INTRODUCTION

Non-convulsive status epilepticus (NCSE) is a persistant (> 30 minutes) change in behaviour and or mental processes from baseline associated with continuous epileptiform EEG changes but without major motor signs ***(Shah et al., 2009)***.

NCSE or non-convulsive seizures has been reported in 8-20 % of critically ill patient populations, and delayed diagnosis and treatment may lead to increased mortality ***(Laccheo et al., 2015).***

NCSE may cause permanent neuronal damage via increased extracellular glutamate, leading to brain swelling and apoptosis ***(Ikuko et al., 2013).***

On the basis of ictal EEG patterns it has been subcategorized into absence status epilepticus, with predominantly symmetrical synchronous ictal discharges, and complex partial-status epilepticus, with continuous or rapidly recurring complex partial seizures ***(Bong et al., 2014).***

The diagnosis and treatment of NCSE are not straightforward and depend on many variables, including the clinical setting and etiology, EEG findings, and the clinical status of the patient. In addition, it is not always clear to what extent the electrograghic activity contributes to clinical impairment or ongoing neuronal injury ***(Brophy et al., 2012).***

NCSE is a potentially treatable emergency, and delayed diagnosis affects prognosis. Emergent EEG (EmEEG) has been defined as an EEG available any time any day which is performed and interpreted within 4-8 h of the EEG request. The key indication for EmEEG is to exclude NCSE ***(Tu et al., 2013).***

EEG waveform morphology were quite variable and included typical and atypical spike and wave discharges, multiple or polyspike discharges and rhythmic sharp delta activity with evolution ***(Stacey et al., 2006).***

Non-aggressive treatment is favored for etiologies with low morbidity and mortality such as absence epilepsy and discontinued antiepileptic drugs. The risk of aggressive treatment is only warranted in etiologies where there was significant risk of seizure-induced neurologic damage, so determination of the optimal management approach to NCSE is complex and is ultimately determined by the inciting etiology ***(Matthew et al., 2013).***

AIM OF THE WORK

The aim of this work was to determine risk factors of nonconvulsive status epilepticus in children.

REVIEW OF LITERATURE

Definition of non-convulsive status epilepticus

Nonconvulsive status epilepticus (NCSE) is currently defined as a continuous nonconvulsive seizure that lasts >30 min, or multiple nonconvulsive seizures during a period of >30 min and between which sensory, motor and/or cognitive function is not fully recovered. The Neurocritical Care Society has suggested shortening the 30 min requirement to 5 min, as single seizures that last longer than 5 min are likely to persist or recur before a full recovery is made ***(Sutter et al., 2016).***

This definition was adopted for the following reasons:

- Most clinical and electrographic seizures last less than 5 min and seizures that last longer often do not stop spontaneously.
- Animal data suggested that permanent neuronal injury and pharmacoresistance may occur before the traditional definition of 30 min of continuous seizure activity have passed.
- More recently, experts have suggested a revised definition of SE which includes seizures lasting for 5 min or longer, although some controversy still remains ***(Gretchen et al., 2012).***

As further evidence of the controversy in defining SE, seizures lasting for at least 5 min have labeled as ‘‘impending status epilepticus,’’ ‘‘early heralds of status,’’ or ‘‘early status epilepticus’’***(Meierkord et al., 2010).***

It was recognized that the proposed 5-min definition will include some patients with prolonged seizures that would not meet traditional criteria for status epilepticus. However, this revised definition of SE builds on the recognition that emergent treatment is paramount in patients with prolonged seizure activity. Status epilepticus can be classified by semiology, duration and underlying etiology ***(Knake et al., 2009).***

SE can be convulsive or non-convulsive in type. Nonconvulsive seizures represent states of various levels of altered awareness, associated with electroencephalographic (EEG) seizure activity, but without outwardly observable convulsive activity. An important feature of convulsive seizures is their potential for evolution into non-convulsive seizures, where the patient can appear "post ictal" but is having electrical seizures, without obvious convulsive activity ***(Kinney and Craig, 2015).***

Convulsive status epilepticus is defined as convulsions that are associated with rhythmic jerking of the extremities. But, Non-convulsive status epilepticus (NCSE) is defined as seizure activity seen on electroencephalogram (EEG) without clinical findings associated with GCSE. Two rather distinct phenotypes of NCSE have been described:

(1) The ''wandering confused'' patient presenting to the emergency department with a relatively good prognosis or chronic epileptic syndromes or,

(2) The acutely ill patient with severely impaired mental status, with or without subtle motor movements (e.g., rhythmic muscle twitches or tonic eye deviation that often occurs in the setting of acute brain injury). This term has also been labeled as ‘‘subtle status’’.

