

No-brain seizures origin - a review

Crisis convulsivas de origen no encefálicas - revisión

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Resumen

Cerca del 9% de la población presentará al menos una crisis a lo largo de la vida. La convulsión es la manifestación neurológica más frecuente en los departamentos de emergencia, correspondiendo a cerca del 1-5% de las atenciones, excluyendo el trauma. Objetivo del presente trabajo es discutir diagnósticos diferenciales para crisis convulsivas de origen no encefálico. Revisión de la literatura a través del PubMed, MEDLINE, Google Scholar, Casos Clínicos, EBSCO, Scielo y Temas de Radiología. Se utilizaron 60 trabajos publicados entre 1927 a 2016. Las crisis convulsivas pueden ocurrir debido a la suspensión brusca de medicamentos antiepilépticos, lesiones estructurales encefálicas, disfunciones metabólicas, intoxicaciones exógenas e interrupción brusca de benzodiazepinas y barbitúricos. También existen infecciones sistémicas o del sistema nervioso central, como meningitis, encefalitis y abscesos. Sólo una pequeña parte no tiene causa definida. Existen diversas causas de crisis convulsivas. Se debe saber hacer el diagnóstico diferencial entre ellas, pues no toda crisis convulsiva debe ser crónicamente tratada con antiepilépticos.

Palabras clave: Convulsión, Estado de Mal Epiléptico, diagnóstico diferencial.

Abstract

About 9% of the population will have at least one seizure lifelong. Seizures are the most common neurological manifestation in the departments of emergency, corresponding 1-5% of cases, excluding trauma. The objective of this paper is to discuss differential diagnoses seizure of non-brain origin. Review of the literature using PubMed, MEDLINE, Google Scholar, Clinical Trials, EBSCO, Scielo, and Radiology topics. Selected 60 papers according to inclusion and exclusion criteria due to 1927-2016. Seizures may result from abrupt discontinuation of use of antiepileptic drugs, structural lesions, metabolic disorders, poisoning, the abrupt cessation drugs such as benzodiazepines and barbiturates. There are also cases as, infections systemic or central nervous system such as meningitis, encephalitis and abscesses. Only a small portion has no defined cause. There are several etiologies to consider when we discuss about seizure. It is of utmost importance to keep in mind the differential diagnoses of seizures, because not every seizure is brain originated and do not need always be treated chronically with anti-epileptics.

Key words: Convulsion, seizure, status epilepticus, differential diagnosis.

Introduction

Epilepsy is a chronic condition characterized by recurrent seizures in the absence of triggering external events. Epileptic crises represent an abnormal electrical discharge, excessive and synchronous, a neuronal group, occurring spontaneously or secondarily to exogenous events, such as fever, electrolyte disturbances or even an encephalitic. Convulsions are epileptic crisis with motor manifestations. Seizures associated with localized changes in posterior areas of the brain with visual, auditory, or exclusively sensory symptoms as well as the absences that are not displayed motor activities, no seizures are called. Finally, the Status Epilepticus (SE) is defined as more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of the level of awareness among crises¹. Currently, some authors have proposed time periods lower as diagnostic criteria for SE, based on the fact that most of the crises that spontaneously give way do the first 5-10 minutes of your beginning².

About 9% of the population will have at least a crisis during the lifetime.³ The frequency of seizures is higher in pediatric patients and is associated with a lower threshold of the immature brain. At least one seizure occurs in 6% of children. Seizures are the most common neurological manifestation in emergency departments, accounting for about 1-5% of cases, excluding trauma⁴. The incidence of SE for the Brazilian population is around 90,000 cases / year. The mortality rate associated with SE is very variable and can reach up to 58% of deaths, depending on the etiology. It is highly dependent on the etiology and affected age group^{3,4}.

Seizures can be classified as caused, for example, caused by disease, cranial trauma (TBIs), metabolic disorders, among other etiologies; as unprovoked when there triggering factors identifiable targets and as idiopathic unprovoked, and those in which the clinical and electroencephalographic findings are well defined, leaving the term idiopathic reserved for genetic epilepsies⁵.

