Status epilepticus of inflammatory etiology

A cohort study

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ABSTRACT

Objective: Inflammation-related epilepsy is increasingly recognized; however, studies on status epilepticus (SE) are very infrequent. We therefore aimed to determine the frequency of inflammatory etiologies in adult SE, and to assess related demographic features and outcomes.

Methods: This was a retrospective analysis of a prospective registry of adult patients with SE treated in our center, from January 2008 to June 2014, excluding postanoxic causes. We classified SE episodes into 3 etiologic categories: infectious, autoimmune, and noninflammatory. Demographic and clinical variables were analyzed regarding their relationship to etiologies and functional outcome.

Results: Among the 570 SE consecutive episodes, 33 (6%) were inflammatory (2.5% autoimmune; 3.3% infectious), without any change in frequency over the study period. Inflammatory SE episodes involved younger patients (mean age 53 vs 61 years, $p = 0.015$) and were more often refractory to initial antiepileptic treatment (58% vs 38%, odds ratio = 2.19, 95% confidence interval = 1.07–4.47, $p = 0.041$), despite similar clinical outcome. Subgroup analysis showed that, compared with infectious SE episodes, autoimmune SE involved younger adults (mean age 44 vs 60 years, $p = 0.017$) and was associated with lower morbidity (return to baseline conditions in 71% vs 32%, odds ratio = 5.41, 95% confidence interval = 1.19–24.52, $p = 0.043$) without any difference in mortality.

Conclusions: Despite increasing awareness, inflammatory SE etiologies were relatively rare; their occurrence in younger individuals and higher refractoriness to treatment did not have any effect on outcome. Autoimmune SE episodes also occurred in younger patients, but tended to have better outcomes in survivors than infectious SE. **Neurology® 2015;85:464–470**

GLOSSARY

GABA = γ -aminobutyric acid; **SE** = status epilepticus; **STESS** = Status Epilepticus Severity Score.

Status epilepticus (SE), a severe neurologic condition associated with significant morbidity and mortality,¹ has an estimated annual incidence of 8.5 to 27.2/100,000.^{2–6} Given that outcome seems to be influenced mostly by nonmodifiable variables, such as age and underlying etiology,^{7–9} a refined understanding on particular SE causes may help in improving current knowledge on risk of mortality and morbidity. SE etiologies are multiple^{2,5,6} and have been classically categorized into acute or remote symptomatic, progressive symptomatic, and unknown or idiopathic.¹⁰ In this context, despite the increasing recognition in recent years of neuronal surface and intracellular autoantibodies as a potential cause of epilepsy,^{11–13} the role of neuroinflammation in SE has received relatively little attention.

Our study aimed to assess the frequency of SE due to inflammatory etiology, and explore whether this subset of patients differs from the general SE population in demographic/clinical features and prognosis.

METHODS Study design and population. This is a retrospective study based on our SE registry, including all adult (older than 16 years) patients with SE (except from postanoxic SE) treated at our tertiary hospital, whose details have been previously described.¹⁴

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We identified episodes occurring in the period between January 2008 and June 2014, and classified them into “inflammatory” and “noninflammatory,” according to the underlying etiology (see below).

Variables and ethics approval. Clinical variables were recorded prospectively in the SE registry, including demographic features, SE etiology, the validated clinical Status Epilepticus Severity Score (STESS),^{15,16} refractoriness to initial treatment (lack of response to one benzodiazepine and one additional nonanesthetic antiepileptic drug¹⁴), need of pharmacologic coma induction for SE treatment, and outcome at discharge (categorized into the following: return to baseline clinical conditions, new handicap, or death). For the infectious and autoimmune SE groups, we additionally retrieved, on our computerized hospital records, immunomodulatory treatments (including corticoids, immunoglobulins, plasma exchange, rituximab) administered during the SE episode. To explore the temporal distribution of the inflammatory SE episodes during the study period, as neuronal autoantibody detection tests have evolved over time, we compared the number of infectious episodes and autoimmune episodes in each half-period of the study. In the context of the SE registry, this observational cohort study was fully approved by our Ethic Commission.

