Original article

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Cerebrospinal fluid findings after epileptic seizures

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ABSTRACT – We aimed to evaluate ictally-induced CSF parameter changes after seizures in adult patients without acute inflammatory diseases or infectious diseases associated with the central nervous system. In total, 151 patients were included in the study. All patients were admitted to our department of neurology following acute seizures and received an extensive work-up including EEG, cerebral imaging, and CSF examinations. CSF protein elevation was found in most patients (92; 60.9%) and was significantly associated with older age, male sex, and generalized seizures. Abnormal CSF-to-serum glucose ratio was found in only nine patients (5.9%) and did not show any significant associations. CSF lactate was elevated in 34 patients (22.5%) and showed a significant association with focal seizures with impaired consciousness, status epilepticus, the presence of EEG abnormalities in general and epileptiform potentials in particular, as well as epileptogenic lesions on cerebral imaging. Our results indicate that non-inflammatory CSF elevation of protein and lactate after epileptic seizures is relatively common, in contrast to changes in CSF-to-serum glucose ratio, and further suggest that these changes are caused by ictal activity and are related to seizure type and intensity. We found no indication that these changes may have further-reaching pathological implications besides their postictal character.

Key words: epilepsy, seizures, CSF, protein, lactate, CSF-to-serum glucose ratio

The diagnostic value of CSF studies in the work-up of epileptic seizures is limited to cases of acute or chronic inflammatory or infectious disease, as well as to some cases of neoplasia as the seizure aetiology. There is, however, data suggesting that ictal activity itself can cause changes in CSF parameters, such as elevation of protein and lactate levels and even reactive pleocytosis in some cases (Beresford *et al*., 1969; Edwards *et al*., 1983; Prokesch *et al*., 1983; Imuekemhe *et al*., 1989; Calabrese *et al*., 1991; Tumani *et al*., 2015). These changes may be difficult to interpret during clinical routine practice. As data on this subject are very limited, we aimed to evaluate postictal CSF parameters in a group of adult patients with acute seizures.

Patients and methods

A total of 151 patients, who were treated in our department within a two-year time frame (2010-2011) due

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to acute epileptic seizures and received lumbar puncture with CSF analysis without showing pleocytosis (>5 cells/μl) or malignant CSF cells, were included in this analysis. Six patients with CSF pleocytosis and coexisting clinical signs of meningoencephalitis (headache and fever) were excluded from further analysis, as CSF changes in these cases were considered to be related to the underlying infection and not necessarily attributable to the epileptic seizures. Unclear events or cases in which there was uncertainty considering the diagnosis of seizures were excluded. CSF was collected according to a standardised procedure, in the usual way, and analysed in the accredited in-house laboratory at our hospital. We used the internal, validated normal values to assess pathological changes in CSF parameters, as stated below. Lumbar puncture was considered indicated in the case of fever, elevated infection parameters based on laboratory examinations, newly reported headache, and/or unclear seizure aetiology. The following CSF parameters (besides cell count) were routinely evaluated: total protein (mg/l; normal range: 200-400 mg/l), CSF-to-serum glucose ratio (normal range: ≥0.4; according to recent European guidelines [Deisenhammer *et al*., 2001]) and lactate (mmol/l; normal range: 0.6-2.2 mmol/l).

The classification of seizures was performed according to the recent concept and suggestions by the International League Against Epilepsy (Berg *et al*., 2010). History of previous seizures was recorded. All patients underwent EEG (21 scalp electrodes placed according to the 10-20 system) and cerebral imaging within 24 hours after admission. MRI was preferred but CT was performed in patients with contraindications to MRI. EEG was evaluated by a certified board of neurologists specialised in EEG, and was declared abnormal if pathological generalized or focal slowing was present, or if epileptiform patterns were found. Brain lesions detected on cerebral imaging were classified as possibly epileptogenic if they showed cortical involvement and the seizure semiology and/or the EEG findings did not contradict this classification.

Seizure aetiology was documented when it could be assumed with a high level of certainty. In order to facilitate analysis, possible epileptogenic brain lesions were divided into the following categories: acute or chronic cerebrovascular event (infarction or haemorrhage), cerebral tumour, history of infectious cerebral disease (previous meningoencephalitis), brain trauma, or other (including lesions that were only found in one or two patients). The local ethics committee approved the use of this data for the purpose of this study.