(Shorvon, 2007)

Table (1): Definition of nonconvulsive status epilepticus (NCSE).

Nonconvulsive status epilepticus (NCSE) is a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms.
Note: 1. NCSE can be most usefully viewed as a form of cerebral response, which is dependant largely on the level of cerebral development of the individual (age and cerebral integrity/development/maturity), epilepsy syndrome, and the anatomical location of the epileptic activity. 2. The electrographic activity can take various forms.

(Shorvon, 2007)

Etiology of non-convulsive status epilepticus

The etiology of NCSE is poorly understood and apparently very heterogeneous. In many cases, NCSE appears to correspond to a conversion of an existing epilepsy syndrome presenting as self-limiting seizures. In the epidemiological studies of NCSE, between 30% and 50% of subjects with NCSE had a prior history of epilepsy ***(Walker et al., 2005).***

Only 31 of 75 patients (41%) had an acute etiology determined for their encephalopathy apart from clinical seizures, if present. The remaining children had apparently "unprovoked" encephalopathy, or unprovoked NCSE, usually occurring with a known history of epilepsy. The most common identified cause for encephalopathy was fever/infection of an extra– central nervous system source. Other etiologies included CNS infection, hypoxia, and toxic-metabolic syndromes ***(Greiner et al., 2012)***.

The aetiology of focal NCSE may involve underlying brain lesions caused by tumours or trauma, as well as cerebrovascular disorders. These can be generally identified by magnetic resonance imaging (MRI). In patients with NCSE associated with coma, the epilepsy may be the cause of the coma in some cases, whereas in others both coma and NCSE can be attributed to another cause, such as hypoxia ***(Towne et al., 2000).***

In addition, certain rare genetic conditions or chromosomal anomalies can present as iterative NCSE. An example is ring chromosome 20 syndrome ***(Van Rijckevorsel et al., 2006).***

Apparently successful treatment of CSE (*ie* absence of convulsive activity) may in a minority of cases actually reflect transformation into NCSE ***(Van Rijckevorsel et al., 2006).***

NCSE may also develop following discontinuation of antiepileptic drugs in general or as part of a benzodiazepine withdrawal syndrome ***(Vinton et al., 2005)***.

Potential underlying etiology

Acute processes

- Metabolic disturbances: electrolyte abnormalities, hypoglycemia, renal failure
- Sepsis
- Central nervous system infection: meningitis, encephalitis, abscess
- Stroke: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral sinus thrombosis
- Head trauma with or without epidural or subdural hematoma
- Drug toxicity
- Withdrawal from opioid, benzodiazepine, barbiturate, or alcohol
- Non-compliance with AEDs
- Hypoxia, cardiac arrest
- Hypertensive encephalopathy, posterior reversible encephalopathy syndrome
- Autoimmune encephalitis (i.e., anti-NMDA receptor antibodies, anti-VGKC complex antibodies), paraneoplastic syndromes

Chronic processes

- Preexisting epilepsy: breakthrough seizures or discontinuation of AEDs
- Chronic ethanol abuse in setting of ethanol intoxication or withdrawal
- CNS tumors
- Remote CNS pathology (e.g., stroke, abscess, TBI, cortical dysplasia)
- Acute symptomatic SE is more frequent in younger children with SE
- Prolonged febrile seizures are the most frequent cause of SE in children
- CNS infections, especially bacterial meningitis, inborn errors of metabolism, and ingestion are frequent causes of SE

(Brophy et al., 2012)