Definitions. In the registry, SE is defined as prolonged or repetitive seizures without full recovery between episodes over more than 5 minutes.¹ Neurology consultants established clinical SE diagnosis and although practically all patients with SE suspicion undergo EEG, this was formally required to confirm nonconvulsive SE forms.¹⁷ SE etiologies were categorized as “acute” if the underlying cause appeared within 7 days before the episode.¹⁰ In the database, we defined *inflammatory* SE as caused by proven acute inflammation of the brain parenchyma, with or without involvement of meninges, associated with neurologic dysfunction¹⁸ (see below); episodes with previous inflammatory CNS lesions without evidence of acute precipitants (e.g., a remote CNS abscess) were classified as *noninflammatory*.

The inflammatory SE group was divided into 2 subsets: one related to infection of the brain (such as viral, bacterial, or parasitic meningoencephalitis, acute abscess or empyema, or prion disease), and one to proven autoimmune disorders. Given that mild CSF pleocytosis (>5 white blood cells/mm³) and disruption of the blood-brain barrier can be observed in the context of SE, independently of its etiology, additional features were needed to define the 2 inflammatory groups. Therefore, we used the diagnosis *infectious SE* if microbiologic studies (serology, blood/CSF cultures, or CSF PCR) demonstrated an infectious agent, or if an infectious agent was not demonstrated, the diagnosis of *probable infectious meningoencephalitis* was suggested by at least one the following: (1) fever $>38.5^{\circ}\text{C}$, (2) increased white blood cell count or C-reactive protein, (3) findings highly suggestive of a bacterial infection, such as turbid CSF, neutrophilic pleocytosis, or low CSF/serum glucose ratio (<0.5), or (4) clinical picture suggestive of a viral origin (such as preceding flu-like syndrome during seasonal endemic periods) and CSF with lymphocytic pleocytosis and negative serum and CSF autoantibodies. Supportive features for *autoimmune SE* were synthesis of immunoglobulin G in the CNS (in absence of the above indicated findings suggestive of an infection), neuroimaging (such as MRI medial temporal lobe abnormalities typical of limbic encephalitis), identification of autoimmune antibodies in serum or CSF (targeting surface, intracellular or synaptic neuronal epitopes), or presumed cellular autoimmune response directed against the CNS (such as Rasmussen encephalitis or multiple sclerosis).

Identification of antineuronal antibodies in serum and CSF samples from our patients with SE was performed as follows: first

the serum and CSF were screened using immunohistochemistry on rat brain tissue (EUROIMMUN, Lübeck, Germany), then confirmed through cell-based assays on human kidney cells HEK293 transfected with recombinant autoantigens (EUROIMMUN), or immunoblot confirmation in case of onconeural intracellular antigens (Fa. Ravo, Freiburg, Germany), as previously reported.^{19,20} Serum autoantibodies to thyroid stimulating hormone receptor were determined by a radioreceptor assay (BRAHMS TRAK RIA 77.5; BRAHMS GmbH, Hennigsdorf, Germany), while radioimmunologic assays were used for both serum autoantibodies to microsomal thyroid peroxidase (BRAHMS Anti TPOn RIA 90.1) and thyroglobulin (BRAHMS Anti TGn RIA 27.1).

Statistical analysis. Comparisons were performed using *t* tests and a 2-tailed Fisher exact test as appropriate. We defined statistical significance as $p < 0.05$. Odds ratios for categorical variables were calculated together with 95% confidence intervals. We did not perform multiple variables analysis given the exploratory character of this study. Calculations were performed using STATA software, version 13 (StataCorp, College Station, TX).

RESULTS During the study period, we identified 570 SE episodes occurring in 484 patients, of which 33 (6%) were attributable to an inflammatory etiology. Demographic features, immunomodulatory treatments, and detailed etiologies of these inflammatory episodes (including antineuronal antibodies studies) are shown in table 1.

Compared with noninflammatory SE episodes, those related to an inflammatory cause involved younger patients and were more often refractory to initial antiepileptic treatment (table 2). By contrast, there was no substantial difference between the 2 groups regarding sex, presence of seizures before the SE episode, seizure type, STESS, need of pharmacologic coma induction for treatment, and clinical outcome including mortality.