Fisher's exact test was used to evaluate associations between parameters of patients' characteristics and seizure aetiologies on the one hand and abnormal CSF findings on the other. In order to compare between patients with abnormal CSF values and patients with normal values concerning metric data (*i.e*. age), we used the Student's t-test. P values of <0.05 were considered statistically significant. Due to the explorative character of the study against the background of sparse data on this subject, we decided against a Bonferroni adjustment in order to not increase the probability of type II errors. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 22 (IBM, USA).

Results

General data

The general characteristics and findings of patients are listed in *table 1*. Of a total of 151 patients, 87 (57.6%) were men and 64 (42.4%) women (p=0.061). The mean age was 50±20 years. A total of 115 patients (76.2%) experienced a first-ever seizure, while 36 patients (23.8%) had a history of previous seizures. There were 34 (22.5%) focal seizures; nine (5.9%) without and 25 (16.6%) with impairment of consciousness. In 117 cases (77.5%), seizures were generalized, including seizures with focal onset with secondary generalization (24 patients). Convulsive status epilepticus was present in 17 patients (11.3%). There were no cases of non-convulsive status.

EEG was abnormal (*i.e*. focal or generalized slowing, or epileptiform patterns were detected) in 73 patients (48.3%). Epileptiform patterns were detected in 15 cases (9.9%).

MRI was performed in almost all patients (149; 98.7%), while two patients (1.3%) received CT because of MRI contraindications. Potentially epileptogenic lesions were found in 32 patients (21.2%). Cerebrovascular lesions were the most common (11; 7.3%), followed by tumours (6; 4%), and post-traumatic (4; 2.6%) and post-infectious (3; 2%) lesions. Specific MRI lesions or abnormalities that were found in no more than two patients each included: hippocampal atrophy/sclerosis (two patients; 1.3%), reversible posterior encephalopathy (two patients; 1.3%), temporal lobe atrophy (one patient; 0.7%), cortical dysplasia (one patient; 0.7%), epidermoid cyst (one patient; 0.7%), and arachnoidal cyst (one patient; 0.7%).

CSF findings

General CSF findings are listed in *table 1*. Protein was elevated in the majority of cases (92; 60.9%); the mean difference above the upper limit of the normal range was 179.8 mg/l (median: 107 mg/l). CSF-to-serum glucose ratio was abnormally decreased (<0.4) in only nine patients (5.9%). Lactate was elevated in 34 patients

Table 1. Patient characteristics and findings (*n*=151).

	Value	**%**
Mean age (years ± SD)	50 ± 20	
Men	87	57.6
Women	64	42.4
First seizure	115	76.2
Previous seizures	36	23.8
Seizure type		
Focal	34	22.5
without impaired consciousness	9	5.9
with impaired consciousness	25	16.6
Generalized	117	77.5
Status epilepticus	17	11.3
Cerebrospinal fluid results		
Protein mean value (mg/l ± SD)	480 ± 219	
Protein elevated	92	60.9
Protein difference from normal value (median, 1st and 3rd quartile) (mg/l)	107 (57; 213)	
Glucose mean value (mg/dl ± SD)	66.7 ± 19	
CSF-to-serum glucose ratio mean value ± SD	0.63 ± 0.17	
CSF-to-serum glucose ratio decreased (<0.4)	9	5.9
Lactate mean value (mmol/l)	1.9 ± 0.6	
Lactate elevated	34	22.5
Lactate difference from normal value (median, 1st and 3rd quartile) (mmol/l)	0.3 (0.2; 0.6)	
EEG		
Any abnormality (generalized/focal slowing, epileptiform patterns)	73	48.3
Epileptiform potentials	15	9.9
Brain imaging		
MRI	149	98.7
CT	2	1.3
Any potentially epileptogenic lesion	32	21.2
Stroke (infarction or haemorrhage)	11	7.3
Tumour	6	4.0
Post-traumatic lesions	4	2.6
Post-infectious lesions	3	2.0
Other lesions	8	5.3

Table 1. (*Continued*)

	Value	%
Hippocampal atrophy/sclerosis	2	1.3
Reversible posterior encephalopathy	2	1.3
Temporal lobe atrophy	1	0.7
Cortical dysplasia	1	0.7
Epidermoid cyst	1	0.7
Arachnoidal cyst	1	0.7

(22.5%); the mean difference above the upper limit of the normal range was 0.5 mmol/l (median: 0.3 mmol/l). The association between CSF values and clinical parameters is shown in *table 2*.

