Cerebrospinal fluid analysis after unprovoked first seizure

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Summary

The aim of this study was to determine cerebrospinal fluid (CSF) characteristics after an unprovoked first seizure (UFS). We reviewed the medical records of 71 patients with UFS who underwent lumbar puncture, and examined the CSF parameters. Each CSF parameter was evaluated separately for potential correlations with the other study variables. We observed an overall frequency of CSF abnormalities of 35.2%. CSF protein was the most common abnormal parameter (31%) and showed significant positive correlations with male gender ($p=0.037$) and older age ($p=0.007$). Only seven patients (9.9%) had an abnormal cell count (5-40 cells/ μ l). Higher CSF cell counts were found to predict a longer hospitalization period ($p=0.005$). No relationship with abnormal EEG findings could be established ($p=0.169$). This study is one of the few to evaluate postictal CSF parameters in a clinical setting, and to our knowledge the first to investigate these parameters specifically in the emergency department. The development of a rapid, easy-to-use test that does not require extensive laboratory equipment to dif-

ferentiate UFS from other conditions could be of great value in everyday clinical practice.

KEY WORDS: cerebrospinal fluid, emergency department, lumbar puncture, unprovoked first seizure

Introduction

A practice parameter developed by the American Academy of Neurology and the American Epilepsy Society provides an evidence-based guideline on the evaluation of adults with an apparent unprovoked first seizure (UFS) (Krumholz et al., 2007). According to the parameter, EEG and brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) should be considered part of the routine neurodiagnostic evaluation (Level B recommendation). Interestingly there are insufficient data to support or refute the use of other studies, including lumbar puncture (LP), for the purpose of determining the cause of such seizures (Krumholz et al., 2007). Most clinicians perform LP only in febrile patients or in specific clinical circumstances, and data concerning its routine use in such cases are conflicting. Our study aimed to assess the possible alterations in cerebrospinal fluid (CSF) values after UFS.

Materials and methods

We reviewed the electronic data of all patients admitted to the Department of Neurology of “Evangelismos” General Hospital between January 1, 2011 and August 31, 2013. In accordance with our department’s protocol for UFS, every patient with an apparent UFS underwent LP in the emergency department (ED); all LPs were performed within 24 hours of seizure onset. All patients who underwent LP gave their consent to the procedure. Two independent investigators reviewed the patients’ medical records for notes, by the attending physician, nurses and ED personnel, regarding physical examinations, previous medical history and eye-witness accounts indicating possible seizure episodes. To confirm a seizure diagnosis we used established seizure feature criteria (Appendix). Our aim was to successfully detect only those patients who had a first and single

seizure at the time of initial presentation without an apparent cause. A single seizure was defined as one episode or more occurring within a 24-hour span, provided the patient showed full recovery of consciousness between the episodes.

Patients were included in the study if they met the following criteria: i) age >16 years, ii) diagnosis of possible UFS on hospital admission, iii) complete workup protocol for UFS [brain imaging (CT and MRI), EEG, laboratory tests and LP]. The tests performed in the ED were brain CT scan, laboratory tests and LP. The patients in the study sample, by definition, had to be UFS patients; consequently, those in whom a secondary cause of seizures was diagnosed during the medical workup, or who had known epilepsy, were excluded. In more detail, the exclusion criteria were: i) febrile or immunocompromised state, ii) the presence of structural damage or lesions on ED brain CT scan, or laboratory tests or any other factor indicating a provoked seizure, iii) episodes of unexplained loss of consciousness during the previous five years for which the patient had been evaluated by a neurologist and/or submitted to complete testing with EEG and/or brain imaging, iv) any contraindication to LP, v) failure to acquire, within 24 hours, information regarding the patient's mental and physical status prior to the seizure, vi) deceased upon arrival at the ED. We also excluded patients with focal neurological deficits that did not subside after 24 hours and those with a diagnosis of stroke on hospital discharge. We included patients with focal maturational imaging findings (heterotopia, cortical dysplasia, etc.) and those with diffuse bilateral white matter lesions consistent with an aging brain.

