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Cerebrospinal fluid findings in non-infectious status epilepticus

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ABSTRACT

Objective: Ictal activity itself can cause pathological cerebrospinal fluid (CSF) findings. However, data regarding pathological CSF findings caused by SE itself to date remain scarce. We here evaluated the frequency and specificity of pathological CSF findings in non-infectious SE.

Methods: We performed a retrospective analysis of CSF samples in adult patients with episodes of non-infectious SE, who had been admitted to the Department of Neurology, University Hospital of Cologne. The following parameters were assessed: cell count, protein, and lactate content, CSF/serum glucose quotient (Q_{Glc}), disturbances of blood-brain-barrier function assessed by CSF/serum albumin quotient (Q_{Alb}), and qualitative intrathecal IgG synthesis assessed by unmatched oligoclonal bands in CSF.

Results: We analysed 54 episodes of non-infectious SE in which CSF had been obtained. CSF pleocytosis was infrequent (6%). Elevated CSF protein content was present in 44% of all cases, whereas elevated CSF lactate content was found in 23% of the cases. A decreased Q_{Glc} was present in 9%. Dysfunction of blood-brain-barrier (BBBD) was the most frequent pathological finding, amounting to 55%. Unmatched oligoclonal bands in CSF were seen in 10% of non-infectious SE.

Further analysis revealed that elevated CSF protein content was found predominantly in recfractory SE ($p = 0.04$). Elevated CSF lactate content was associated with shorter latency between onset of SE and CSF retrieval ($p = 0.004$), positive history of epilepsy ($p = 0.02$) and an acute symptomatic etiology ($p = 0.04$). BBBD was also present more often in acute symptomatic SE ($p = 0.001$) and was the sole pathological CSF parameter associated with clinical outcome: presence of BBBD was associated with a less favorable outcome ($p = 0.02$).

Significance: Non-infectious SE itself does not commonly cause CSF pleocytosis. Data suggest that the detection of CSF pleocytosis should prompt further diagnostics for an underlying infectious or neoplastic etiology. In contrast, elevation of CSF protein content and BBBD were found frequently in non-infectious SE.

1. Introduction

Status epilepticus (SE) as a frequent neurological condition is associated with high mortality and morbidity. (Brophy et al., 2012) Etiology in adults with SE is predominantly withdrawal of antiepileptic drugs (AED) or an acute symptomatic etiology, mainly acute stroke. (DeLorenzo et al., 1996) Analysis of cerebrospinal fluid (CSF) in SE is used to reveal a CNS inflammation or, in rare cases, meningeal carcinomatosis as etiologies. A CNS infection as etiology of SE is seen in less than ten percent of patients, (DeLorenzo et al., 1996; Knake et al., 2001; Gaspard et al., 2015) moreover, meningeal carcinomatosis causing SE is a rarity. (Dexter et al., 1990) Apart from that, data of CSF findings in non-infectious SE and in patients with history of epilepsy to date remain scarce because CSF investigation is not routinely implemented in the diagnostic work-up of SE. There are reports that ictal activity itself can cause pathological CSF findings, such as CSF pleocytosis, elevated protein and lactate content, and blood-brain-barrier-disturbances (BBBD). (Schmidley and Simon, 1981; Calabrese et al., 1991; Barry and Hauser, 1994; Tumani et al., 2015) Previously reported patient cohorts were inhomogeneous including children and adults, various seizure types, including SE as one type, and in part SE of infectious etiology, so that the evaluation of CSF findings caused by non-infectious SE itself is still limited. For that reason, we here aimed at evaluating the frequency and specificity of pathological CSF findings in patients with non-infectious SE.

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2. Patients and methods

2.1. Patient cohort

We performed a retrospective analysis of all episodes of SE in adult patients (≥18 years) admitted to the Department of Neurology, University Hospital Cologne, an academic tertiary care center, over a period of 10 years (2006–2015) in which CSF analysis had been undertaken in search for an underlying etiology during acute in-hospital treatment. Episodes of SE were identified through electronic hospital database search with documented ICD-10 diagnoses of SE (G41.X).

SE was defined according to previous recommendations (Lowenstein et al., 1999; Trinka et al., 2015) as a prolonged seizure lasting i) more than five min for generalized tonic-clonic seizures, and ii) more than 10 min for all other seizures, or iii) as a series of at least two seizures without regaining inbetween the previously known state of consciousness. Diagnosis of SE was made clinically if an epileptic semiology was clearly present. In case of unspecific signs and symptoms, ictal EEG features were required as proposed earlier. (Beniczky et al., 2013)

SE was assumed to be terminated if seizure activity stopped clinically in alert patients or if the EEG was free of any evidence of ictal activity in intubated patients or those with persistent altered state of consciousness.

Semiology of SE was classified as convulsive SE, if bilateral convulsions were observed, or as non-convulsive SE.