On analysis of the 2 inflammatory SE subsets (table 3), infectious episodes more frequently involved older individuals, were more often related to an acute etiology, and were more severe according to the STESS. Moreover, they displayed worse functional outcome regarding new handicap at hospital discharge; however, mortality was similar, as was refractoriness to antiepileptic medication.

The incidences of autoimmune vs infectious SE episodes were similarly distributed over the study period: we observed 8/14 and 8/19 SE episodes in the first 39 months (from January 2008 to June 2011), and 6/14 and 11/19 episodes in the last 39 months (between July 2011 and June 2014) ($p = 0.49$, Fisher).

DISCUSSION The principal findings of this study are that inflammatory causes of adult SE in a hospital cohort are relatively rare, accounting for 6% of all SE episodes, and that despite being more often difficult to treat, their outcome at hospital discharge does

Table 1 Demographic features of 33 inflammatory SE episodes occurring in 29 patients (patient 25 presented 5 SE episodes), with specific etiologies, supporting evidence for diagnosis and immunomodulatory therapy during SE episodes

Pt	Sex	Age, y	Etiology	Supporting evidence	IT
1	F	82	Viral E (VZV)	VZV PCR in cutaneous vesicles, CSF LymP	—
2	F	90	Creutzfeldt-Jakob disease	Spongiform changes in brain autopsy	Cs
3 ^a	M	71	Probable viral ME	CSF LymP, MRI les	—
4	M	78	Viral E (HSV-1)	HSV-1 PCR in CSF	—
5	M	67	Multiple abscesses (nocardia) in immunocompromised pt	Bacteriology from stereotactic biopsy	Cs
6	F	30	Probable viral ME	Fever >39°C, CSF LymP	—
7	M	71	Probable bacterial ME complicating mastoiditis	CSF NeuP, high lactate, MRI meninges thickening	—
8	F	32	Probable bacterial ME	CSF NeuP, hypoglycorrhachia	—
9	M	70	Subdural empyema (<i>Klebsiella</i>)	CT subdural collection, microbiology	—
10	M	75	ME complicating mastoidectomy for cholesteatoma (<i>Aspergillus fumigatus</i>)	Temporal (mastoid) Gado+ MRI les, microbiology	—
11	F	56	Epidural abscess postcraniotomy for severe cranial traumatism	MRI les, purulent surgical drainage	—
12	F	54	Ventriculoperitoneal shunt infection	Turbid CSF from shunt, CSF P	—
13	F	34	Cerebral abscess (<i>Toxoplasma</i>) in pt with HIV	MRI les, serology	—
14 ^a	F	72	Probable viral ME	MRI les, CSF OCB	—
15	M	39	Ventriculoperitoneal shunt infection	CSF NeuP and LymP	—
16	F	48	Viral ME (HIV)	CSF LymP, serology, CSF HIV high HIV load	—
17	M	55	Epidural abscess postmastoidectomy	MRI les, purulent surgical drainage	Cs
18	M	77	PML in immunosuppressed pt (JCV)	JCV PCR in CSF, MRI les (confluent)	RTX
19	M	36	Cerebral abscess (<i>Toxoplasma</i>) in pt with HIV	MRI les, serology	Cs
20	M	59	Hashimoto encephalopathy	Anti-TPO Ab	Cs
21	F	36	Lupic vasculitis with acute hemorrhagic stroke	Antinuclear and antiphospholipid Ab, clinical criteria (cutaneous, mucosal, articular, renal affection, venous thrombosis), CSF P, MRI les	Cs
22	F	55	Relapsing-remitting MS	Radiologic, clinical, and CSF criteria	Cs, AZT
23	F	68	Relapsing-remitting MS	Radiologic, clinical, and CSF criteria	—
24	F	69	Paraneoplastic limbic E (neuroendocrine carcinoma)	Serum ANNA-2, CSF LymP and OCB, bi-temporal MRI les	Cs
25	F	41	Adult-onset Rasmussen E	Cerebral biopsy with typical inflammation changes and autoreactive CD8 T cells; MRI progressive cerebral atrophy	—
		41			—
		43			Cs
		45			Cs
		45			—
26	M	52	Progressive MS	Radiologic, clinical, and CSF criteria	—
27	M	21	Relapsing-remitting MS	Radiologic, clinical, and CSF criteria	—
28	F	25	NMDA receptor E	Serum Ab	Cs
29	F	21	NMDA receptor E	Serum and CSF Ab	Cs, IVIg RTX