The determination of the etiology of seizures has changed significantly since the introduction of neuroimaging methods, especially computed tomography (CT) brain. In the decade of 70 already proposed an anatomic electroclinical

assessment for classification of epileptic syndromes, such the relevance of CT for the etiologic diagnosis of same. It is currently believed that the best method to investigate structural changes in cerebral seizures is magnetic resonance imaging (MRI). CT, however, still appears as an important diagnostic tool⁶. Seizures may result from abrupt discontinuation of use of antiepileptic drug (AED), structural lesions (stroke, cranial tumors and traumas), metabolic disorders (hypo or hyperglycemia, changes in levels of calcium, sodium, magnesium, phosphorus, urea and creatinine) of poisoning (theophylline, imipenem, isoniazid, clozapine, cyclophosphamide, fentanyl, meperidine, propoxyphene and intravenous beta-lactam antibiotics) and abrupt withdrawal of drugs such as benzodiazepines and barbiturates. There are also other cases, caused by systemic infections or central nervous system infections such as meningitis, encephalitis and abscesses. Only a small part has no definite cause⁷. The objective of this paper is to discuss briefly some of the main differential diagnoses for seizures of not-brain origin.

Methods

In this article, the authors reviewed the literature in order to clarify a number of etiologies related to seizures of non-cerebral origin, proposing a new algorithm for performing a differential diagnosis for seizures admitted at the emergency room. We include non-brain injury cases and include the brain injury cases. Review of the literature using PubMed, MEDLINE, Google Scholar, Clinical Trials, EBSCO, Scielo, radiology topics. Found 256 papers, were selected 60 according to inclusion and exclusion criteria due to 1927-2016. Among the seizures of non-cerebral origin cited there are electrolyte disturbances, metabolic disorders, infectious tropical diseases, cancers, among many other causes. Therefore, conducted a systematic review of the recent literature in several languages, using the descriptors "Seizures" and "Status epilepticus".

Etiologies

1. Febrile seizures

Febrile seizures (FS) is defined as sei-

zure accompanied by fever (greater than or temperature of 38°C by any measurement method) that occurs in children from 6 to 60 months without evidence of infection or inflammation of the central nervous, metabolic changes and no previous history of seizures. Febrile seizures are the most common neurological disorder of childhood and it is estimated that 2% to 5% of children under five years of age will present at least one episode of seizures in fever duration in life⁸.

The treatment of febrile seizures encompasses acute phase, prevention and guidance to family members. Most crises ends before the patients arrive at the emergency room and the doctor most often assesses the child already in the post-ictal period. Post-treatment of febrile seizures in the acute phase should be done as any seizure⁹. Given the benign characteristics of simple febrile seizures and potential adverse effects of anticonvulsant therapy is not recommended prophylactic treatment to prevent recurrence of crises, only lower the temperature and eliminate the underlying cause. No medication has been shown to reduce the risk of afebrile attack after a simple febrile seizure¹⁰.

2. Infectious

2.1 Dengue, Chikungunya and Zika

The three diseases are transmitted by the same vector, *Aedes aegypti*, however the etiological agents are distinct. The Chikungunya virus is caused by CHIKV, the zika by ZIKV virus, dengue already presents five different serotypes, DEN-1, DEN-2, DEN-3, DEN-4 and DEN-5¹¹.

In atypical cases dengue can affect the central nerve system, causing classic signs and neurological symptoms associated with the acute phase, as, convulsion, delirium, insomnia, restlessness, irritability and depression. To these may be associated discrete meningism without change in level of consciousness or focal neurological impairment, sensory depression, seizures and behavioral disorders, as well as pyramidal signs and meningeal involvement signals.^{11,12} Atypical cases in Chikungunya that affects central nervous system are more common in newborns. The signs and symptoms of central nervous system are similar to those found in dengue^{11,12}. Atypical cases of involvement of the

central nervous system by Zika virus are more common than in dengue and Chikungunya. The signs and symptoms of central nervous system are similar to those found in dengue^{11,12}.

