at doses that increase serum level from 0.81 mM to 3.5 mM (loading dose and then continuous infusion).

POTASSIUM ABNORMALITIES

Unlike other electrolyte abnormalities, hypokalemia or hyperkalemia rarely cause symptoms in the CNS, and seizures do not occur. Changes in the extracellular potassium serum levels exert their effects mainly on the function of the cardiovascular and neuromuscular systems. Severe potassium abnormality may therefore provoke fatal arrhythmias or muscle paralysis before CNS symptoms appear.[2,3,86]

THE EPILEPTOLOGICAL POINT OF VIEW

Seizures occurring as a consequence of electrolyte imbalance do not entail a diagnosis of epilepsy, but are currently classified as acute symptomatic seizures. The key point and at the same time the clinical problem is to assign a seizure to a cause. According to Shorvon[87] a causal relationship is present when the following five criteria should be fulfilled.

1) Temporal association: The exposure to the risk factor, in this case electrolyte disturbance, should precede the development of a seizure.

2) Strength of association: The greater the difference on patients with or without a certain electrolyte disturbance is, the more likely it is a true association.

3) Consistency: the association should be reducible.

4) Biological gradient: There should be evidence for a dose response.

5) Biological plausibility: The mechanisms of seizure generation should be related to the electrolyte abnormality.

With electrolyte disturbances and acute seizures the temporal relationship is most often the clue to the diagnosis. For metabolic conditions with subsequent alterations of homeostasis such as in the case of electrolyte imbalance, a diagnosis of acute symptomatic seizures should be made by taking into consideration specific cutoff values having high specificity in order to reduce the risk of false positive (i.e., the risk that the seizures were not caused by a metabolic derangement).[6] To classify a seizure as acute symptomatic due to metabolic condition, the proposed cutoffs and a temporal relationship of the seizure (usually less than 24 h) need to be met.[6] The greatest problem in interpreting the studies on electrolyte disturbances and seizures is the criterion of a biological gradient. In acute electrolyte derangements there seems to be an association with the severity of symptoms, especially with hyponatremia, but in chronic forms severe abnormalities are tolerated without any clinical signs. To assign a seizure in chronic electrolyte abnormality is sometimes impossible, and prudent clinical judgment is necessary to manage acute symptomatic seizures in electrolyte disturbance the patient appropriately.

Unlike epilepsy which is defined as "a disorder characterized by an enduring predisposition to generate epileptic seizures",[88] acute symptomatic seizures are not necessarily characterized by such a tendency to recur,[6,89] unless the underlying causal condition reoccurs. It is however of great importance to treat the underlying cause, as acute symptomatic seizures carry a higher early mortality, compared to unprovoked seizures.[89]

As a consequence, most patients experiencing acute symptomatic seizures may not need a prolonged antiepileptic treatment, although they necessarily require a simultaneous management aimed at resolving the underlying cause of the seizures.[6,90] Obviously, when choosing an AED to treat acute symptomatic seizures, it is reasonable to prefer medications which are easily and rapidly administered and have no influence themselves on electrolyte balance as it is the case with CBZ, OXC or ESL acetate.[90]

CONCLUSION

Seizures represent an important clinical manifestation of electrolyte disorders and are more frequently observed in patients with hyponatremia, hypocalcemia, and hypomagnesemia. In these subjects, the successful management of seizures begins with an accurate diagnosis of the underlying electrolyte disturbances. Complete serum chemistry, including sodium, calcium, and magnesium, should therefore be part of the initial diagnostic workup in patients with seizures. Early identification and correction of these disturbances are necessary to control seizures and prevent permanent brain damage, as AED alone are generally ineffective if the electrolyte disorder persists. In fact, treatment of seizures secondary to electrolyte imbalances is determined by the underlying cause of the disturbance, and in most cases administration of AED is not necessary as long as the underlying disturbance is rectified.[2-4,6] The physicians should therefore be aware of the existence of acute seizures due to electrolyte disturbances and have an understanding of the underlying medical conditions leading to electrolyte imbalance, for this may provide the means of controlling the disease and initiate a rapid and appropriate therapy.

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