Abbreviations: Ab = antibodies; ANNA-2 = antineuronal nuclear antibody type 2; AZT = azathioprine; Cs = corticosteroids (prednisone or methylprednisolone or dexamethasone); E = encephalitis; HSV-1 = herpes simplex virus 1; IT = immunomodulatory treatment; IVIg = IV immunoglobulins; ME = meningoencephalitis; MRI les = parenchymal abnormalities on cerebral MRI; MS = multiple sclerosis; OCB = oligoclonal bands; P = CSF pleocytosis (Lym = lymphocytic; Neu = neutrophilic); PML = progressive multifocal leukoencephalopathy; Pt = patient; RTX = rituximab; SE = status epilepticus; TPO = thyroid peroxidase.

Patients 1 to 19 presented SE related to infectious etiologies and 20 to 29 to autoimmune etiologies. Infectious agents are specified in parentheses, otherwise are undetermined.

^aPatients with probable viral meningoencephalitis (undetermined infectious agent) who presented a negative autoimmune workup (patients 3 and 14). Details of patients 24, 25, and 28 have been previously published (Refs. 46–48, respectively).

Table 2 Characteristics of the 570 SE episodes, comparing the groups of inflammatory vs noninflammatory etiologies

	Inflammatory	Noninflammatory	OR (95% CI)	Test	p Value (<0.05)
SE episodes (570)	33 (6)	537 (94)			
Patients with SE (484)	29	455			
Mean age, y (range)	53 ± 18.9 (47–60)	61 ± 18.7 (60–63)		t	0.015 ^a
Female	20 (61)	262 (49)	1.61 (0.78–3.31)	F	0.211
Previous seizure	16 (48)	284 (53)	0.83 (0.41–1.69)	F	0.720
Etiology acute	21 (64)	301 (56)	1.37 (0.66–2.84)	F	0.470
Seizure type					
Generalized convulsive	11 (33)	228 (42)	0.67 (0.32–1.42)	F	0.690
Nonconvulsive SE in coma	2 (6)	23 (4)	1.44 (0.32–6.39)		
Simple partial	8 (24)	97 (18)	1.45 (0.63–3.31)		
Complex partial	12 (36)	181 (34)	1.12 (0.54–2.33)		
Absence	0	8 (1)	0.92 (0.05–16.45)		
STESS ≥3	17 (51)	262 (49)	1.11 (0.55–2.25)	F	0.858
Intubation for treatment	5 (15)	52 (10)	1.66 (0.61–4.49)	F	0.362
Refractory (>2 treatments)	19 (58)	205 (38)	2.19 (1.07–4.47)	F	0.041 ^a
Outcome					
Return to baseline	16 (48)	299 (56)	0.74 (0.37–1.51)	F	0.378
New handicap	13 (39)	176 (33)	1.33 (0.64–2.74)		
Mortality ^b	4 (14)	62 (14)	1.01 (0.34–3.01)	F	1.000

Abbreviations: CI = confidence interval; F = Fisher exact test; OR = odds ratio; SE = status epilepticus; STESS = Status Epilepticus Severity Score.

Data are n (%) unless otherwise indicated.

^a Statistically significant results.

^b Percentages and statistics for mortality refer to patients with SE (and not episodes).

not significantly differ from that of the remainder of the cohort. Moreover, we did not observe any marked change in frequency of inflammatory SE over time.