The definitive diagnosis is made by serology or PCR. All three diseases are treated with symptomatic, hydration and rest. Importantly, aspirin, and NSAIDs should be avoided, especially in dengue, where its use is already contraindicated. It is preferred the use of painkillers^{11,12}.

2.2 Malaria

Malaria is a potentially serious infectious disease caused by protozoa of the genus *Plasmodium*, which is transmitted by the bite of the *Anopheles* mosquito. By the denomination of "nervous malaria" are grouped clinical forms in which it highlights the involvement of the central nervous system. Almost all cases of nervous malaria is caused by *Plasmodium falciparum*, with few cases reported in the literature caused by *Plasmodium vivax*^{13,14}.

Infection of individuals not immunized by *P. falciparum* may result in serious and complicated form, characterized by involvement and dysfunction of various organs or systems: central nervous system, hematopoietic system, respiratory system, liver, cardiovascular system, kidneys and coagulation sanguínea^{13,14}. The corresponding clinical involvement of the nervous system consists of neurological and psychiatric symptoms. Neurological signs, the predominant disturbance of consciousness ranging from drowsiness to coma, convulsions that, in general, are the generalized type, can sometimes manifest itself in the form of status epilepticus. Motor disorders can occur, such as myoclonus, hemiplegia, monoplegia, impairment of cranial nerves (facial and ocular motor) and cerebellar ataxia. Meningeal irritation signs are discreet and sensory manifestations are difficult to be perceived. Changes may occur at deep tendon reflexes and can be noticed the Babinski sign, unilaterally or bilaterally. Sometimes occurs intracranial hypertension syndrome. It should also highlight the shock, respiratory changes and thermal deregulation that, at least in part, can be attributed to a neuroaxial involvement^{13,14}.

3. Vaccination

Vaccines can produce adverse effects

that depend on individual susceptibility, their composition and vaccine programming errors. These aforementioned factors are responsible for many of the local and systemic manifestations that can occur in a variable period of time, and minutes or hours to weeks or months.¹⁵⁻¹⁸ Systemic adverse effects are rare and present in about 10% of vaccinated patients, the most common are fever, irritability, muscle pain and malaise. Much less frequent systemic reactions are febrile seizures, anaphylaxis, hypotonic hiporreativa syndrome, thrombocytopenia and irritability. Fever is considered a normal body reaction in the presence of various stimuli (immunogenic, toxic metabolites, conditions, etc.) and occurs at a frequency between 1% - 50% of vaccinees¹⁵⁻¹⁸.

Several studies indicate that febrile seizures are always trivial and self-limited, appear on the first day, when the temperature rises or falls sharply, almost always above 38 °C, and is associated with a high percentage vaccinees with Pertussi component. Its evolution depends on the duration and the number of seizures occurring in the same febrile process. The literature indicates that children with a greater tendency to have seizures in the presence of fever, are those with a predisposition, that is, those who inherit from their parents. This inheritance is present in 20-30% of cases¹⁵⁻¹⁸.

4. Cardiac and Vascular

4.1 Arrhythmias

There is a correlation between EEG abnormalities and changes in heart rate (HR) with epileptiform activity. It is not known if seizures are due to arrhythmias or arrhythmias generate seizures. However, both relationships have been cited in studies. The frequency of cardiac arrhythmia as epileptic manifestation is not well determined. Cardiac disorders are described in epileptic patients, the most frequent being heart rhythm disturbances, especially the increase in HR¹⁹⁻²³.

Li et al. Studied 61 electrocardiographic complex partial seizures originated in the temporal lobe of 20 patients and found a 39% rate of tachycardia and bradycardia in 5%. There are few serious cardiac arrhythmia records associated with epilepsy, such as Brugada syndrome²⁰. Pritchett et al., described two cases of severe arrhythmia, possi-

bly related to epilepsy²² and Constantin et al., described five patients with bradycardia as epileptic manifestation, drawing attention that this unusual cause of cardiac arrhythmia should be considered in the differential diagnosis of syncope²³. Keilson et al., studied the electrocardiogram during electroencephalographic record of 338 patients with epilepsy, and found no difference in the incidence of severe cardiac arrhythmia in these patients and the normal population²⁰.

