

Inflammatory markers associated with seizures

Hong Seok Sohn, Sung Keun Kim, Seo-Young Lee

Department of Neurology, Kangwon National University School of Medicine, Chuncheon, Korea

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ABSTRACT – *Aim.* Seizures can produce systemic changes, including elevated body temperature, white blood cell count, and C-reactive protein levels, which raises concern for potential infection. We describe seizure-induced inflammation-like responses and discuss how these changes may be distinguished from those associated with infection.

Methods. We prospectively investigated 140 consecutive visits to the emergency room, in which patients presented with seizures. We defined elevated body temperature, white blood cell count, or C-reactive protein levels as inflammation-like responses. We investigated the occurrence of inflammation-like responses, characteristics of the seizures, neurological status at the initial visit, outcomes, and clinical findings to determine the presence of infection. We ascertained whether the patients had infection or not based on the overall information post-discharge.

Results. An inflammation-like response was observed in 56.3% of all visits and 19.3% were diagnosed with concurrent infection. Among the visits with inflammation-like response, 34.7% were shown to have an infection. Increases in body temperature and C-reactive protein levels were milder ($<39^{\circ}\text{C}$ and $<6\text{ mg/dl}$, respectively) in patients without infection compared to those with infection, whereas there was no difference in leukocytosis, with regard to the presence or absence of infection. Increased body temperature occurred only in cases of generalized tonic-clonic seizures, whereas leukocytosis and elevated C-reactive protein levels were reported in patients with any type of seizure. Body temperatures returned to normal within eight hours in uncomplicated cases.

Conclusions. Seizures frequently induce an increase in body temperature, white blood cell count, or C-reactive protein levels, making it challenging to distinguish these changes from those associated with infection. Nonetheless, elevated body temperature in the absence of generalized tonic-clonic seizures, above 39°C , or persisting for more than eight hours after recovery of consciousness, and C-reactive protein levels above 6 mg/dl warrant close observation and consideration for concurrent infection.

Key words: seizure, hyperthermia, fever, leukocytosis, C-reactive protein

Correspondence:

Seo-Young Lee
Department of Neurology,
Kangwon National University School of
Medicine,
156 Baengnyeong-ro,
Chuncheon 200-722, Korea
<leeseoyoung@kangwon.ac.kr>

Seizures are often associated with abnormal vital signs and laboratory data, which may raise concerns for concurrent systemic conditions. However, seizures *per se* may cause

transient systemic changes. Systemic changes secondary to generalized convulsive status epilepticus have been clearly described, including a rise in body temperature (BT),

hypertension, cardiac arrhythmia, leukocytosis, acidosis, and hyperglycaemia (Simon, 1985; Walton, 1993). However, it is unclear how frequent these systemic changes occur and how severe they are in patients with other types of seizures.

In this study, we focused on an inflammation-like response (I response), which included elevated BT, white blood cell (WBC) count, and C-reactive protein (CRP) levels, associated with acute seizures. Elevated BT is frequently encountered in patients with seizures, sometimes in combination with leukocytosis or elevated CRP levels. This may lead clinicians to assume that there is a concurrent infection, as seizures can be provoked by infection and, conversely, infection may occur as a complication following a seizure.

We investigated the frequency and severity of I responses, associated clinical factors, and whether we can differentiate these transient responses induced by the seizure itself from those induced by concurrent infection, among patients who presented to the emergency room (ER) with seizures.

Methods

We prospectively investigated patients who presented to the ER with acute seizures from January 31, 2006 to October 31, 2008. We excluded visits in which patients presented more than 24 hours after having recovered from the seizure. We collected the data using standardized forms, specifically created for this study, which included any history of preceding fever or infection, symptoms suggestive of infection, semiology and duration of the seizure, the time from onset to arrival at the ER, neurological status at the time of the visit, vital signs, use of antibiotics or antipyretics, clinical outcomes, laboratory tests including blood cell count, CRP level, chest X-ray, urine analysis for all cases, and urine or blood cultures to determine the presence of infection in selected cases. Cerebrospinal fluid (CSF) analysis, including cell count, cell differential, total protein, and glucose, was performed in patients who demonstrated prolonged periods of confusion and signs suggestive of infection which could not be otherwise explained. Culture and viral studies of CSF were performed only for one patient who was found to have CSF pleocytosis. Antibiotics were not prescribed unless there were clinical symptoms suggestive of infection.