SE etiology represents one of the principal factors influencing prognosis, together with age, degree of consciousness impairment at SE onset, and, to some extent, medical comorbidities.^{7–9,21} Previous population-based studies pointed out that cerebrovascular diseases, including both acute and remote stroke, represent the first cause of SE in adults, accounting for almost half of all SE episodes, especially in the elderly.^{3–6,22} By contrast, the contribution of other etiologies to SE seems less clear, and classification methods are heterogeneous among studies. Thus, comparisons may be arduous, also in consideration that the aforementioned studies encompass a long period of time from 1965 to 2014, during which SE definitions, etiology identification, and management have considerably changed: this is particularly the case for neuronal surface antibodies causing autoimmune encephalitis identified in late 2000s.

Our study allows a new insight into the inflammatory causes of SE, assessing the frequency in an adult cohort, considering both infectious and autoimmune

conditions. Indeed, inflammatory etiologies have been difficult to retrieve from the previously cited epidemiologic studies, since they are often dispersed into different categories of the International League Against Epilepsy classification.¹⁰ In the present assessment, we found that fewer than half of inflammatory SE etiologies were related to autoimmune mechanisms, which suggests that the role of autoimmunity among all SE cases, at least in adults, is somewhat limited. A recent European multicenter study, considering retrospectively a period between 2003 and 2011,²³ identified 13 cases of SE due to antineuronal antibodies. Similarly, a recent review²⁴ reported 62 adult and 40 pediatric autoimmune SE published between 1992 and 2014, including those linked to antibodies directed against neuronal surface (NMDA, AMPA, γ -aminobutyric acid [GABA]_A and GABA_B, CASPR2, DPPX), targeting intracellular antigens (GAD) or thyroid. However, these analyses do not address the denominator of the cohort, and likely reflect a publication bias, as suggested by the fact that the majority of cases were reported after 2008, namely, after the first descriptions of antibody-mediated encephalitis. Another recent multicenter

Table 3 Characteristics of the 33 inflammatory SE episodes, comparing infectious vs autoimmune etiologies

	Autoimmune	Infectious	OR (95% CI)	Test	p < 0.05
SE episodes (33)	14 (42) (2.5% of 570)	19 (58) (3.3% of 570)			
Patients with SE (29)	10	19			
Mean age, y (range)	44 ± 15.5 (35-54)	60 ± 18.8 (52-68)		t	0.017 ^a
Female	11 (79)	9 (47)	4.07 (0.85-19.43)	F	0.087
Previous seizure	9 (64)	7 (37)	3.08 (0.73-12.98)	F	0.166
Etiology acute	5 (36)	16 (84)	0.10 (0.02-0.54)	F	0.009 ^a
Seizure type					
Generalized convulsive	2 (14)	9 (47)	0.18 (0.03-1.06)	F	0.071
Nonconvulsive SE in coma	1 (7)	1 (5)	1.38 (0.07-24.23)		
Simple partial	6 (43)	2 (11)	6.37 (1.04-38.85)		
Complex partial	5 (36)	7 (37)	0.95 (0.22-4.00)		
Absence	0	0	1.34 (0.02-71.86)		
STESS ≥3	3 (21)	14 (41)	0.09 (0.01-0.49)	F	0.004 ^a
Intubation for treatment	2 (14)	3 (16)	0.88 (0.12-6.18)	F	1.000
Refractory (>2 treatments)	9 (64)	10 (53)	1.62 (0.39-6.67)	F	0.722
Immunomodulatory therapy	8 (57)	5 (26)	3.73 (0.85-16.24)	F	0.148
Outcome					
Return to baseline	10 (71)	6 (32)	5.41 (1.19-24.52)	F	0.043 ^a
New handicap	3 (21)	10 (53)	0.24 (0.05-1.17)		
Mortality ^b	1 (10)	3 (16)	0.59 (0.05-6.57)	F	1.000

Abbreviations: CI = confidence interval; F = Fisher exact test; OR = odds ratio; SE = status epilepticus; STESS = Status Epilepticus Severity Score.

Data are n (%) unless otherwise indicated.

^a Statistically significant results.