Identifying seizure causing cardiac arrhythmia is needed, as it implies specific therapy with anti-epileptic drugs. The identification of cardiovascular abnormalities related to seizures, leading to cardiac rhythm disorders and pulmonary function is important because these can be a cause of sudden death in epileptic patients and should be readily treated according to their etiology¹⁹⁻²³.

4.2 Hypertension

Epilepsies and hypertension are chronic diseases with high incidence and prevalence in Brazil. From a clinical point of view, it is well reported that seizures are commonly found in patients with systemic diseases, especially hypertension, due to the secondary injury in encephalic vessels. The treatment is based on the strict control of blood pressure levels²⁴.

4.3 Valvopathies

In Brazil, the valve disease represents a significant portion of hospital admissions for cardiovascular disease. The Rheumatic Fever is the main cause of valve disease in Brazil, responsible for 70% of cases valvopathies can cause disorders in the central nervous system due to blood flow change that goes to the brain or due to cerebral damage caused by metabolic acidosis or sepsis with primary focus on cardiac valves. Treatment may be medical or surgical, depending on the affected valve and the intensity of involvement²⁸.

5. Electrolyte Disturbances

5.1 Hyponatremia

Hyponatremia is a decrease in serum sodium concentration < 136 mEq / L²⁶. Represents the most common electrolyte disorder in hospitalized patients and is associated with increased mortality^{27,28}. The speed of installation determines the severity. In chronic cases,

there is a cerebral adaptation and less tissue damage. The cases considered emergencies are those occurring in less than 48 hours and severe hyponatremia (< 125 mEq / L)²⁹.

Acute hyponatremias are usually symptomatic and may lead to seizures (cerebral edema). In these cases, the $[Na^+]$ may be increased by up to 2 mEq / L / hr during the first 2 hours, until there is improvement in symptoms. Then, the correction rate should be reduced to not exceed the recommendation of < 10 -12 mEq / L in the first 24 hours. Chronic cases may have spare 12 mEq / L in 24 hours. Also, it must be diagnosed and treated the underlying cause of hyponatremia³⁰.

5.2 Hyponatremia

Hyponatremia is the serum sodium concentration > 145 mEq / L. It is believed that has a frequency of 0.2% in hospital admissions, reaching 6% in patients in intensive care unit (ICU). The most common early symptoms are: lethargy, asthenia and irritability. The most common late symptoms are seizures and coma³¹.

The emergency treatment must be made for cases in which serum sodium is from 158 to 160 mEq / L, and especially when patients are symptomatic. The exact rate of decrease of hypernatremia is not well determined. Hydration should be limited to 6.8 mL / kg / h and the correction of sodium should not exceed 0.05 mEq / hr. Also, should be always diagnosed and treated the underlying cause of hypernatremia³².

5.3 Hypokalemia

Hypokalemia is the concentration of serum potassium < 3.5 mEq / L. It is considered one of the most found electrolyte abnormalities in clinical practice, occurring around 50% of survivors after PCR ventricular fibrillation^{33,34}.

In severe hypokalemias < 2.5 mEq / L, the most affected tissues become the muscles and renal tubular cells with the appearance of weakness, or paralysis, with serum levels about 2 mEq / L can cause ascending paralysis and respiratory failure. Furthermore, myopathy may progress to rhabdomyolysis, that generates myoglobinuria and acute renal failure. Seizures and even coma can occur³⁴.

Treatment intravenous should be set at levels below 3,0 - 2.5 mEq / L or symptoms associated with hypokalemia. The

replacement of potassium should be individualized based on the severity of each case. Patients must be under cardiac monitoring while performing the replacement, detecting early arrhythmias generated by potassium infusion. The most important thing is to treat the underlying cause of hypokalemia³⁴⁻³⁶.