Etiology was classified according to the corresponding ILAE-definition into acute symptomatic, remote symptomatic, progressive symptomatic, or cryptogenic. (Guidelines for epidemiologic studies on epilepsy 1993) If patients had a known epilepsy, we grouped them in absence of an acute provocation as remote symptomatic etiology. In episodes of SE without history of epilepsy or acute provocation factors, etiology was determined cryptogenic. Patients with post-hypoxic myoclonic encephalopathy, meningeal carcinomatosis, cerebral vasculitis, agent-related CNS infections and autoimmune antibody associated encephalitis were excluded from further analyses.

Adequate treatment regimens and sequences were adopted from current guidelines. (Brophy et al., 2012; Glauser et al., 2016; Trinka et al., 2016) Our in-house treatment protocol implemented a staged approach. Proposed drugs in step-wise order were benzodiazepines, followed by AED and by anesthetics. SE was supposed to be refractory if adequate first- and second-line therapy regimens failed. Favorable outcome was present if modified ranking scale (mRS) at discharge did not deteriorate compared to preclinical baseline status (includes pre-SE functional deficits), or if mRS was ≤2 at discharge. Fatal outcome was defined as in-hospital mortality or in case of discharge under strictly palliative supportive care with expected short-time mortality.

2.2. CSF analysis

All data were obtained as part of clinical routine diagnostics during in-hospital treatment. Complete CSF analysis included cell count, protein and lactate content, CSF/serum glucose quotient (Q_{Glc}), disturbances of blood-brain-barrier function, and qualitative intrathecal IgG synthesis. CSF samples with blood contamination were excluded from further analysis because several parameter, *e.g.* cell count, protein content, were supposed to be distorted. White cell counts (WBC) ≥ 5/µl and CSF protein > 0.45 g/l were defined as abnormally elevated. Elevated CSF lactate content was determined ≥ 2.4 mmol/l, pathological Q_{Glc} was assumed at a decreased ratio < 0.5. As internationally accepted parameter for blood-brain barrier function age-dependent albumin-CSF/serum-quotient Q_{Alb} was used. (Reiber, 1998) Intrathecal IgG synthesis as an indicator for humoral immune response was assessed qualitatively by oligoclonal bands (OCB) in isoelectric focusing (IEF) according to international consensus. (Freedman et al., 2005) Unmatched OCBs in CSF and not in serum were considered as markers for autochthone intrathecal IgG production.

We explored the association of pathological CSF findings with clinical characteristics and outcome parameters, such as age, gender, history of epilepsy, etiology, type of SE, refractoriness to AED, favorable or fatal outcome and time from onset to CSF analysis. Because of the retrospective design, latency from onset of SE to CSF analysis could not be determined precisely in all cases. Pragmatically, we assessed time of admission to our hospital as onset time in case of acute transfer to our department. If SE occurred during in-hospital treatment, we assessed documented day of clinical onset at 12:00 p.m. as onset time.

2.3. Statistics

Statistical analyses were performed using SPSS 23.0 for Windows (IBM, Armonk, New York, USA). For comparisons of categorical independent data, chi-square test or Fisher's exact test (if less than 5 items) were performed; for comparisons of independent metrical data, the *t*-test for unpaired variables was performed. All tests were performed two-tailed. P-values < 0.05 were estimated as significant.

3. Results

3.1. Patient cohort

A total of 236 patient files was screened for the diagnosis SE. Of these, in 184 cases diagnosis of SE could be confirmed. One-hundred-sixty-nine episodes of SE were of non-infectious etiology and without evidence of meningeal carcinomatosis. In 61 episodes of SE from 59 patients, CSF analysis had been performed. From them, we had to exclude seven episodes due to blood contamination of CSF samples. Together, 54 episodes of SE from 52 patients were included in further analyses.

Clinical characteristics and demographical data are given in Table 1. Median age at onset was 74 years with most patients aged ≥ 60 years (76%). The majority of 41 (76%) SE were of symptomatic etiology, whereas etiology of 13 (24%) SE remained cryptogenic. Sixteen (30%) SE turned out to be refractory to anticonvulsive medication. A favorable

Table 1
Demographical and clinical data for episodes of SE.

Age at onset	Median 74 years (range24–89, SD 16)
≥ 60 years at onset	N = 41 (76%)
Gender	31 females (57%)
Semiology	*Convulsive*: 26 episodes of SE(48%)
	Non-convulsive: 28 episodes of SE(52%)
Known epilepsy	N = 16
Etiology	*Symptomatic*: 41
	- Acute symptomatic 19
	drug withdrawal: 4
	alcohol abuse: 6
	metabolic/toxic: 6
	acute cerebral bleeding: 0
	acute cerebral infarction: 2
	New cerebral neoplasm: 1
	Acute head injury: 0
	- Remote symptomatic: 18
	Infarction in the past: 8
	Cerebral bleeding in the past: 4
	Head injury in the past: 1
	Perinatal encephalopathy: 1
	Cavernoma: 1
	Known epilepsy without provocation: 3
	- Progressive symptomatic: 4
	Known tumor without meningeal carcinomatosis: 4
	Cryptogenic: 13
Refractory SE	N = 16 (30%)
Outcome of episodes of SE	
Favorable	N = 24 (44%)
Fatal	N = 3 (6%)