Data collected included demographic data, seizure type, LP results (cell count, CSF/serum glucose ratio and total protein), prescription of anti-epileptic drug treatment on discharge, days of hospitalization, and final diagnosis. The following were considered normal LP findings: CSF cells $\leq 5/\mu\text{l}$, protein $< 45 \text{ mg/dl}$ and CSF/serum glucose ratio ≥ 0.4 . In the event of blood-contaminated CSF we used the corrected CSF white blood cell (WBC) count = $(\text{CSF WBC count} - [\text{CSF red blood cell count}/500])$. Lactate CSF measures were not obtained in the ED as a standard procedure and therefore could not be included in the study.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 21.0) software (SPSS Inc., Chicago, IL, USA). Each CSF parameter was evaluated separately for potential correlations with the other study variables. CSF cell count and CSF protein level were both treated as quantitative (absolute count) and as qualitative variables (normal – abnormal). CSF/serum glucose ratio was treated only as a quantitative variable, due to the absence of cases with hypoglycorrhachia in our sample. Normality tests (Kolmogorov-Smirnov) and Q-Q plot inspections revealed a lack of normality between groups for most quantitative variables, except for age and CSF/serum glucose ratio. As a result we performed non-parametric tests for most comparisons

(Mann-Whitney, Kruskal-Wallis, Spearman's), and parametric tests (t-test, ANOVA, Pearson's rho) in a few cases where these were applicable. Comparisons between qualitative variables were performed with the Pearson's chi square test. The level of significance was set at 0.007 for quantitative analyses after Bonferroni correction and at 0.05 for chi square tests. Effect size of significant correlations was investigated by Spearman's, Pearson's rho or OR (odds ratio), depending on which measure was applicable in each case.

Results

During the period of time considered, 13,938 patients were evaluated at the neurological ED and a total of 3,844 were subsequently admitted to the neurology department. A total of 71 patients met the inclusion criteria and were ultimately eligible for our study.

Table I presents the main characteristics of the study sample. Our patients were predominantly male (63.4%), with a mean age of 36.2 years. Generalized tonic-clonic seizures were most common type encountered (78.9%). CSF analysis showed at least one abnormal characteristic in 25 cases (35.2%). CSF protein level was abnormal in 31% of cases, while CSF cell count was abnormal in 9.9% of cases. Mean CSF/serum glucose ratio was $0.68 (\pm 0.12)$. The majority of patients had normal imaging (80.3%) and abnormal EEG (57.8%), although epileptiform findings were present only in 25.4%. Most patients were hospitalized for periods shorter than a week. Finally, the majority of cases were prescribed an antiepileptic agent on discharge (69%).

Table II presents the results of univariate analyses examining potential correlations of the study variables with CSF cell count. Abnormal imaging correlated significantly with higher counts ($p=0.007$), increasing the risk modestly (Spearman's 0.25). There was also a significant correlation of hospitalization days with higher CSF cell counts ($p=0.005$), increasing the probability modestly to moderately (Spearman's 0.33).

Table III presents the results of univariate analyses examining potential correlations of the study variables with CSF protein level. Abnormal levels showed a significant ($p=0.037$) positive correlation with male gender (OR 3.67). Higher and/or abnormal levels correlated significantly with age ($p=0.001$ and 0.007 respectively), with a moderate (Spearman's 0.39) and a modest (OR 1.04) increase in probability, respectively, in older patients.

Table IV presents univariate analyses examining potential correlations of the study variables with CSF glucose level. Higher levels displayed a significant ($p=0.007$) negative correlation with abnormal EEG, decreasing the risk modestly to moderately (Pearson's -0.31). Finally, patients receiving treatment after discharge showed a trend towards lower CSF glucose levels ($p=0.033$).

Discussion

In the present study we examined abnormal CSF values after UFS in a sample of 71 patients hospitalized in our department. The overall frequency of CSF abnormalities was 35.2%. To our knowledge, few studies have evaluated postictal CSF values in the setting of clinical practice in adult patients (Devinsky et al., 1988; Peltola et al., 2002; Li et al., 2013). None of these studies recruited more than 37 patients (31, 37 and 27 respectively). Edwards et al. (1983) recruited 91 patients but, as in the aforementioned studies, these authors did not exclude febrile patients or those with secondary epileptic seizures, thus limiting the

generalization of their results. Our study focused on UFS patients, in order to examine CSF findings attributable to seizures only and not to a possible chronic epileptic state, or other neurological conditions.

