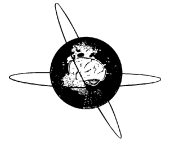




Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Epileptic activity in neurological deterioration after ischemic stroke, a continuous EEG study

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ARTICLE INFO

Article history:
Accepted 15 September 2019
Available online xxx

Keywords:
Ischemic stroke
Neurological deterioration
cEEG
Penumbra
Metabolic crisis
Periodic abnormalities

HIGHLIGHTS

- Epileptic activities (EA) are found in 44% of acute stroke neurological deterioration.
- Ictal patterns and Periodic discharges (PDs) responds to anti-epileptic drugs.
- Treating ictal patterns and PDs could prevent adverse metabolic consequences of EA.

ABSTRACT

Objective: Despite improvement in acute stroke care, almost 40% of patients with ischemic stroke present neurological deterioration. Neurological deterioration is associated with higher death and dependency rates. Neurological deterioration mechanisms are unknown, and half of neurological deterioration remains unexplained. We postulate that a substantial proportion of neurological deterioration in ischemic stroke is associated with periodic discharges/non-convulsive seizures that negatively impact the recovery of ischemic stroke and worsen symptoms.

Methods: Retrospective review of 24 h continuous EEG monitoring (cEEG) performed for neurological deterioration in the stroke unit of a tertiary academic centre.

Results: Eighty-one patients were included. cEEG detected epileptic activities in 44% of cases (Non-convulsive seizures/non-convulsive status epilepticus: 10/81 (12%), periodic discharges: 17/81 (21%) and sporadic epileptiform discharges in 14/81 (17%). The proportion of patients who did not receive recanalization therapy was significantly higher in the NCSE/NCSz/PDs group than in the group devoid of NCSE/NCSz/PDs: 17/22 (77%) vs 13/59 (22%); $p < 0,001$. Treatment of Non-convulsive seizures /non-convulsive status epilepticus and periodic discharges was followed by EEG improvement in respectively 7/8 and 10/16 of treated patients.

Conclusions: Non-convulsive seizures /non-convulsive status epilepticus /periodic discharges are associated to neurological deterioration after ischemic stroke.

Significance: Treatment of Non-convulsive seizures /non-convulsive status epilepticus and periodic discharges, if such patterns are detected, could help prevent adverse metabolic consequences of epileptic activities on ischemic brain tissue.

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1. Introduction

Stroke is a leading cause of death and the first cause of permanent disability in industrialized countries (Feigin et al., 2003). The “core” of irreversible brain tissue injury in ischemic stroke (IS) is surrounded by a zone of “penumbra” that is impaired by the ische-

mia but may still fully recover. Improvement of blood supply in the penumbra through recanalization of the occluded vessel or compensatory mechanisms, such as vascular collateral opening, can resume normal neuronal functioning and lead to neurological stabilization and recovery. However, the threshold between neuronal death and recovery in the penumbra is narrow and depends on a tight balance between metabolite supply and consumption by the affected neurons. Despite improvement in prevention and monitoring of complications, early neurological deterioration (ND) after IS occurs in up to 38% of cases (Seners et al., 2014, 2018) and is associated with a four-fold increase in death or

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dependency at 3 months compared to patients without ND (Seners et al., 2014). In about half of cases, ND is caused by haemorrhagic conversion, oedema, recurrent ischemia or systemic medical complications that either impair blood oxygenation or increase neuronal metabolism (Karepov et al., 2006; Siegler et al., 2013). In the remaining 50% of cases, the underlying mechanism of ND remains unclear, preventing the development of adequate management strategies (Jauch et al., 2013).