We defined increases in BT, WBC count, and CRP levels as an I response. BT was measured using a tympanic membrane thermometer when the patients arrived at the ER and every one to four hours if the BT was elevated. Elevated BT was defined as above 37.7°C (Dinarello and Porat, 2012). Blood samples were drawn as soon as the patients arrived at the

ER. Leukocytosis was considered for a WBC count above 12,000 cells/mm³ in patients aged below 9 years, and above 10,500 cells/mm³ for patients aged nine and above (Wallach, 1996). CRP levels were measured with a high sensitive-CRP reagent (Denka Seiken, Tokyo, Japan) using an Automated Chemistry Analyzer Toshiba 200FR (Toshiba Medical Systems Co.; Tochigi-ken, Japan). We considered CRP levels above 1 mg/dl to be elevated (Calderon and Wener, 2012). We defined more than 5 mononuclear cells/mm³ or the presence of any polymorphonuclear cells, and CSF protein levels of 50 mg/dl or greater, as abnormal (Robbins and Hauser, 2012).

We determined whether the patients had any preceding infection based on medical history; febrile sensation, sore throat, cough, rhinorrhoea, sputum, urinary frequency, urgency, diarrhoea, *etc.* The presence or absence of a concurrent infection was determined post-discharge, not only based on I responses but also the clinical presentation.

Status epilepticus was defined as a clinical or electrographic prolonged seizure lasting more than 30 minutes or repeated seizures without full recovery of consciousness between seizures (Chen and Wasterlain, 2006).

Statistical significance in the differences in I response between the two groups with or without infection was assessed by independent t-tests. To identify the clinical factors associated with an I response, a logistic regression analysis was applied. The associations between continuous variables were assessed using Pearson's correlation coefficient and re-tested with the Chi-squared test after categorizing the data into normal and abnormal values. A *p* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using a SPSS program (version 19.0; IBM SPSS Statistics, Chicago, Illinois).

This study was approved by the institutional review board (approval number: KNUH-2015-10-009).

Results

There were 146 ER visits with presentation of seizures from January 31, 2006 to October 31, 2008, during the study period. Six visits were excluded because of the following reasons: transfer to another hospital, refusal to be examined, returning to the ER the following day for recurrent seizure, coming to the ER one week after recovery from a seizure, and other multiple systemic symptoms. Thus, data of the total 140 visits were analysed from 131 patients.

Those aged from 14 months to 89 years were included in the study. Of the patients, 85% arrived at the ER within one hour of a seizure and 77.1% returned to baseline on admission, at the time of the visit.