Among the aforementioned results, CSF protein was the most common abnormal parameter (31%), showing higher than normal values. This finding implies disruption of blood-brain barrier (BBB) in patients with UFS. Over recent decades there has been growing evidence of a positive correlation between BBB disruption and seizures. Several experimental studies, both in animal models and human hippocampal tissue, suggest high albumin levels as an indicator of BBB disruption and inflammation (Seiffert et al., 2004; Oby and Janigro, 2006; Ivens et al., 2007; Friedman et al., 2009). Inflammation can either occur due to albumin, or it can preexist and lead to BBB disruption and high albumin levels (van Vliet et al., 2007). To reinforce the epileptogenic features of albumin, studies have shown enhanced slow-wave or spiking EEG activity in areas with high albumin levels and disruption of the BBB (Cornford et al., 1998; Tomkins et al., 2001). In our study we could not establish a connection with abnormal EEG findings ($p=0.169$), although abnormal protein levels showed significant positive correlations with male gender and older age. It must be noted that due to the study design we were not able to determine the total serum albumin level in the ED, and thus we lack data concerning the CSF/serum albumin ratio, which could have allowed age-dependent corrections of normal values. Lumbar degenerative changes and/or stenosis found in older patients can potentially confound the correlation of age with CSF protein elevation.

Another issue to be addressed, since a disruption of BBB is suspected, is whether USF affects the CSF cell count. In the present study only seven patients (9.9%) showed an abnormal cell count (5–40 cells/ μ l). Higher CSF cell counts were significantly more frequent in patients with imaging findings, but did not correlate with type of seizures. A review of the literature reveals very limited data concerning postictal pleocytosis. A review of a sample of 91 patients by Edwards et al. (1983) revealed two with CSF pleocytosis (12 and 65 WBC), but in both these patients seizures were attributed to chronic secondary causes (post-traumatic encephalomalacia and alcohol abuse with Korsakoff's psychosis respectively). Devinsky et al. (1988) found that pleocytosis was related to the time of CSF sample collection but their study did not answer the question of whether focal or generalized seizures lead to increased leukocyte counts in CSF. Another published review (Aminoff and Simon, 1980) described pleocytosis (>5 cells/ mm^3 , mean: 10.2 cells/ mm^3 , range: 0–71 cells/ mm^3) in patients with status epilepticus in whom infection had first been excluded. Recent experimental data comparing human cortical CNS tissue from epileptic patients and controls found higher leukocyte counts in the first, suggesting a possible role of leukocyte-vascular adhesion in the pathogenesis of seizures and epilepsy (Fabene et al., 2008). In the

Table I - Main characteristics of the study sample (n=71).

Variable	n (%)	Mean (SD) ¹	Median (min-max)
Gender			
- Male	45 (63.4)		
- Female	26 (36.6)		
Age known	69 (97.1)	36.2 (16.1)	34 (16–69)
Age missing ²	2 (2.9)		
Seizure type			
- Focal	2 (2.8)		
- Secondary generalized	13 (18.3)		
- Generalized tonic-clonic	56 (78.9)		
CSF cell count			1 (0–40)
- Normal	64 (91.1)		1 (0–4)
- Abnormal	7 (9.9)		16 (6–40)
CSF protein level			35 (18–95)
- Normal	49 (69)		30 (18–44)
- Abnormal	22 (31)		55 (45–95)
CSF glucose ³ known	70 (98.6)	68 (11.1)	66.5 (37–108)
CSF glucose missing	1 (1.4)		
Imaging (CT or MRI)			
- Normal	57 (80.3)		
- Focal maturational ⁴	11 (15.5)		
- Missing	3 (4.2)		
EEG			
- Abnormal	41 (57.8)		
Epileptiform	18 (25.4)		
Slow non-epileptiform	23 (32.4)		
- Normal	30 (42.2)		
Hospitalization days			5 (2–35)
Treatment after discharge			
- Yes	49 (69)		
- No	21 (29.6)		
- Missing	1 (1.4)		