5.4 Hyperkalemia

It is set as a concentration of serum potassium > 6.0 . Occurring in about 1.3% of hospitalized patients, reaching 10% when concentration of serum potassium > 5.3 . High levels appear to be associated with poor prognosis and recent studies show that even levels between 4.5 and 5.5 have worse clinical outcome³⁷.

The symptoms are nonspecific and occur only in severe cases, may reach seizures and coma occur. If there is electrocardiographic impact, calcium gluconate at 10% is used to stabilize membranes of cardiac cells and cause the decrease in heart rate. Increasing the displacement of potassium from the extracellular space to the intracellular with the use of 10 to 20 IU doses of insulin (every 1 IU / glucose 2.5 g) causes a decrease of serum potassium from 0.45 to 0.87 mEq / L within 15 minutes. The use of β -adrenergic inhalation in doses of 10 to 20 mg got the same result in 30 minutes. It should also increase the excretion of potassium by other ways³⁷⁻⁴².

5.5 Uraemia

It is defined as elevated blood urea above normal. Acute renal failure (ARF) is a common and critical clinical entity responsible for uraemia that affects about 5% to 7% of all hospitalized patients. Despite advances in clinical treatment, will further carries a significant morbidity and mortality rate of 20% to 70%^{43,44}.

Symptoms include sensory faintness, delirium, coma, headache, visual abnormalities, tremor, flapping, multifocal myoclonus, chorea, seizures, focal motor signs, among others. The treatment relies on dialysis. As the final treatment the resolution of the underlying cause uremia, generally carried out through the liver or kidney transplantation⁴⁵⁻⁴⁷.

6. Metabolic Disorders

6.1 Hypoglycemia

Hypoglycemia is a metabolic state

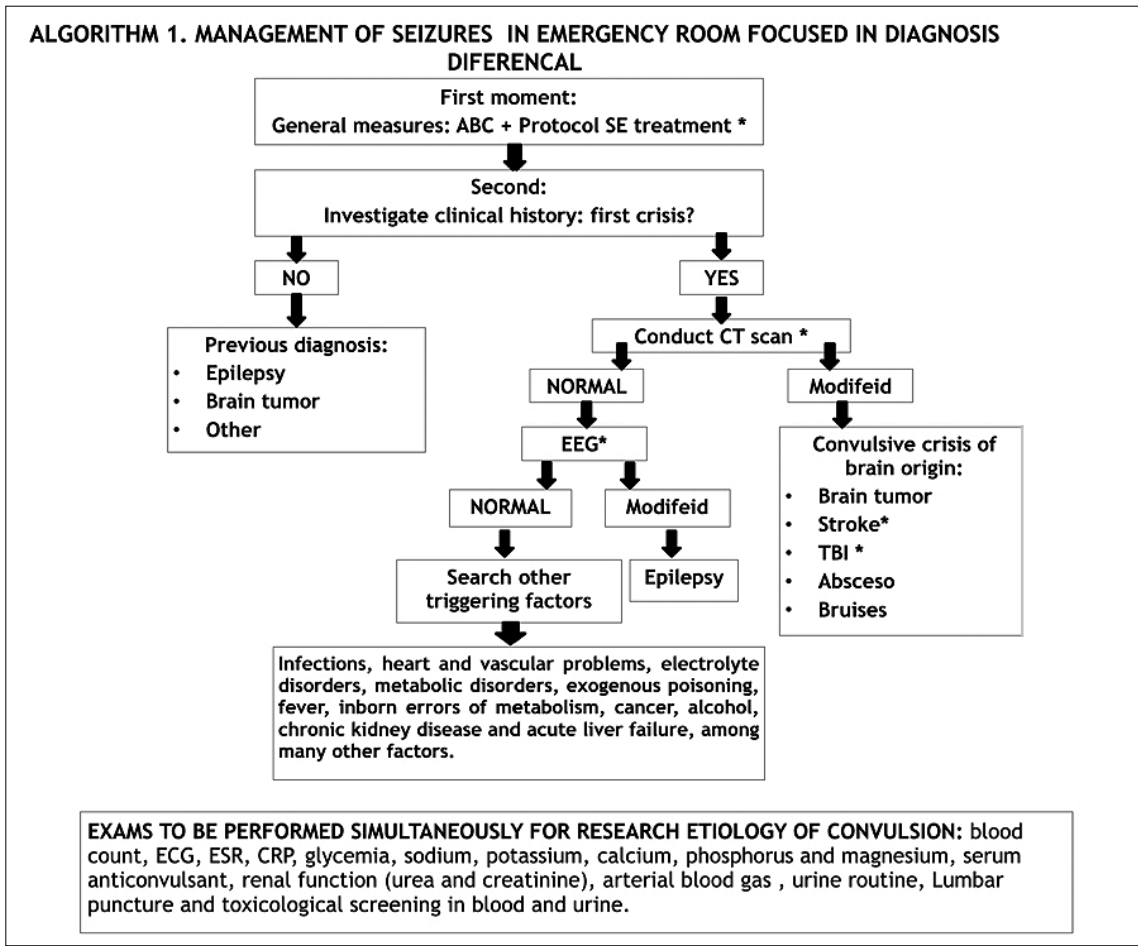
characterized by levels of plasma glucose less than 50 mg / dl, accompanied by clinical manifestations intensity and variable expressions. The symptoms may be didactically divided in neuroglycopenic, resulting from decreased glucose supply in the central nervous system, and adrenergic symptoms, resulting from the activation of the autonomic nervous system. Neuroglycopenic symptoms: blurred vision, loss of sense of time, drowsiness, dizziness, asthenia, headache, slow movements and thoughts, difficulty concentrating and reduced activity. Prolonged hypoglycemia: confusion, irritability, impatience, behavioral disorders, convulsions and coma. Adrenergic symptoms: sweating, tremors, tachycardia, palpitations, anxiety, nausea, hunger, paresthesias⁴⁸. At the time of hypoglycemia, the treatment will depend on the intensity of the clinical picture and should be used glucose at 50% and/or glucagon intramuscular or intravenous. The Thiamine association to the regimen is also widely used. Depending on the etiology, it also consists in dietary changes, drug therapy and / or surgical treatment⁴⁸.