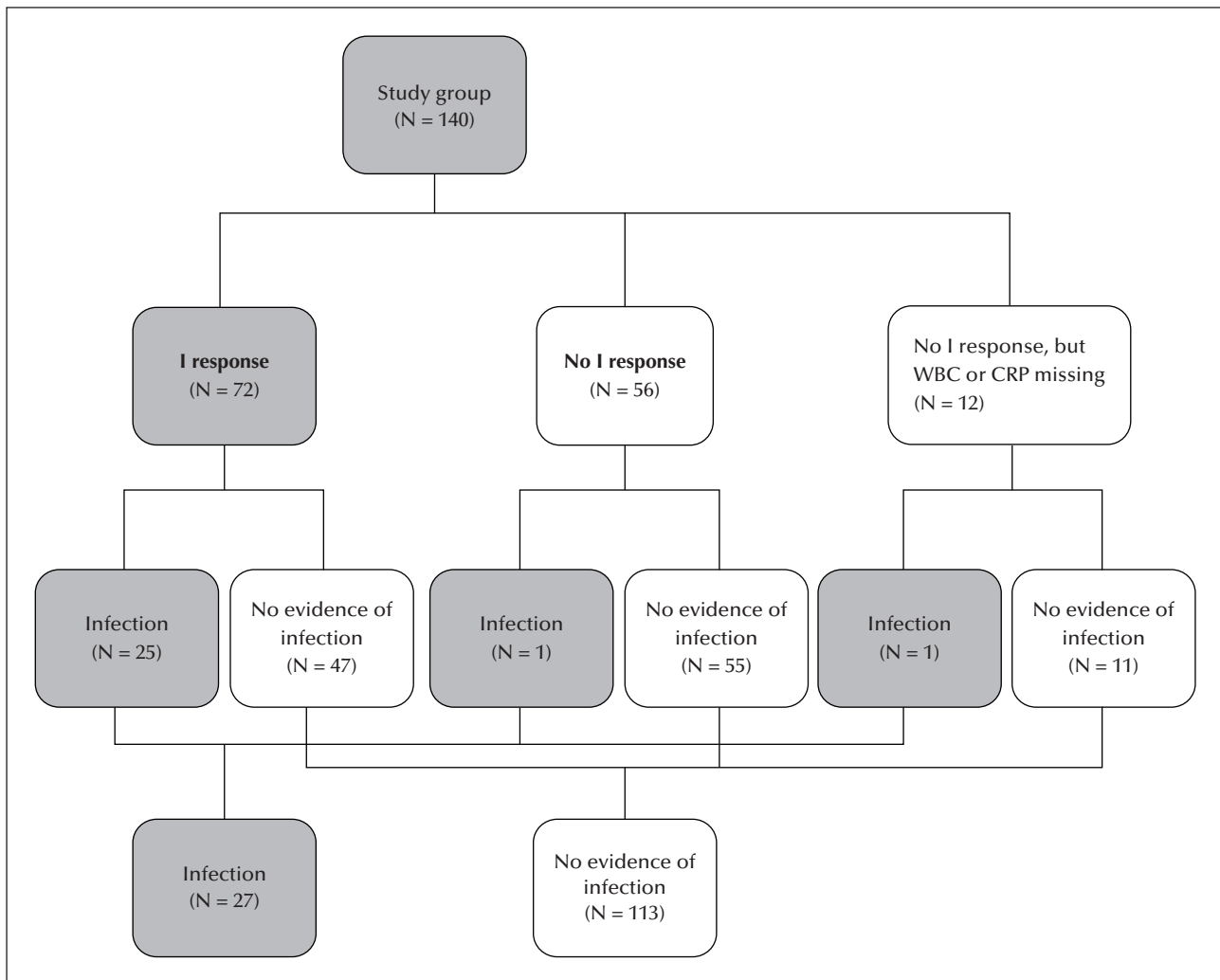


Figure 1. Frequency of seizure-induced I response and concurrent infection.

I response: inflammation-like response, such as elevated body temperature, leukocytosis or elevated C reactive protein.

Seizure types consisted of 120 generalized tonic-clonic seizures (GTCS), 13 complex partial seizures (CPS), and seven simple partial seizures (SPS), including 11 recurrent GTCS within a day, 14 GTCS in status epilepticus, one CPS in status epilepticus lasting for 30 minutes, and another SPS in status epilepticus lasting for one hour. Thirty-two (22.9%) visits demonstrated a high possibility of pre-existing infection within the past week, including upper respiratory infection ($n=30$), acute gastroenteritis ($n=1$), and bacterial meningitis ($n=1$). Among these 32 visits, 25 had persistent symptoms at the time of the visit. Signs of new infection were found during two visits; one had a subarachnoid haemorrhage and later died due to sepsis, and the other had a urinary tract infection, which was treated with antibiotics. Antibiotics were started empirically in two cases in which the fever had lasted more than 72 hours, but further evaluation did not reveal any data that

were suggestive of any concurrent infection, and we finally determined that there was no infection. Hence, 27 (19.3%) of all the patients were considered to have concurrent infection and 113 (80.7%) were considered to have no infection (*figure 1*). None of the patients had any underlying conditions which might have caused an I response, such as inflammatory diseases, allergies, myeloproliferative disease, or glucocorticoids. Regarding other conditions that might potentially affect the immune system, three patients had cancer, one had a history of leukaemia which was in remission, 13 had diabetes, and 19 had alcoholism or alcoholic liver disease (*table 1*).