Abbreviations and notes: n=number of patients; SD=standard deviation; min-max= minimum count/level – maximum count/level; CSF=cerebrospinal fluid; CT=computerized tomography; MRI=magnetic resonance imaging; EEG=electroencephalogram.¹ Shown only for variables with a normal distribution; ²“Missing” category is omitted in variables where data were available for all patients; ³% of serum; ⁴heterotopias, cortical dysplasias, etc.

present study the exact time of CSF sample collection was not recorded, but all the patients underwent LP in the ED, within 24 hours of seizure onset. Interestingly, higher CSF cell counts were found to predict a longer hospital stay.

As regards the remaining evaluated parameters, we did not establish positive conclusions. Glucose CSF data showed no correlation with the study variables, with the exception of the finding that higher levels were significantly less frequent in patients with abnormal EEG recordings. The analyses concerning non-CSF parameters failed to reveal any significant correlations of abnormal imaging with demographic data,

hospitalization days, or probability of antiepileptic treatment after discharge. Notably, abnormal imaging did not even correlate with seizure classification (performed by an experienced neurologist in the ED). Abnormal EEG showed no significant correlations with seizure type, patient age, or days of hospitalization. A possible explanation for the lack of correlations between EEG and seizure type is that both primary and secondary generalized seizures were reported and documented as generalized tonic-clonic seizures in the ED. Nevertheless, EEG showed significant positive correlations with female gender [$p=0.017$, OR 3.65 (1.23–10.83)] and probability of antiepileptic

Table II - Univariate analyses examining potential correlations of the study variables with CSF cell count.

Variable	Abnormal CSF cell count, n(%)	Test ¹	p value ²	Effect size (OR or Spearman's)	95% CI for OR
Gender		Mann-Whitney	0.683	Spearman's 0.05 (male) $p=0.686$	NE
- Male	4 (8.9)	Pearson's chi square test ³	0.718	OR 0.84 (male)	0.34–2.09
- Female	3 (11.5)				
Age		Spearman's	0.486	Spearman's 0.09 $p=0.486$	NE
		t-test	0.558	OR 0.99 (older age)	0.94–1.04
Seizure type		Kruskal-Wallis	0.898	Spearman's –0.04 (focal/secondary) $p=0.752$	NE
- Focal (n=2)	0 (0)	Pearson's chi square test	0.846	OR 0.91 (focal/secondary)	0.66–1.27
- Secondary generalized (n=13)	1 (7.7)				
- Generalized tonic-clonic (n=56)	6 (10.7)				
Imaging (CT or MRI)		Mann-Whitney	0.007	Spearman's 0.25 (focal) $p=0.044$	NE
- Normal (n=57)	4 (7)	Pearson's chi square test	0.138	OR 1.52 (focal)	0.79–2.91
- Focal maturational ⁴ /Aging (n=11)	3 (27.3)				
EEG		Kruskal-Wallis	0.870	Spearman's 0.06 (normal) $p=0.605$	NE
- Abnormal (n=41)	4 (9.8)	Pearson's chi square test	0.965	OR 1.03 (normal)	0.52–2.02
- Epileptiform (n=18)	2 (11.1)				
- Slow non-epileptiform (n=23)	2 (8.7)				
- Normal (n=30)	3 (10)				
Hospitalization days		Spearman's	0.005	Spearman's 0.33 $p=0.005$	NE
		Mann-Whitney	0.254	OR 1.07 (prolonged hospitalization)	0.94–1.21
Treatment after discharge		Mann-Whitney	0.358	Spearman's 0.11 (Yes) $p=0.362$	NE
- Yes (n=49)	7 (14.3)	Pearson's chi square test	0.164	OR 1.33 (Yes)	0.78–2.54
- No (n=21)	0 (0)				

Abbreviations and notes: CSF=cerebrospinal fluid; OR=odds ratio; CI=confidence interval; n=number of patients; NE=not estimated; CT=computerized tomography; MRI=magnetic resonance imaging; EEG= electroencephalogram; ¹ In the first line of each row CSF cell count is treated as a quantitative variable. In the second line of each row CSF cell count is treated as a qualitative variable (normal – abnormal); ² Level of significance $p=0.007$ for all quantitative comparative analyses after Bonferroni correction. Level of significance $p=0.05$ for Pearson's chi square tests; ³ Yates correction for 2X2 tables; ⁴ heterotopia, cortical dysplasia, etc.

treatment after discharge [$p=0.003$, OR 6.07 (1.96–18.85)]. It should be stressed, though, that we did not examine EEG recordings in relation to lateralized findings.