Elevated CSF protein was significantly associated with older age ($p<0.001$), male sex ($p<0.001$), and generalized seizures ($p=0.045$). No significant associations were found relating to history of seizures, focal seizures, status epilepticus, EEG abnormalities, or any kind of epileptogenic lesion. Decreased CSF-to-serum glucose ratio was not significantly associated with any other parameter. Elevated CSF lactate was significantly associated with older age ($p<0.001$), focal seizures with impaired consciousness ($p=0.038$), status epilepticus ($p<0.001$), EEG abnormalities in general ($p=0.001$) and epileptiform potentials in particular ($p=0.007$), as well as with the presence of an epileptogenic lesion ($p=0.036$).

Patients with pleocytosis

There were six patients with CSF pleocytosis, who were diagnosed with meningoencephalitis and were excluded from further analysis. For the sake of completeness, data from these patients is shown in *table 3*. Mean cell count was 1420/μl, mean protein 1418.5 mg/l, mean glucose ratio 0.45, and mean lactate 9.4 mmol/l.

Discussion

There is only scarce data on the subject of CSF changes after epileptic seizures, probably because CSF analysis is not part of the routine epilepsy work-up in most cases. In selected patients with additional symptoms of encephalitis, pathological CSF findings are certainly common and primarily explained by the underlying infection. Since patients with meningitis, encephalitis or meningeal carcinomatosis were excluded from our study, we identified CSF changes related to the seizure itself.

The most interesting finding is that protein elevation is relatively common (61%) and significantly associated with generalized seizures. There is very limited data in the literature showing this phenomenon, mostly in children with complex febrile seizures or status epilepticus (Rider *et al*., 1995; Frank *et al*., 2012) and, interestingly, in one case after electroconvulsive therapy (Alexopoulos *et al*., 1978). In a recent study by Tumani *et al*. (2015), the albumin quotient was found to be pathological in 34% of patients with various seizure types, which, in accordance with our data, also suggests that postictal protein elevation is relatively frequent. The assumed underlying mechanism of transient disturbance of the blood-brain barrier caused by ictal activity has been suggested before, based on albumin values and metalloproteinase-9 concentrations (Li *et al*., 2013).

Abnormal (*i.e*. decreased) CSF/serum glucose ratio was rarely found in our patients (about 6%) and was not significantly associated with any of the analysed parameters. This finding confirms previous data which show that CSF glucose does not seem to be influenced by seizures (Frank *et al*., 2012).

In a similar context, CSF lactate has more often been the focus of previous studies. About 23% patients are reported to have elevated lactate values. Data on the frequency of CSF lactate elevation in similar patient groups is very rare in the literature. Most data on this subject is derived from studies of children with epileptic seizures (Simpson *et al*., 1977; Imuekemhe *et al*., 1989; Livingston *et al*., 1989; Frank *et al*., 2012; Shahim *et al*., 2013). In the aforementioned study by Tumani *et al*. (2015), a similar percentage of pathological lactate values (14%) was reported in a patient collective with various seizure types. Although lactate elevation was overall relatively minor, there were several hints of an association with stronger ictal activity; status epilepticus, focal seizures with impaired consciousness, EEG abnormalities in general and the presence of epileptiform potentials in particular, as well as the presence of epileptogenic lesions were all

Table 2. Relationship between cerebrospinal fluid findings and patient characteristics and findings.