An I response was observed in 72 (56.3%) of all visits except for 12 visits in which there was no elevated BT and a lack of testing for WBC or CRP. In 26 (18.6%) of the visits BT was elevated, in 52 (37.7 %) leucocytosis was reported, and in 21 (17.4%) CRP levels were

Table 1. Clinical characteristics of study population.

Characteristics	Numbers
Age (N*=131)	37.8 (14 months-89 years)
Gender (N*=131)	88 men, 43 women
Time from onset to arrival at the ER (N**=140)	119: <1 hr; 13: ≥1 hr/< 2 hr; 8: ≥2 hr
Neurological status at the time of visit (N**=140)	108 normal, 11 confused, 7 drowsy, 12 stupor, 2 with seizures
Type of seizure (N**=140)	120 GTCS, 13 CPS, 7 SPS
Status epilepticus	14 GTCS, 1 CPS, 1 SPS
Epilepsy classification (N**=140)	8 GE, 59 LRE, 12 febrile convulsion, 12 alcohol withdrawal seizure; 49 undetermined
Concurrent infection (N**=140)	25 had pre-existing infection, 2 had newly developed infection
Conditions which possibly affect immunity (N*=131)	3 cancer, 1 previous history of leukaemia with remission, 13 diabetes, 19 alcoholism or alcoholic liver disease

N*: total number of patients; N**: total number of visits; ER: emergency room; GTCS: generalized tonic-clonic seizure; CPS: complex partial seizure; SPS: simple partial seizure; GE: generalized epilepsy; LRE: localization-related epilepsy.

Table 2. Incidence and positive predictive value (PPV) of each component of the inflammation-like response for infection.

Inflammation-like response	Incidence	PPV
Any type of inflammation-like response	56.3%	34.7%
Elevated BT	18.6%	61.5%
Leukocytosis	37.7%	32.7%
Elevated CRP	17.4%	42.9%
Elevated BT & leukocytosis	9.42%	69.2%
Leukocytosis & elevated CRP	8.26%	60.0%
Elevated BT & CRP	6.61%	62.5%
Elevated BT, leukocytosis & elevated CRP	3.31%	75.0%

BT: body temperature, CRP: C-reactive protein

elevated (table 2). There was no correlation between any of these findings in either the group with infection or the group without infection.

We performed CSF analysis during five visits. One patient was diagnosed with bacterial meningitis. Among the four cases without any infection of the central nervous system, both WBC count and protein

levels were normal (37.7-47.6 mg/dl), except for one with protein levels elevated to 120.2 mg/dl. This patient was a 47-year-old male with alleged epilepsy of unknown cause and had visited the ER following a GTCS, which lasted for five minutes, and had elevated BT (37.9°C), leukocytosis (28,800 cells/mm³), and elevated CRP levels (1.79 mg/dl).

Differential diagnosis for the I response: was there concurrent infection?

Among the 72 visits with an I response, infection was confirmed in 25 (34.7%) and absent in 47 (65.3%) (figure 1). The positive predictive values (PPVs) of elevated BT, WBC, and CRP for infection were 61.5%, 32.7%, and 42.9%, respectively. The PPV of combined elevated BT, leukocytosis, and elevated CRP for infection was 75.0% (table 2).

The degree of elevated BT was milder (37.8 to 38.7°C) among the patients without any infection than in those with concurrent infection (38.1 to 40°C), with overlap between the two groups. The WBC count and the proportion of segmented neutrophils was 10,800-32,800 cells/mm³ and 16-91% in the group without infection and 10,800-19,400 cells/mm³ and 22-92% in the group without infection, respectively, without any significant difference between the two groups. The degree of increase in CRP levels was 1.02-5.72 mg/dl in the group without infection and 1.16-38.7 mg/dl in the group with infection (table 3).

Table 3. Differences in inflammation-like response between patients with or without infection.