7. Withdrawal Syndrome

The withdrawal syndrome is responsible for a significant increase in morbidity and mortality associated with the use of medications (neuroleptics, tricyclic, benzodiazepines, opioid), drugs (cocaine, marijuana) and alcohol. It also serves as one of the diagnostic criteria for dependence syndrome. These signs and symptoms are insidious and unspecific, which makes recognition and evaluation complex processes; vary in intensity and severity, may appear after a partial or total reduction of the dose usually used. The most common signs and symptoms include agitation, anxiety, mood changes (dysphoria), tremors, convulsions, hallucinations, nausea, vomiting, tachycardia and hypertension.⁴⁹⁻⁵⁴

Clinical research

The investigation of the etiology of seizure should be done as early as possible, and recommended a thorough clinical examination looking for systemic infections, neurological examination, evaluation of the fundus, large vein puncture and collection of material



aimed at achieving the following tests laboratory: Blood count erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), glycemia, sodium, potassium, calcium, phosphorus and magnesium, serum anticonvulsant (if the patient makes use of such drugs), liver function and kidney function, blood gas analysis, urine routine and toxicological screening of blood and urine. Imaging tests are needed to diagnose tumors, stroke, abscesses, hematomas, etc. If there is fever, evidence of otitis, mastoiditis, or infection in any other facial structures or neck stiffness, it is shown performing a lumbar puncture. It is recommended to also request electrocardiogram or the use of a heart monitor and EEG as soon as possible⁵⁵⁻⁵⁸.