	Protein			**Glucose ratio**			**Lactate**		
	Normal (%)	**High (%)**	***p* value**	**Normal (%)**	**Abnormal (%)**	***p* value**	**Normal (%)**	**High (%)**	***p* value**
Mean age (years ± SD)	43 (±21)	56 (±18)	<**0.001**	50 (±20)	60 (±23)	0.138	48 (±9)	60 (±17)	**0.001**
Men	23 (15.2)	64 (42.4)	<**0.001**	80 (53.0)	7 (4.6%)	0.303	65 (43)	22 (14.6)	0.560
Women	36 (23.8)	28 (18.5)		62 (41.1)	2 (1.3%)		51 (33.8)	13 (8.6)	
First seizure	48 (31.8)	67 (44.4)	0.248	107 (70.9)	8 (5.3)	0.687	87 (57.6)	28 (18.5)	0.654
Previous seizures	11 (7.3)	25 (16.6)		35 (23.2)	1 (0.7)		29 (19.2)	7 (4.6)	
Seizures									
Focal without impaired consciousness	2 (1.3)	7 (4.6)	0.483	9 (6.0)	0	1.000	7 (4.6)	2 (1.3)	1.000
Focal with impaired consciousness	6 (4)	19 (12.6)	0.117	23 (15.2)	2 (1.3)	0.644	15 (9.9)	10 (6.6)	**0.038**
Generalized	51 (33.8)	66 (43.7)	**0.045**	110 (72.8)	7 (4.6)	1.000	94 (62.3)	23 (15.2)	0.067
Status epilepticus	6 (4)	11 (7.3)	0.798	16 (10.6)	1 (0.7)	1.000	6 (4)	11 (7.3)	<**0.001**
No status epilepticus	53 (35.1)	81 (53.6)		126 (83.4)	8 (5.3)		110 (72.8)	24 (15.9)	
EEG abnormalities	30 (19.9)	43 (28.5)	0.739	69 (45.7)	2 (2.6)	1.000	47 (31.1)	26 (17.2)	**0.001**
No EEG abnormalities	29 (19.2)	49 (32.5)		73 (48.3)	5 (3.3)		69 (45.7)	9 (6)	
EEG epileptiform potentials	4 (2.6)	11 (7.3)	0.407	15 (9.9)	0	0.600	7 (4.6)	8 (5.3)	**0.007**
No EEG epileptiform potentials	55 (36.4)	81 (53.6)		127 (84.1)	9 (6.0)		109 (72.2)	27 (17.9)	
Potentially epileptogenic lesion	9 (6)	23 (15.2)	0.220	30 (19.9)	2 (1.3)	1.000	20 (13.2)	12 (7.9)	**0.036**
No potentially epileptogenic lesion	50 (33.1)	69 (45.7)		112 (74.2)	7 (4.6)		96 (63.6)	23 (15.2	
Infarction / haemorrhage	2 (1.3)	9 (6)	0.203	11 (7.3)	0	1.000	7 (4.6)	4 (2.6)	0.281
Tumour	2 (1.3)	4 (2.6)	1.000	5 (3.3)	1 (0.7)	0.313	4 (2.6)	2 (1.3)	0.623
Post-infectious lesions	0	3 (2)	0.281	2 (1.3)	1 (0.7)	0.169	2 (1.3)	1 (0.7)	0.549
Trauma	2 (1.3)	2 (1.3)	0.644	4 (2.6)	0	1.000	2 (1.3)	2 (1.3)	0.230
Other lesions	3 (2)	5 (3.3)	1.000	8 (5.3)	0	1.000	5 (3.3)	3 (2)	0.388

Percentages refer to the total number of patients (151).

significantly associated with lactate elevation. Generalized seizures also tended to be associated with higher lactate, however, this was just below the threshold of statistical significance. Postictal CSF lactate elevation has been demonstrated before, in humans as well as in animal studies. It is thought to be the result of excessive metabolic activity of the brain during seizures (Beresford *et al*., 1969; Calabrese *et al*., 1991). In accordance with our results, this elevation is usually related to prolonged seizures or status epilepticus (Imuekemhe *et al*., 1989; Calabrese *et al*., 1991; Tumani *et al*., 2015).

There was no significant association between history of previous seizures or epilepsy, or the type of

Table 3. CSF findings of excluded patients with pleocytosis.

	Cell count (/μl)	Protein (mg/l)	Glucose ratio	Lactate (mmol/l)
Patient 1	32	1890.0	0.52	5.1
Patient 2	69	314.8	0.67	1.5
Patient 3	55	496.8	0.72	1.5
Patient 4	306	2000.0	0.03	20.0
Patient 5	64	393.1	0.60	3.1
Patient 6	7993	3416.3	0.20	25.4

epileptogenic lesion and any of the examined CSF parameters. We therefore postulate that these findings are connected to the acute seizure itself and not to a chronic epileptogenic activity or structural cerebral abnormality.

With regards to CSF results and symptoms associated with possible inflammation, as mentioned above, we could not with certainty interpret pleocytosis as a direct effect of seizures, but rather as an inflammatory process. Postictal CSF pleocytosis is generally not very common and data vary greatly; occurrence is reported at between 4% and 30% (Schmidley and Simon, 1981; Edwards *et al*., 1983; Prokesch *et al*., 1983; Tumani *et al*., 2015). The recent study by Tumani *et al*. (2015) showed pleocytosis in 6% of the examined seizure patients. However, pleocytosis was defined as a cell count >4/μl (as opposed to our 5/μl limit) and the maximum cell count was 24/μl. Different interpretation of CSF cell count, due to a lack of generally accepted limits defining postictal pleocytosis, as well as different patient selection for lumbar puncture, could account for the variable data on this subject in the literature.