A less explored explanation for ND is epileptic activities triggered by the IS. Indeed, in rat stroke models with simultaneous cortical EEG, occlusion of the middle cerebral artery leads to periodic discharges (PDs) in over 80% of cases without associated convulsive or motor activity (Hartings et al., 2003). In humans, acute brain injuries and severe systemic diseases are commonly associated with interictal discharges (IED), periodic discharges (PDs), non-convulsive seizures (NCSz) and non-convulsive status epilepticus (NCSE) (Claassen et al., 2004; Naeije et al., 2014). Such epileptic activities are non-convulsive in up to 90% of cases in studies using continuous EEG monitoring (cEEG) (Claassen et al., 2004; Panayiotis, 2004). Yet, while non-convulsive, NCSz, NCSE and PDs are associated with changes in brain metabolism that could prove deleterious for the neurons in the penumbra. Metabolic modifications induced by neuronal discharges result in increased neuronal oxygen and metabolite needs, cerebral blood flow (CBF), intracranial pressure (Vespa et al., 2007; Witsch et al., 2017) and intracerebral lactate/pyruvate ratio (LPR) (Marcoux et al., 2008), a phenomenon coined by some authors as “metabolic crisis” (Ko, 2013; Claassen et al., 2014; De Marchis et al., 2016; Vespa et al., 2016). In intensive care settings, PDs are also associated with poorer outcomes (Foreman et al., 2012; Osman et al., 2018). All those mechanisms could potentially contribute to ND in IS.

In this work, we studied if epileptic activities were associated with ND in acute IS. To that aim, cEEG recordings performed for ND in IS were retrospectively reviewed to assess the prevalence and type of epileptic activities and evaluate if treating ictal and periodic EEG patterns could be effective.

2. Materials and methods

2.1. Study design and inclusion criteria

We retrospectively searched our prospective database for cEEG performed in patients with ND after IS at Hôpital Erasme (Université Libre de Bruxelles, Brussels, Belgium) between January 2014 and December 2016.

ND was defined as either (1) worsening of existing neurological deficits assessed by the neurologist or two or more points loss on the NIHSS (2) alteration of consciousness defined as fluctuating mental state or degradation of the Glasgow Coma Scale by one or more points (3) new clinical symptoms not attributable to the topography of the initial ischemic lesion. Medical causes of ND were not excluded as they are also known to favour epileptic activities (Delanty et al., 1998; Kurtz et al., 2014).

2.2. Clinical variables

Standard of care for acute IS management in our institution has been described elsewhere (Naeije et al., 2017). Medical charts were reviewed and the following information retrieved: demographics, stroke etiology according to the TOAST classification (Adams et al., 1993), stroke localization, history of previous stroke, epilepsy and cognitive disorders, use of recanalization therapy (thrombolysis or thrombectomy), latency from admission to cEEG and current medications on admission and at the onset of cEEG recording. Functional outcome at three months was obtained from follow-

up visit notes and assessed with the modified Rankin Scale (mRS), with a good outcome defined as mRS \leq 2.

2.3. EEG recording and variables

cEEG was performed using 21 scalp electrodes placed according to the international 10–20 system (Software: BrainRT, OSG Inc., Rumst, Belgium) and reviewed by a clinical neurophysiologist certified in the ACNS Critical Care EEG Terminology (Hirsch et al., 2013). Interictal EEG findings were classified according to published consensus criteria (Hirsch et al., 2013) into periodic (PDs) and sporadic epileptiform discharges (SEDs). Periodic discharges (PDs) were further classified in: generalized PDs (GPDs), lateralized PDs (LPDs), bilateral independent PDs (BIPDs), or multifocal PDs (MfPDs). Non-convulsive seizures (NCSz) and non-convulsive status epilepticus (NCSE) were defined according to consensus criteria (Beniczky et al., 2013; Hirsch et al., 2013).

2.4. Seizure treatment

The antiepileptic drug (AED) treatment was managed at the discretion of the treating physician according to the type of status/seizure, co-morbidity, and co-medications. Our institution protocol for the treatment of NCSE is based upon international guidelines detailed elsewhere (Hirsch and Gaspard, 2013) and consists of a first line of intravenous benzodiazepine (Lorazepam 0.1 mg/kg) followed by intravenous AED either Leviteracetam or Sodium Valproate. In some cases, AEDs were administered prior to EEG results due to high suspicion of seizures or status epilepticus (SE).