Our study has several limitations that should be considered when interpreting the results. One important factor is that it is difficult to draw any strong conclusions from this relatively small sample (71 patients). Larger samples are therefore needed in order to evaluate the accuracy and reproducibility of the findings. Moreover, due to the study design we did not use a

control group to evaluate CSF findings in normal subjects. For this reason, we were unable to investigate the possible differentiating value of LP in patients with UFS. We can simply point out that our findings appear consistent with similar studies and with results obtained in experimental models and that we hope to supplement the existing literature on this topic. An important limitation concerns the determination of the eligible subject list. Although we manually screened these patients' records to ensure that each met the eligibility requirements, it is possible that some cases

Table III - Univariate analyses examining potential correlations of the study variables with CSF protein level.

Variable	Abnormal CSF protein level, n (%)	Test ¹	p value ²	Effect size (OR or Spearman's)	95% CI for OR
Gender					
- Male (n=45)	18 (40)	Mann-Whitney	0.01	Spearman's 0.31 (male) $p=0.009$	NE
- Female (n=26)	4 (15.4)	Pearson's chi square test ³	0.037	OR 3.67 (male)	1.08–12.43
Age					
		Spearman's	0.001	Spearman's 0.39 $p=0.001$	NE
		t-test	0.007	OR 1.04 (older age)	1.01–1.08
Seizure type					
- Focal (n=2)	2 (100)	Kruskal-Wallis	0.065	Spearman's 0.03 (primary) $p=0.818$	NE
- Secondary generalized (n=13)	2 (15.4)				
- Generalized tonic-clonic (n=56)	18 (32.2)	Pearson's chi square test	0.06	OR 1.08 (primary)	0.76–1.54
Imaging (CT or MRI)					
- Normal (n=57)	18 (31.6)	Mann-Whitney	0.154	Spearman's -0.17 (focal) $p=0.156$	NE
- Focal maturational ⁴ /Aging (n=11)	2 (18.2)	Pearson's chi square test	0.372	OR 0.84 (focal)	0.60–1.16
EEG					
- Abnormal (n=41)	11 (26.8)	Kruskal-Wallis	0.169	Spearman's 0.16 (normal) $p=0.180$	NE
- Epileptiform (n=18)	5 (27.8)				
- Slow non-epileptiform (n=23)	6 (26.1)	Pearson's chi square test	0.611	OR 1.25 (normal)	0.78–2.01
- Normal (n=30)	11 (36.7)				
Hospitalization days					
		Spearman's	0.585	Spearman's 0.07 $p=0.585$	NE
		Mann-Whitney	0.353	OR 1.09 (prolonged hospitalization)	0.91–1.31
Treatment after discharge					
- Yes (n=49)	12 (24.5)	Mann-Whitney	0.184	Spearman's 0.16 (no) $p=0.186$	NE
- No (n=21)	9 (42.8)	Pearson's chi square test	0.211	OR 1.75 (no)	0.87–3.51

Abbreviations and notes: CSF=cerebrospinal fluid; OR=odds ratio; CI=confidence interval; n=number of patients; NE=not estimated; CT=computerized tomography; MRI=magnetic resonance imaging; EEG=electroencephalogram; ¹ In the first line of each row CSF protein level is treated as a quantitative variable. In the second line of each row CSF protein level is treated as a qualitative variable (normal – abnormal); ² Level of significance $p=0.007$ for all quantitative comparative analyses after Bonferroni correction. Level of significance $p=0.05$ for Pearson's chi square tests; ³ Yates correction for 2X2 tables; ⁴ heterotopia, cortical dysplasia, etc.

Table IV - Univariate analyses examining potential correlations of the study variables with CSF glucose level.

