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Persistent generalized periodic discharges: A specific marker of fatal outcome in cerebral hypoxia

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HIGHLIGHTS

- Generalized periodic discharges (GPDs) were seen in about 25% of the EEGs performed in patients who had suffered circulatory arrest.
- The occurrence of persistent GPDs is almost invariably associated with fatal outcome.
- The occurrence of GPDs was not associated with the (non-)use of pharmacologic sedation.

ABSTRACT

Objectives: Electroencephalography (EEG) is one of the methods used in predicting the outcome after cerebral hypoxia. In this study we aim to evaluate the significance of generalized periodic discharges (GPD) as a prognostic marker.
Methods: We retrospectively analyzed the medical histories of patients, who underwent an EEG after cardiac arrest during the time period from 2005 to 2013 at the University Hospital Zurich. All EEGs were reinterpreted using the 2012 American Clinical Neurophysiology Society (ACNS) classification for intensive care unit (ICU) EEGs.
Results: Out of 131 patients, in which an EEG was recorded after cardiopulmonary resuscitation, 119 were included in our study. The average interval between cardiac arrest and EEG-recording was 3.8 ± 3.0 days (range: 0–14 days). Persistent GPDs (i.e. GPDs more than 24 h after the event) were found in thirty-two (26.9%) of the patients initial EEGs. The appearance of persistent GPDs preceded fatal outcome in 100% of all cases (vs. 69.0% in the non-GPD-group, $p < 0.0001$).
Conclusion: Among other encephalopathic markers in EEG persistent GPDs are a highly specific prognostic marker of fatal outcome in patients with hypoxic encephalopathy.
Significance: Using standardized EEG interpretation, this study identified persistent GPDs as a specific prognostic marker in post cardiac arrest syndrome.

1. Introduction

Cerebral hypoxia is the main reason of impairment or death after an initially successful cardiopulmonary resuscitation (CPR) (Neumar et al., 2008). Estimating the patients' individual prognosis after CPR remains a difficult task. Especially in comatose patients, Somatosensory evoked potentials (SSEPs) (Zandbergen et al., 2006), biomarkers like neuron-specific enolase (NSE) (Zandbergen et al., 2006), cerebral imaging (e.g. Howard et al., 2012) electroencephalographic (EEG) recordings (e.g. Hofmeijer et al., 2015; Rossetti et al., 2010) have been suggested as means to obtain an estimate. Apparent advantages of EEG are its non-invasive character and its sensitivity with regard to cortical function.

Neurophysiologists base their predictions on various patterns associated with encephalopathy. Among them are background slowing, burst-suppression patterns (Hofmeijer et al., 2014) and/or generalized periodic discharges (GPDs), which are commonly seen after severe cerebral hypoxia.

Overall GPDs are a rarely seen pattern – according to monocenter studies occurrence rates range from 0.15% in all patients (Kuroiwa and Celesia, 1980) up to 3.8% in inpatients (Foreman

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et al., 2012) – and are deemed an unspecific marker of encephalopathy. On the other hand they are a relatively common finding in patients after CPR. A retrospective study (Yamashita et al., 1995), described GPDs in 23% of the patients after CPR, while a more recent study reported an occurrence in roughly one third of the patients with postanoxic encephalopathy (Rossetti et al., 2009). They are thought to be associated with poor outcome (e.g. Bauer et al., 2013; Pedersen et al., 2013).

However few studies exist, that evaluated the specificity of GPDs as a separate entity (Ribeiro et al., 2015; San-Juan et al., 2009; Yemisci et al., 2003; Husain et al., 1999). Furthermore, there has until recently been no consensus on a terminology describing periodic patterns. For example there is no clear distinction between GPDs and generalized subtypes of non-convulsive status epilepticus (Rossetti et al., 2007; Trinka and Leitinger, 2015). Not until 2012 a proposal of terminology for describing intensive care unit (ICU) EEGs was presented by the American Clinical Neurophysiology Society (ACNS) (Hirsch et al., 2013).

Through this retrospective study we aimed to reevaluate the significance of GPDs as prognostic markers using the standardized classification provided by the ACNS (Hirsch et al., 2013). We intended to analyze clinical data of in-hospital patients, who suffered cerebral anoxia due to cardiac arrest and had an EEG afterwards.

We addressed the following questions: how often did GPDs occur in these EEGs, and to which extent did their occurrence correlate with an unfavorable outcome. In order to evaluate their prognostic value we compared GPDs with other encephalopathic changes in EEG. Furthermore we analyzed whether other clinical variables such as age, sex, duration of anoxia or the use of antiepileptic drugs (AED) altered the outcome.