2.5. Statistical analysis

Results are presented as mean (\pm standard deviation [SD]) or median [interquartile range (IQR)] for quantitative and count (percentage) for qualitative variables.

Fisher's exact test was used for comparison of clinical characteristics between patients with ND and NCSE/NCSz/PDs and patients with ND without NCSE/NCSz/PDs. *p*-values under 0.05 were considered as statistically significant.

Chi-square test was used for outcome analysis (mRS) in two groups (presence versus absence of NCSE/NCSz/PDs).

3. Results

3.1. Study cohort

Of 1355 cEEG performed during the study period, 81 (6%) cEEG were performed for ND in patients with IS, representing 7% (81/1247) of all patients admitted to the stroke unit during the study period. Median [IQR] age was 71 [63–80] years, 46 (57%) were males. 70 (86%) of the ND observed occurred within 3 days of stroke onset. Stroke was mainly located in the carotid artery territory (N = 57, 70%) and attributed to large artery disease in 22 (27%), cardio-embolism in 36 (45%), lacunar in 1 (1%), cryptogenic in 11 (14%) and other etiologies in 11 (14%) patients. Fifty-one patients had recanalization therapy for their ischemic stroke that consisted of intravenous thrombolysis in 23, thrombectomy in 18 and both in 10 patients.

Other patients' characteristics are detailed in Table 1.

3.2. cEEG results

Epileptic abnormalities were observed in 36/81 (44%) patients and consisted of NCSz/NCSE in 10 (12%), PDs in 17 (21%) and SEDs

Table 1
Demographic and clinical characteristics.

Variable	Entire cohort (N = 81)	With NCSz or PDs (N = 22)	Without NCSz or PDs (N = 59)	p value
Age	71 [63–80]	71	71	0.47
Gender, male	46 (56%)	13	33	0.90
NIHSS	11 [5–19]	14 [5–23]	11 [5–18]	0.38
Outcome (mRS)				0.65
0–1	15 (19%)	3 (14%)	12 (20%)	0.50
2–5	30 (37%)	8 (36%)	22 (37%)	0.94
6	36 (44%)	11 (50%)	25 (42%)	0.55
TOAST Classification				0.77
Large artery	22 (27%)	7 (32%)	15 (25%)	0.57
Cardioembolic	36(44%)	9 (41%)	27 (46%)	0.60
Lacunar	1 (1%)	0	1 (2%)	0.54
Cryptogenic	11 (14%)	4 (18%)	7 (12%)	0.47
Other	11 (14%)	2 (9%)	9 (15%)	0.48
Localisation				
Anterior				
Cortical	57 (70%)	17 (77%)	40 (68%)	0.59
Sub-cortical	58 (72%)	18 (81%)	40 (68%)	0.27
Posterior				
Cortical	33 (41%)	11 (50%)	22 (37%)	0.32
Sub-cortical	27 (33%)	9 (41%)	18 (31%)	0.43
Stroke treatment				
rtPA only	23 (28%)	4 (18%)	19 (32%)	0.22
Thrombectomy only	18 (22%)	1 (5%)	17 (29%)	0.027
rtPA + Thrombectomy	10 (12%)	0	10 (17%)	0.053
None	30 (37%)	17 (77%)	13 (22%)	<0.001
Latency to cEEG (days)	2 [0.5–4]	1 [0–3]	2 [1–5]	0.13
Medical history				
Stroke	19 (24%)	5 (23%)	14 (24%)	> 0.90
Dementia	6 (7%)	3 (14%)	3 (5%)	0.33
Epilepsy	3 (3%)	0	3 (5%)	0.56
Treatment				
Psychotropic				
Recent initiation	4 (5%)	1 (5%)	3 (5%)	1
Recent stop	8 (8%)	1 (5%)	7 (12%)	0.44
Chronic use	33 (40%)	9 (41%)	24 (40%)	1
Antibiotics				
Recent initiation	20 (25%)	3 (14%)	17 (77%)	0.25
Recent stop	2 (2%)	0	2 (9%)	1
Chronic use	1 (1%)	0	1 (1,7%)	1
Antiepileptic drugs				
Start	25 (30%)	17 (77%)	15 (25%)	0.11
Stop	1 (1%)	0	1 (1,7%)	1
Chronic	6 (7%)	2 (9%)	4 (6,5%)	0.66

Data are presented as median [interquartile range] or count (column percentage).