Classification of Nonconvulsive Status Epilepticus

A) Aetiological classification

NCSE that develops in critically ill patients usually has a different course and a worse outcome than NCSE in non-critically ill patients, which is usually related to underlying epilepsy. This difference has led to suggestions that the condition should be classified into two groups: ambulatory or 'genuine' NCSE, which occurs in the general population and in

patients with epilepsy, and NCSE that emerges in coma, which usually occurs in patients in the ICU ***(Bauer et al., 2010) (Fernandez-Torre et al., 2012).*** However, outcomes of NCSE are driven largely by the aetiology, and a large variety of causes can underlie the condition. Furthermore, in a study of 100 patients with NCSE with different aetiologies, mortality was 27% in patients with acute aetiologies, higher than in patients with epilepsy or cryptogenic NCSE (3% and 18%, respectively) ***(Shneker and Fountain, 2003).*** For this reason, the Neurocritical Care Society recognizes the prognostic value of NCSE aetiology, and a classification on the basis of aetiology might be more appropriate, and would separate NCSE associated with chronic conditions, such as epilepsy, slowly progressive brain tumours, cerebral microangiopathy and neurodegenerative diseases), from that associated with acute conditions, such as the transformation of generalized convulsive status epilepticus (GCSE) to NCSE, acute structural lesions, acute metabolic derangements and intoxication ***(Sutter et al., 2016).***

1. NCSE with chronic pathological conditions:

Epilepsy is considered to be the chronic pathological condition that is most frequently associated with NCSE, although formal studies are lacking. Up to 50% of patients with any type of status epilepticus have a prior diagnosis of epilepsy ***(Knake et al., 2001).*** Typical absence status epilepticus (ASE) is the first clinical manifestation of epilepsy in approximately one-third of patients, and recurs in up to 85% ***(Walker et al.,***

2005). Simple partial status epilepticus (SPSE), complex partial status epilepticus (CPSE) and atypical ASE can also occur in patients with epilepsy, although data on the incidence of these conditions in outpatients with epilepsy are scarce and inconclusive. These associations of status epilepticus in general with epilepsy suggest that NCSE is similarly associated, and estimations indicate that the prevalence of NCSE is ~6% among patients with juvenile myoclonic epilepsy ***(Dziewas et al., 2002)*** and ~15% among patients with idiopathic generalized epilepsies with ongoing typical absence seizures ***(Agathonikou et al., 1998).*** Although NCSE can be a manifestation of an epileptic syndrome itself, most initial episodes of NCSE in epilepsy seem to be triggered by changes in AED or interactions with concurrent medication that lower serum levels of AEDs ***(Patsalos et al., 2002).***

Data regarding associations of NCSE with chronic pathological conditions other than epilepsy are scarce. Chronic diseases are less frequently associated with NCSE than are acute pathologies, but a prospective study of 170 patients with neurocritical illness identified nonconvulsive seizures or NCSE in 21% of those with several chronic pathological conditions that are common risk factors for NCSE; these conditions included a history of epilepsy in 31% of patients with NCSE, a slowly progressive intracranial tumour in 19%, and evidence of encephalomalacia on brain imaging in 17% ***(Laccheo et al., 2015).***

2. NCSE with acute pathological conditions:

Transformation of generalized convulsive status epilepticus to NCSE. The transformation of GCSE to NCSE is common: NCSE accounts for up to 50% of all status epilepticus in patients in the ICU, and an additional third of all patients with status epilepticus develop NCSE that results from transformation of GCSE into NCSE ***(Rudin et al., 2011).*** However, when NCSE follows GCSE, the diagnosis is likely to be delayed or missed because the persistent altered level of consciousness can mimic postictal transient encephalopathy or delirium ***(Jordan et al., 1999).*** Such misinterpretation is associated with increased mortality ***(Young et al., 1996).***

Critical illness. In a prospective study of 236 patients in a coma without clinical evidence of seizures, 8% met the EEG criteria for NCSE ***(Towne et al., 2000).*** Among critically ill patients admitted to the ICU, almost 30% of patients monitored have been found to have NCSE ***(Sutter et al., 2011);*** introduction of continuous EEG monitoring in the 1990s in the ICU increased the detection rate, although an increase in the number of patients monitored with EEG has led to estimates that the overall rate of NCSE among adults monitored in the ICU is 10–20% ***(Kondziella et al., 2015).*** NCSE is the admission diagnosis for only a small subset of patients in the ICU, as most patients who develop status epilepticus in this context do so after acute critical illness ***(Walker et al., 2003).***