Treatment

Treatments depend on the underlying cause as seen previously. However all

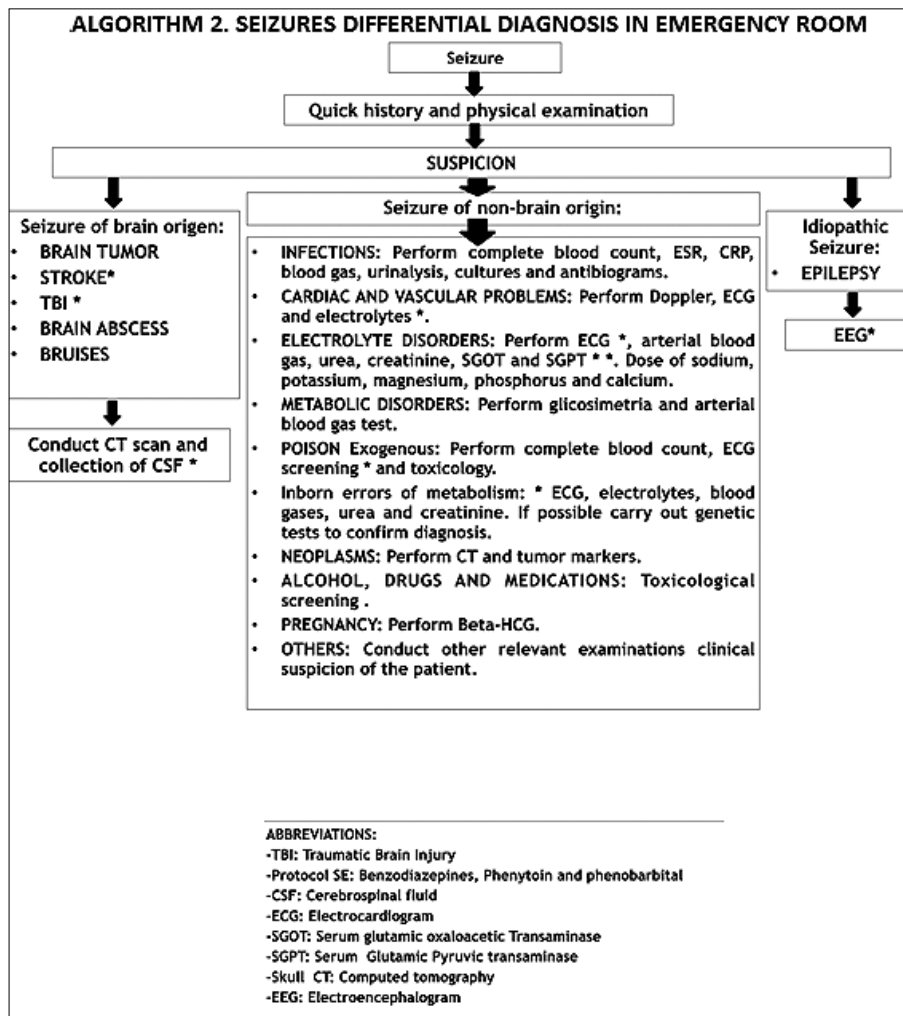
seizures can be addressed by the SE protocol, to prevent further damage to the central nervous system. All emergency service must have a systematic protocol for treatment of SE, based on current recommendations in the literature^{56,57}. The most effective drugs in the acute phase of the EME are the benzodiazepines. The control SE can be obtained between 1 and 10 minutes after administration of diazepam (10 mg for adult and 0.2 to 0.3 mg / kg for children). Phenytoin (adults and children is 15-20 mg / kg bolus) should be used in sequence, even if the crisis have already been aborted due to the high probability of them relapse due to the short half life of benzodiazepines^{56,57}. Control of the SE can be expected between 10 to 30 minutes of administration. In resistant cases can use additional doses of diazepam to a total dose of 30 to 40 mg in adults and 0.4 to 0.5 mg / kg for children, pending the effects of phenyt-

oin infusion⁵⁷. Phenobarbital is effective in the treatment of CME but not significantly different from that of lorazepam or diazepam followed by phenytoin. In fact, phenobarbital has only been used when initial therapy fails^{56,57}. Two new algorithms for the differential diagnosis of seizures (Algorithm 1 and 2).

Conclusion

In addition to all the causes of non-brain seizures mentioned in this article, there are many others. It is of utmost importance to keep in mind the differential diagnoses of seizures, because not every seizure is brain originated and do not need always be treated chronically with anti-epileptics.

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