2. Material and methods

2.1. Selection of the study cohort

We selected EEGs of adult patients (male and female, age >16 years) in our database of ICU EEGs, who suffered a definite episode of cardiac arrest between 2005 and 2013.

The main inclusion criterion was:

(1) EEG within two weeks after cardiac arrest of at least three minutes length.
(2) Full documentation of the patient's history, EEG, drugs taken during the time of EEG monitoring, diagnosis and general outcome after one month.
(3) No neurodegenerative disease known before cardiac arrest.
(4) No severe traumatic brain injury.

The exclusion criterion was:

(1) The patients declined to the use of their data. (Though patients were not specifically asked for consent for this retrospective study, some patients generally declined to the use of their data for study purposes).

Information of the outcome was gathered from all available medical reports (discharge reports from intensive care unit (ICU) and/or reports from the rehabilitation clinic, which were very detailed in most cases). The outcome was assessed one month after CPR as described by Yamashita et al. (1995) and measured in following terms: death within one month; severely impaired, – i.e. requiring continuous care in all aspects of life corresponding to modified Rankin Scale 4 and 5; slightly and moderately affected (i.e. at least able to communicate and not fully dependent on help) = mRS 1–3.

After 2008 patients were increasingly treated with mild hypothermia (34 °C) for at least 24 h in the aftermath of cardiac arrests if the breakdown of circulation lasted longer than 10 min and if there were no contraindications. EEGs were always performed after the warming up.

2.2. Standard EEG study procedure

All EEGs were recorded according to the 10–20 system with needle or pad electrodes. In addition, a one-channel electrocardiogram was recorded via additional skin surface electrodes. EEG traces were evaluated through bipolar longitudinal and transverse montages, as well as through average reference montage. During EEG recordings of comatose patients, standardized acoustic stimuli (loud clicking sounds) and painful tactile stimuli were performed by EEG technicians. Standard trigger maneuvers (hyperventilation and/or intermittent photic stimulation) were not routinely performed in the ICU.

Our routine EEGs complied with the requirements of the German Society for Clinical Neurophysiology (DGKN 2006) and had a minimum standard length of 20 min.

The EEG system used was a Nihon Kohden EEG-1100 EEG Recorder. Data were reviewed using 'Megis EEGFocus' software. All EEGs were evaluated and interpreted a posteriori by the study investigators and were consequently reclassified according to the standardized criteria provided by the ACNS (Hirsch et al., 2013, see below). The reviewers of the EEG data were blinded for the outcome.

Interictal epileptiform activity as a separate entity was diagnosed applying the criteria of IEAs provided by (Gloor, 1977).

If present, the results of cerebral imaging (either CT or MRI) were also included into the dataset.

2.3. Terminology and statistical analysis

All EEGs were re-interpreted according to ACNS Critical Care EEG Terminology 2012 version (Hirsch et al., 2013): For each patient, we analyzed the following parameters: (1) background activity (alpha-, theta-, delta-dominant), (2) background voltage (normal, low, suppressed), (3) spontaneous reactivity/ reactivity to stimuli, (4) occurrence of periodic discharges or rhythmic delta waves, their distribution (lateralized/generalized) and their frequency (in the case of GPDs we defined a low frequency threshold of 1/30 Hz, as there was none given in the ACNS criteria), (5) occurrence of burst-supression patterns, (6) occurrence of other graphoelements indicating encephalopathy, – including nonperiodic generalized discharges with blunt triphasic morphology and classic interictal epileptiform discharges. As all EEGs showing GPDs were recorded at least 24 h after resuscitation, we consistently used the term "persistent GPDs", as there are reports on dramatic changes of the dominating EEG patterns already in the first 24 h after resuscitation (Spalletti et al., 2016; Sivaraju et al., 2015).

The frequency of any pattern was described in following standardized terms: continuous, abundant, frequent, occasional and rare.

For convenience EEGs showing discontinuous or no discernible background were categorized as "disturbed background continuity".

Clinical and statistical parameters sampled were: (1) underlying illness leading to the cardiac arrest, (2) Glasgow coma scale (GCS) at the time of the recordings, (3) approximate length of cardiac arrest, which was defined as time from arrest to return of spontaneous circulation (ROSC), (4) timespan between the event and the EEG recording, (5) the sedative and/or antiepileptic