	Overall	With infection		Without infection		
		Number	Range	Number	Range	
Elevated BT	26	16	38.1~40	10	37.8~38.7	$p=0.002$
Leukocytosis	52	17	10.8~19.4	35	10.8~32.8	NS
Elevated CRP	21	9	1.16~38.7	12	1.02~5.72	NS

BT: body temperature, CRP: C-reactive protein

The I response in those without concurrent infection

An I response was observed in 47 (46.1%) visits among the group without infection. BT elevation developed only in cases specifically with GTCS, and more frequently in cases with GTCS status or recurrent GTCS (OR=4.97 [1.170-21.119]; $p=0.03$, with multiple logistic regression, adjusted according to the time from onset to arrival at the ER). This elevation in BT lasted up to 96 hours. Among the four patients who had elevated BT for more than 24 hours, three had GTCS status and the other was in a prolonged semi-comatose state for more than two hours after having a GTCS lasting less than five minutes, hence non-convulsive status could not be excluded. The BT returned to normal within eight hours in the rest of the cases.

Neither the type of seizure nor the presence of status epilepticus affected leukocytosis or elevation of CRP levels. Elevated CRP levels were associated with elevated creatine phosphokinase (CPK) levels ($p=0.006$; Fisher-exact test), whereas elevated BT and leukocytosis were not.

We were able to classify the seizures in 42 of the 113 visits which were not associated with infection, according to the ILAE criteria for epileptic syndromes. Eight were classified as generalized epilepsy and 34 as localization-related epilepsy (17 originating from the right hemisphere, 13 from the left hemisphere, three of bilateral multifocal origin, and one benign childhood epilepsy with centrotemporal spikes). Ten cases had temporal lobe epilepsy; six from the right and four from the left temporal lobe. The origin of seizures, whether this was in the temporal lobe or not, did not affect the occurrence of I response.

Eight patients visited our hospital twice or more during the study period. The seizure type was GTCS for all of these cases. One patient had isolated leukocytosis (16,100 and 32,800 cells/mm³; segmented cells: 84 and 90%) without any evidence of infection at both visits when the patient was seen for GTCS, lasting for less than five minutes. The patient's wife remembered that he had marked leukocytosis when he visited another ER years ago, and further evaluation did not reveal

any abnormalities. Four patients did not demonstrate an I response in either visit, and the remaining three patients had isolated leukocytosis at only one visit. We could not find any clinical difference between visits, whether leukocytosis was present or not.

Age and gender were not associated with occurrence of I response.

Discussion

An I response was frequently observed among ER visits associated with seizures. However, only 34.7% of those with any of the I response components were associated with infection, and 75% with combined elevated BT, leukocytosis, and elevated CRP truly had an infection. Leukocytosis was the most frequent non-specific finding. Seizure itself resulted in marked leukocytosis, up to 32,800 cells/mm³, with varying degrees of segmented neutrophilia, making it difficult to distinguish from an infection. The elevation in BT was mild (<39°C) in the group without infection compared to that with infection, and normalized within eight hours in most cases, although elevated BT above 39°C was observed in a previous study on generalized motor status epilepticus (Aminoff and Simon, 1980). An increase in CRP level was modest (<6 mg/dl) in the group without infection.

An I response may be a result of sustained tonic-clonic activity and associated muscle injury or inflammation. However, leukocytosis and elevated CRP levels were observed regardless of the seizure type, whereas an elevation in BT developed only after GTCS. Elevated BT and leukocytosis were not associated with CPK levels, whereas elevated CRP levels were associated with CPK levels, which represents muscle damage associated with convulsion. Elevated BT, leukocytosis, and a rise in CRP may each develop during seizures via different specific mechanisms because their occurrence and severity were independent of each other.

Elevated BT represents either fever or hyperthermia. Fever usually develops with infection and hypothalamic damage, which are assumed due to increase in the hypothalamic thermoregulatory set point.

Hyperthermia is caused by exogenous heat exposure or endogenous heat production (Dinarello and Porat, 2012). In animals with limbic self-sustained status epilepticus, a significant elevation in BT developed only in those with motor convulsions, which suggested that hyperthermia was the consequence of motor convulsions and not of epileptic activity itself (Schmitt *et al.*, 2005). However, as a few patients with complex partial status epilepticus were reported to exhibit elevated BT as an ictal phenomenon, thermoregulatory neurons in hypothalamus may be affected by circumscribed propagation of epileptic activity (Semel, 1987; el-Ad and Neufeld, 1990).