Traumatic brain injury. Seizures occur in up to 50% of patients with traumatic brain injury (TBI) ***(Yablon, 1993),*** and continuous EEG monitoring reveals that 10% of patients with TBI have nonconvulsive seizures ***(Vespa et al., 1999)*** with 30% presenting in the first three days after injury ***(Ronne-Engstrom and Winkler, 2006).*** Seizures after TBI are linked to elevated intracranial pressure and cerebral metabolic distress, and might lead to additional brain damage ***(Vespa et al., 2007)*** and a worse outcome ***(Thapa et al., 2010).*** However, these data do not allow a clear differentiation between brain damage caused by seizures and brain damage as the result of elevated intracranial pressure and cerebral metabolic distress directly related to TBI. Nevertheless, serial brain MRI has revealed that seizures after TBI can lead to hippocampal atrophy ipsilateral to the seizures ***(Vespa et al., 2010).***

Cerebrovascular insults. Only a few studies have investigated the association between ischaemic stroke and NCSE, and these have indicated that, among the 9% of patients with acute stroke who develop status epilepticus, nonconvulsive seizures and NCSE are more common than are convulsive seizures ***(Velioglu et al., 2001).*** Synergistic effects of the injuries from status epilepticus and cerebral ischaemia might increase mortality ***(Waterhouse et al., 1998)***.

Studies of the association between NCSE and intracranial haemorrhages are similarly limited. Continuous EEG monitoring of patients with intracerebral haemorrhage

(ICH) showed that 18% have NCSE ***(Claassen, 2007)***, although NCSE did not predict a poorer outcome in these patients ***(De Herdt, 2011).***

More data are available about the association of NCSE with subarachnoid haemorrhage (SAH). Studies have shown that NCSE occurs in 8% of patients with aneurysmal SAH ***(Dennis, 2002),*** a proportion that increases with the severity of the cerebral insult ***(Hart, 2011),*** and that the incidence of NCSE in spontaneous nonaneurysmal SAH is lower, at 3% ***(Little, 2007).***

Encephalitis. Acute infectious and noninfectious encephalitis are pathological conditions that can be associated with NCSE. Noninfectious encephalitides, such as autoimmune encephalitides, lead to (usually nonconvulsive) seizures in 78% of patients ***(Schmitt, 2012).*** In one study that did report on the incidence of NCSE specifically, continuous EEG monitoring in critically ill patients showed that infectious encephalitides and metabolic encephalopathy accounted for NCSE in 13% of all patients who developed the condition ***(Claassen et al., 2004).***

Hypoxic–ischaemic brain injury. Status epilepticus, usually nonconvulsive, occurs in up to 30% of patients who remain comatose after surviving cardiorespiratory arrest (CRA) ***(Rossetti et al., 2009).*** Most of these patients exhibit signs of severe hypoxic–ischaemic brain injury, and status epilepticus is not regarded as the principal cause of coma, or the driver of outcome ***(Crepeau et al., 2014).*** NCSE after hypoxic–ischaemic

brain injury should, therefore, be considered as a different entity to other acute forms of NCSE, as the underlying brain damage is largely irreversible and usually associated with an extremely poor outcome. If patients in this small subgroup have markers of a favourable outcome (such as age <65 years, conversion to a shockable rhythm and return of spontaneous circulation during resuscitation, reactive pupillary and motor reflexes 3 days after CRA, and a continuous reactive EEG background activity) treatment with AEDs might improve their catastrophic prognosis ***(Claassen, 2013).***

Adverse drug effects. Broad-spectrum antibiotics are frequently linked to NCSE. In a systematic review of 143 articles that involved 25,712 patients and 25 different antibiotics, unsubstituted penicillins, fourth generation cephalosporins, imipenem and ciprofloxacin were associated with an increased risk of symptomatic seizures — most of which were nonconvulsive in patients who received cephalosporins — when used in patients with renal dysfunction, brain lesions or epilepsy ***(Sutter et al., 2015).*** However, a recent systematic review revealed that the evidence for the association of antibiotic drugs with symptomatic seizures and NCSE is low to very low, according to the American Academy of Neurology classification of evidence scheme (evidence class III–IV) ***(Sutter et al., 2016).***

Other drugs that have been linked to NCSE are ifosfamide, methotrexate, ketorolac, baclofen, lithium, opioids,