This study has several limitations, including the relatively small sample size, mainly because of the fact that CSF analysis cannot be part of routine practice for every seizure patient. Therefore, in this context, there may have been a selection bias with regards to the patients who received a lumbar puncture. We tried to reduce the bias by excluding the few patients with CSF pleocytosis in the first place. Another limitation is that CSF studies were rather limited to the aforementioned parameters and did not include further serological/immunological examinations or follow-up. Our study demonstrates that CSF changes, especially protein elevation, are common after seizures and that the preceding ictal activity could, at least partly, account for these changes. At least in the case of lactate, there are hints that intensive or longer ictal activity might determine these changes. Further research is necessary to put these presumably postictal CSF changes into an appropriate context. □

Disclosures.
None of the authors have any conflict of interest to disclose.

References

Alexopoulos GS, Kocsis JH, Stokes PE. Increase in CSF protein in association with ECT. *J Neurol Neurosurg Psychiatry* 1978; 41(12): 1145-6.

Beresford HR, Posner JB, Plum F. Changes in brain lactate during induced cerebral seizures. *Arch Neurol* 1969; 20(3): 243-8.

Berg AT, Berkovic SF, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51(4): 676-85.

Calabrese VP, Gruemer HD, James K, Hranowsky N, DeLorenzo RJ. Cerebrospinal fluid lactate levels and prognosis in status epilepticus. *Epilepsia* 1991; 32(6): 816-21.

Deisenhammer F, Bartos A, Egg R, *et al*. Routine cerebrospinal fluid (CSF) analysis. In: Gilhus NE, Barnes MP, Brainin M, eds. *European handbook of neurological management: Volume 1, 2nd Edition*. Blackwell Publishing Ltd, 2001, 5-17.

Edwards R, Schmidley JW, Simon RP. How often does a CSF pleocytosis follow generalized convulsions. *Ann Neurol* 1983; 13(4): 460-2.

Frank LM, Shinnar S, Hesdorffer DC, *et al*. Cerebrospinal fluid findings in children with fever-associated status epilepticus: results of the consequences of prolonged febrile seizures (FEBSTAT) study. *J Pediatr* 2012; 161(6): 1169-71.

Imuekemhe SO, Obi JO, Sykes RM. Cerebrospinal fluid/serum lactic acid in febrile convulsions. *East Afr Med J* 1989; 66(9): 589-93.

Li YJ, Wang ZH, Zhang B, *et al*. Disruption of the blood-brain barrier after generalized tonic-clonic seizures correlates with cerebrospinal fluid MMP-9 levels. *J Neuroinflammation* 2013; 10: 80.

Livingston JH, Brown JK, Harkness RA, McCreanor GM, O'Hare AE. Cerebrospinal fluid nucleotide metabolites following short febrile convulsions. *Dev Med Child Neurol* 1989; 31(2): 161-7.

Prokesch RC, Rimland D, Petrini Jr. JL, Fein AB. Cerebrospinal fluid pleocytosis after seizures. *South Med J* 1983; 76(3): 322-7.

Rider LG, Thapa PB, Del Beccaro MA, *et al*. Cerebrospinal fluid analysis in children with seizures. *Pediatr Emerg Care* 1995; 11(4): 226-9.

Schmidley JW, Simon RP. Postictal pleocytosis. *Ann Neurol* 1981; 9(1): 81-4.

Shahim P, Darin N, Andreasson U, *et al*. Cerebrospinal fluid brain injury biomarkers in children: a multicenter study. *Pediatr Neurol* 2013; 49(1): 31-9, e2.

Simpson H, Habel AH, George EL. Cerebrospinal fluid acid-base status and lactate and pyruvate concentrations after short (less than 30 minutes) first febrile convulsions in children. *Arch Dis Child* 1977; 52(11): 836-43.

Tumani H, Jobs C, Brettschneider J, Hoppner AC, Kerling F, Fauser S. Effect of epileptic seizures on the cerebrospinal fluid – a systematic retrospective analysis. *Epilepsy Res* 2015; 114: 23-31.