Leukocytosis is frequently a sign of an inflammatory response. It may also occur as a result of physical and emotional stress; not only seizures but also overexertion, anxiety, anaesthesia and epinephrine administration (Abramson and Melton, 2000). One possible pathophysiological mechanism of seizure-associated leukocytosis is demargination of leukocytes caused by high levels of catecholamines (Simon, 1985).

CRP is an acute-phase plasma protein which increases in response to infection or tissue injury, and has been studied for use in a screening test for inflammation or as a marker of disease activity (Ansar and Ghosh, 2013). GTCS, temporal lobe onset, and longer duration were shown to affect the increase in CRP levels in a study of 31 patients with refractory epilepsy who had received video-EEG monitoring (Alapirtti *et al.*, 2012). This finding was not reproduced in our study, which consisted of patients presenting to the ER. Elevated CRP levels were associated with CPK levels but neither the type nor the origin of the seizure, which suggests that elevated CRP levels could be the result of muscle damage. The lack of increase in serum neuron-specific enolase levels, a marker for neuronal injury, also supports the notion that an increase in CRP may not be the result of neuronal injury (Peltola *et al.*, 2002). In our study, it was not possible to identify effects of the origin of seizures or a syndrome of epilepsy on the I response because most of the patients presented to the ER with GTCS and did not receive any presurgical evaluation for localization. Variation in the time from seizure onset to the time blood samples were drawn may be another reason for the discrepancy, because CRP levels have been previously shown to rise steadily from 3 to 24 hours post-seizure based on a video-EEG monitoring study (Alapirtti *et al.*, 2012).

We observed an increased CSF protein level, reaching a value of 120.2 mg/dl, without CSF pleocytosis, in the absence of any other pathology. In larger studies of patients who underwent CSF examination, CSF pleocytosis was found in 14~18% of patients with status epilepticus and 2% among those with seizures other than status epilepticus, in the absence of other causes.

Increased protein was observed in 21% of the cases of status epilepticus and 6% of the cases of seizures other than status epilepticus. The degree of pleocytosis and elevation in protein levels was modest, with the WBC count ranging up to 65 cells/mm³ and protein levels up to 99 mg/dl (Aminoff and Simon, 1980; Edwards *et al.*, 1983; Wong *et al.*, 2001).

There are several limitations to our study. Our protocol did not include follow-up after discharge from the ER, hence we cannot rule out the possibility that the patients might have presented to other hospitals with signs of infection. However, patients were discharged after a sufficient length of observation, except for two patients who left against medical advice. Prescribing antibiotics empirically could have affected the decision as to whether there was a concurrent infection. However, we did not start antibiotics unless there were clinical symptoms suggestive of any concurrent infection, except for two aforementioned cases with prolonged fever, who were finally shown not to have any concurrent infection, as further evaluation did not reveal any evidence that was suggestive of any concurrent infection. Therefore, the possibility that patients with infection were misdiagnosed to have no infection was low. Another potential bias is that the time from seizures and neurological status when I responses were measured varied, although most patients presented to the ER within one hour after a seizure, in a state of alertness. However, in the absence of any previous data concerning the distinction between seizure-associated I response and concurrent infection, this study may provide insights into clinical decision-making and future studies.

In summary, an I response is common among acute seizures. However, determining whether this is induced by the seizure itself or due to concurrent infection may be difficult at the time of presentation. Treatment or work-up for infection can be placed on hold in the absence of any clinical signs of infection. In cases of acute seizures with elevated BT occurring in the absence of GTCS or complex partial status epilepticus, above 39°C in the absence of GTCS status, or persisting for more than eight hours after recovery of consciousness, and with CRP levels higher than 6 mg/dl, one might consider concurrent infection. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

The authors report no conflicts of interest. This was a non-funded study.

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TEST YOURSELF



- (1) If a patient presenting with generalized tonic-clonic seizures also shows signs of elevated body temperature, what should you do?
- (2) When should we consider concurrent infection in cases of acute seizures with elevated body temperature, leukocytosis or elevated CRP?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".