Abbreviations: National institute of health stroke scale (NIHSS), modified Rankin score (mRS), Trial of Org 10172 in Acute Stroke Treatment (TOAST), Recombinant Tissue Plasminogen Activator (rtPA).

in 14 (17%). Some patients had multiple patterns so that 22 (27%) had either NCSz or PDs. Four patients with NCSz fulfilled the criteria for NCSE. Eight cases of NCSz/NCSE were focal and two were generalized. Of 17 patients with PDs, 10 had LPDs, 6 had GPDs and 1 had MfPDs. NCSz/NCSE were preceded by PDs in 5 patients.

3.3. Comparison of patients with and without NCSE/NCSz/PDs

The proportion of patients who did not receive recanalization therapy was significantly higher in the NCSE/NCSz/PDs group than in the group devoid of NCSE/NCSz/PDs (17/22 (77%) vs 13/59 (22%); $p < 0,001$ – Table 1). Other studied characteristics were comparable (Table 1).

3.4. Response to treatment

AEDs were started in 17/22 patients with NCSE/NCSz/PDs. AEDs were given in 8/10 cases of NCSz/NCSE (the two remaining patients were given best palliative care due to co-morbidities) and were followed by EEG NCSz/NCSE pattern disappearance in 7/8 (88%). Sixteen out seventeen patients with PDs received AEDs (in five of those patients, PDs preceded NCSz/NCSE patterns), AED treatment

was followed by the disappearance of EEG periodic pattern in 10 patients (62%). Of notice, the two patients who took AEDs prior to the stroke had PDs in one case and NCSE in the other, and both patterns disappeared after intravenous AED treatment.

3.5. Outcome

Nineteen (23%) patients achieved a good neurological outcome and 36 (44%) died. We found no differences in mRS between patients with NCSE/NCSz/PDs and controls ($p = 0.65$) nor between patients who had AED and those who did not ($p = 0.57$).

4. Discussion

Using cEEG monitoring, ND after IS was associated with epileptic activities in 44% of cases, of which 12% were NCSz/NCSE, 21% PDs and 17% SEDs.

High rates of epileptic anomalies have previously been described after IS. Studies performing systematic 20-min EEG after unselected IS yielded a proportion of SEDs ranging from 12 to 37% and PDs from 8 to 25% of patients (Bentes et al., 2017; Lima et al., 2017) while NCSz/NCSE prevalence ranged from 1.3% to 4.3%

(Mecarelli et al., 2011; Bentes et al., 2017). No studies with cEEG were performed after IS, yet, Carrera et al. (2006) used a set of 10 electrodes placed between 1 hour to 37 hours after IS onset (mean recording time 17 h) in 100 patients and reported IEDs in 14%, PDs in 3%, NCSz in 2% and no NCSE. These prior studies highlighted both the high prevalence of epileptic anomalies in acute vascular brain injury and the association between occurrence of epileptic anomalies, worse prognosis (Knake et al., 2006) and long-term risk of seizures (Lamy et al., 2003; Chung, 2014) but provided no information on ND. In our population with ND after IS, the rate of NCSE/NCSz was higher than those reported by studies using systematic EEG regardless of the clinical evolution suggesting that epileptic activities may be involved in the ND.