^b Percentages and statistics for mortality refer to patients with SE (and not episodes).

study performed in Europe and the United States²⁵ identified 3 of 212 patients (1.4%) with inflammatory etiologies, of which only one was antineuronal antibodies while 5.6% were related to CNS infections. This finding is similar to the prevalence of less than 5% of infectious adult SE cases in a previous study from Virginia²; both observations appear in accordance to our findings regarding infections, while no specific data were mentioned in other European population-based studies.^{5,6} We acknowledge that these numbers only apply to the “Western” world: CNS infections (such as cerebral malaria, neurocysticercosis, or opportunistic infections associated with AIDS) represent the first cause of SE in developing countries,²⁶ and may be associated with high mortality.

Our findings outline that patients with inflammatory SE are younger than those with noninflammatory SE. This difference, particularly evident regarding the autoimmune subgroup, is not surprising, as autoimmune diseases generally occur in younger individuals.²⁷⁻²⁹ We observed that inflammatory SE was significantly more refractory to initial antiepileptic treatment. This has indeed been described for

seizures in the setting of autoimmune encephalitis mediated by neuronal antibodies, such as GABA_B-R,³⁰⁻³² GABA_A-R,³³ AMPA-R,^{34,35} NMDA-R,^{19,36} DDPX,³⁷ or LGI-1,^{13,38} which tend to respond better to immunomodulatory therapies or tumor removal than to anticonvulsants. It has indeed been shown that the binding of autoantibodies to ionotropic neuronal membrane/synaptic receptors alters their structure and/or function, and thus interferes with the physiologic electrical cortical activity.^{19,39-44} Our results are corroborated by another study in which more than 90% of antibody-mediated SE cases proved refractory to anticonvulsant treatment.²³

While mortality did not appear to be influenced by the underlying etiology, functional prognosis was significantly different between autoimmune and infectious SE, since the latter was more frequently associated with new handicap at discharge. This could be attributable to the older age of patients with CNS infections, which might associate with a slower recovery, or with a more frequent underlying lesion (such as an abscess or empyema). The observed mortality rate in the immune-mediated SE group (10%) was not strikingly dissimilar to the previously mentioned

series^{23,24} (16% and 23%), also in view that the design in those studies might have a selection bias toward more severe cases. Data on the case fatality of infectious SE are limited and based mostly on systemic infections: a US study on patients with SE and sepsis reported a mortality of 28%.⁴⁵

This study has limitations. Patients were retrospectively identified, although all variables were recorded prospectively, including etiology, which in our view strongly reduces the risk of underascertainment. Because the etiologic workup was not standardized, we cannot formally exclude that some patients with autoimmune etiologies, particularly those linked to neuronal surface antibodies, were unrecognized, especially in the early period of the cohort. Nevertheless, since most of the cryptogenic episodes from the noninflammatory group were tested for antineuronal antibodies, as well as all patients presenting with a lymphocytic pleocytosis and a negative infectious workup in the inflammatory group, the probability of having underestimated the number of SE due to autoimmune causes seems low. Moreover, we observed no significant difference in their temporal distribution during the study period, which argues against a selective information bias. Furthermore, we did not perform a multivariate analysis, given the exploratory character and the relatively small sample size of our study. Finally, we do not have information on comorbidities, but this aspect seems to exert a secondary role in prognostic terms.²¹

Additional large and ideally population-based studies are warranted to confirm our findings and better characterize patients with inflammatory SE, who despite representing a relatively small subgroup, could benefit from specific therapeutic approaches. In patients with SE of apparently unknown origin, screening for antineuronal antibodies (including CSF studies) should be considered, not only given their responsiveness to immunomodulatory treatment, but also in the light of the growing discovery of novel neuronal targets and the associated spectrum of neurologic syndromes.

AUTHOR CONTRIBUTIONS

All authors gave substantial intellectual contribution to the submitted manuscript. Marianna Spatola contributed to the design and conceptualization of the study, performed the analysis and interpretation of the data, and drafted the manuscript. Jan Novy contributed to the interpretation of the data and revised the manuscript for intellectual content. Renaud Du Pasquier contributed to the interpretation of the data and revised the manuscript for intellectual content. Josep Dalmau contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. Andrea Rossetti designed and conceptualized the study, contributed to the interpretation of the data and to the manuscript draft, and revised the manuscript for intellectual content.

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