Variable	Mean glucose level (SD)	Test	p value ¹	Effect size (Pearson or Spearman's)	Unstandardized B +/-95% CI
Gender		t-test	0.384	Pearson 0.11 (males)	2.41 [(-3.08) – 7.89]
- Male (n=45)	68.91 (10.63)				
- Female (n=26)	66.50 (11.90)				
Age		Pearson	0.650	Pearson -0.06	-0.04 [(-0.20) – 0.13]
Seizure type		ANOVA	0.351	Pearson 0.17 (primary vs focal/secondary) p=0.149	4.69 [(-1.71) – 11.08]
- Focal (n=2)					
- Secondary generalized (n=13)	64.33 (12.59)				
- Generalized tonic-clonic (n=56)	69.02 (10.56)				
Imaging (CT or MRI)		t-test	-0.654	Pearson -0.06 (focal)	-1.68 [(-9.11) – 5.76]
- Normal (n=57)	68.40 (11.32)				
- Focal Maturational ² /Aging (n=11)	66.73 (11.21)				
EEG		ANOVA	0.034	Pearson -0.31 (abnormal)	-6.94 [(-12.18) – (-1.69)]
- Abnormal (n=41)	65.24 (9.92)				
- Epileptiform (n=18)	64.39 (12.93)	t-test (normal vs abnormal)	0.007		
- Slow non-epileptiform (n=23)	65.91 (6.97)				
- Normal (n=30)	72.18 (11.79)				
Hospitalization days		Spearman's	0.676	Spearman's 0.05, p=0.676	NE
Treatment after discharge		t-test	0.033	Pearson -0.26 (yes)	-6.29 [(-12.04) – (-0.53)]
- Yes (n=49)	66.27 (11.38)				
- No (n=21)	72.55 (9.44)				

Abbreviations: CSF=cerebrospinal fluid; SD=standard deviation; CI=confidence interval; n=number of patients; CT=computerized tomography; MRI=magnetic resonance imaging; EEG=electroencephalogram; NE=not estimated; ¹ Level of significance p=0.007 for all quantitative analyses after Bonferroni correction; ² heterotopia, cortical dysplasia, etc.

escaped our attention. We also assumed that all features of seizures were observed and noted in the patients' records. Nevertheless the high ratio of generalized tonic-clonic seizures to secondary generalized seizures (56 to 15) raises the suspicion that, in fact, a large proportion of the first group were cases of focal onset with secondary generalization. Future studies on this topic may focus on enrolling patients prospectively so as to gain a comprehensive understanding of the role of CSF abnormalities in patients with UFS. New research may show CSF analysis in patients with UFS or epilepsy to be useful for detecting antineuronal or paraneoplastic antibodies. Furthermore, future studies may allow the relationship between CSF findings and EEG abnormalities to be evaluated in a more consistent way and may also re-assess the usefulness of LP in UFS.

In conclusion, CSF collected within 24 hours in patients with UFS demonstrated pleocytosis in 10% and protein elevation in 30%. These findings may reflect temporary disruption of the BBB soon after UFS. The development of a rapid, easy-to-use test that does not require extensive laboratory equipment

to differentiate UFS from other conditions could be of great value in everyday clinical practice.

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APPENDIX (Adapted from Hirtz et al., 2000)

Symptoms during seizure (ictal)

Aura: Subjective sensations

Behavior: Mood or behavioral changes before the seizure

Pre-ictal symptoms: Described by patient or witnessed

Vocal: Cry or gasp, slurring of words, garbled speech

Motor: Head or eye turning, eye deviation, posturing, jerking (rhythmic), stiffening, automatisms (purposeless repetitive movements such as picking at clothing, lip smacking); generalized or focal movements

Respiration: Change in breathing pattern, cessation of breathing, cyanosis

Autonomic: Pupillary dilation, drooling, change in respiratory or heart rate, incontinence, pallor, vomiting
Loss of consciousness or inability to understand or speak

Symptoms following a seizure (postictal)

Amnesia for events

Confusion

Lethargy

Sleepiness

Headaches and muscle aches

Transient focal weakness (Todd's paresis)

Nausea or vomiting

Biting of tongue