Mechanisms underlying ND and epileptic activities could involve metabolic disturbances in fragilized brain tissues. Indeed, while epileptic activities may reflect severe neuronal damage secondary to ischemic insult, as suggested by the higher rate of NCSE/NCSz/PDs in patients without recanalization therapy, the underlying mechanism of epileptic activities is not clear. Alteration in intracellular concentration of ions, metabolic dysfunction, excitatory neurotransmitter release and hyper-excitability could concur in epileptic activity genesis (Pulsinelli, 1992; Kessler et al., 2002; Silverman et al., 2002). Neuronal discharges, in turn, could lead to increased stress on the vulnerable but viable penumbra by increasing neuron oxygen consumption, CBF and LPR, potentially worsening stroke symptoms. Aggravation of acute brain lesions by NCSE/NCSz/PDs is described in subarachnoid haemorrhage (SAH) (Ko, 2013), intracranial haemorrhage (ICH) (Vespa et al., 2003) and traumatic brain injury (TBI) (Krauss, 2008). Even in absence of brain disorders, NCSE/NCSz/PDs, in critically ill patients are associated with increased morbidity and mortality, probably through mechanisms involved in the "metabolic crisis". Cerebral microdialysis investigations confirm that hypothesis by showing elevated LPR during seizures or PDs but not during electrically non-epileptic epochs (Vespa et al., 2016).

In patients with IS, the metabolic alterations associated with epileptic activities could bear even more negative effects by aggravating ischemia in the penumbra and increasing intracranial pressure (Witsch et al., 2017) leading to the worsening of focal symptoms and alteration of the mental state. The fact that in our patients with ND, NCSE/NCSz/PDs were significantly associated with lack of recanalization therapy suggests that the ischemic insult may be the trigger of that vicious circle, while restoring blood supply in the affected area may prevent NCSE/NCSz/PDs genesis and ND. NCSz/NCSE are closely linked to the presence of PDs and NCSz/NCSE in ND after IS were preceded by PDs in 50% of cases. This parallels findings in critically ill patients where the risk of seizures is highest in patients with LPDs, amounting to a 44% risk of seizures at 24 h (Ruiz et al., 2017).

Interestingly, AED treatment of NCSz/NCSE and PDs was followed by the disappearance of those patterns in 80% and 62% respectively, suggesting that adverse metabolic consequences of EA could be partly prevented when those patterns are detected and treated. However, this should be confirmed in prospective studies to assess the exact role of AED and the treatment timing in that context. Indeed, PDs tend to disappear spontaneously when associated to acute brain injury (García-Morales et al., 2002; Kim et al., 2006). Our retrospective cohort is probably biased towards more severe cases: mortality rate at three months is higher in our cohort (44%) compared to natural history of stroke patients where mortality rates range from 7% (Kolominsky-Rabas et al., 2001; Wei et al., 2018) to 23% (Feigin et al., 2003). Furthermore, only 7% of our stroke patients benefited from cEEG for ND, whereas ND is expected to occur in up to 38% of IS, suggesting that only the more severe cases underwent cEEG. Still, the mortality rate in our population that underwent cEEG is within the range of rates

reported for IS with ND (Kwan and Hand, 2006; Roquer et al., 2008; Siegler et al., 2016), suggesting that our results could be representative of ND after IS. No difference in clinical outcomes was found between ND associated with and without NCSE/NCSz/PDs which is probably explained by the limited sample of the study and the fact that the patients had already severe deficits and poor outcome in both groups. The impact of cEEG systematic detection and treatment of EA in IS with ND should thus be addressed in dedicated prospective studies to assess the yield of AED in stroke neuroprotection by preventing damageable increase in neuron metabolism due to epileptic activities.

5. Summary

cEEG monitoring in IS with ND detects epileptic activities in 44% of cases of which 12% are NCSz/NCSE and 21% PDs suggesting a role for epileptic activities in ND in IS. This effect on ND is likely to occur through deleterious metabolic effects induced by neuronal discharges on neurons that suffered from ischemia. Treatment of NCSz/NCSE and PDs may have a role in post stroke neuroprotection.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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