Clastrum damage and refractory status epilepticus following febrile illness

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ABSTRACT

Objective: To characterize the clinical, EEG, and brain imaging findings in an adult case series of patients with de novo refractory status epilepticus (SE) occurring after a febrile illness.

Methods: A retrospective study (2010–2013) was undertaken with the following inclusion criteria: (1) previously healthy adults with refractory SE; (2) seizure onset 0–21 days after a febrile illness; (3) lacking evidence of infectious agents in CSF; (4) no history of seizures (febrile or afebrile) or previous or concomitant neurologic disorder.

Results: Among 155 refractory SE cases observed in the study period, 6 patients (17–35 years old) fulfilled the inclusion criteria. Confusion and stupor were the most common symptoms at disease onset, followed after a few days by acute repeated seizures that were uncountable in all but one. Seizures consisted of focal motor/myoclonic phenomena with subsequent generalization. Antiepileptic drugs failed in every patient to control seizures, with all participants requiring intensive care unit admission. Barbiturate coma with burst-suppression pattern was applied in 4 out of 6 patients for 5–14 days. One participant died in the acute phase. In each patient, we observed a reversible bilateral claustrum MRI hyperintensity on T2-weighted sequences, without restricted diffusion, time-related with SE. All patients had negative multiple neural antibodies testing. Four out of 5 surviving patients developed chronic epilepsy.

Conclusions: This is a hypothesis-generating study of a preliminary nature supporting the role of the claustrum in postfebrile de novo SE; future prospective studies are needed to delineate the specificity of this condition, its pathogenesis, and the etiology. *Neurology*® 2015;85:1224–1232

GLOSSARY

ADC = apparent diffusion coefficient; **AED** = antiepileptic drug; **FIRES** = febrile infection-related epilepsy syndrome; **ICU** = intensive care unit; **IVIg** = IV immunoglobulin; **NORSE** = new-onset refractory status epilepticus; **PEX** = plasma exchange; **SE** = status epilepticus.

In the last 2 decades, several authors described a series of syndromes characterized by the development of a difficult to treat status epilepticus (SE) in previously healthy children after a febrile illness.^{1–7} The condition is characterized by a refractory SE and followed by drug-resistant epilepsy, with often severe neuropsychiatric sequelae or death. These entities have been identified by different acronyms, but febrile infection-related epilepsy syndrome (FIRES) is the one that best underscores the main features of the disorder.⁸ Cases with a similar clinical picture have been described also in adults and in these case series the most frequently used definition is new-onset refractory SE (NORSE).^{9–13} Recently, it was pointed out that different terms probably have been used to describe the same condition.^{14,15} However, there is no consensus among investigators. Adult cases are more heterogeneous, some with clear similarities with FIRES cases (with only the age at onset as the main difference), others probably representing different conditions.

We describe a case series and a literature review of young adults fulfilling the definition of FIRES, all showing in the early acute phase of the disease a striking alteration of the claustrum on MRI, mainly bilaterally.

Supplemental data
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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Table 1 Clinical data of the reported patients

Patient	Age, y, sex, ethnicity	Fever ^a (d)	Presenting symptoms	Seizures semiology	Frequency of seizures	Evolution of SE	Need for ICU	AEDs used	Other drugs	Barbiturate coma (d) ^a	Immunotherapy	Clinical outcome	Seizure outcome
1	29, F, Caucasian	Yes (5)	Confusion/stupor	Staring/eye deviation and focal hemiconic; then generalized myoclonic state	Uncountable	Super-refractory	Yes	PHT, LEV, LCM	MDZ, propofol	Yes (10)	Steroids, IVlg	Normal life; mild deficits in executive functions	Focal epilepsy on LEV, CLB
2	24, F, Caucasian	Yes (7)	Confusion/sleepiness	Focal hemiconic, myoclonic; then generalized	Uncountable	Refractory	Yes	PHT, LEV, TPM, CLB	MDZ, propofol	No	Steroids	Cognitive and behavioral deficits	Focal epilepsy (2-3 s/m) on LEV, CBZ, CLB
3	29, F, Asian	Yes (5)	Confusion/stupor	Focal hemiconic, myoclonic; then generalized	Uncountable	Super-refractory	Yes	VPA, PHT, TPM, LEV, LCM, CBZ	MDZ, propofol	Yes (14)	Steroids	Death	—
4	35, M, Caucasian	Yes (6)	Seizures	Eye deviation and focal hemiconic, with alternating side; then generalized	Uncountable	Refractory	Yes	VPA, LEV, PHT	MDZ	No	Steroids, PEX	Normal life, slight attentional deficits	Focal epilepsy (1 s/m) on LTG, LEV
5	21, M, Arabian	Yes (3)	Headache/sleepiness	Focal hemiconic, with alternating side; then generalized	Uncountable	Super-refractory	Yes	VPA, PHT, LEV, TPM	MDZ, propofol	Yes (5)	Steroids, IVlg	Normal life	Not available
6	17, F, Caucasian	Yes (6)	Stupor/severe sleep disruption	Focal motor, tonic, chewing and complex automatisms	Isolated seizures	Super-refractory	Yes	VPA, CBZ, PB	MDZ, propofol	Yes (7)	Steroids, IVlg	Mild cognitive deficit, attention deficit	Seizure-free final follow-up

Abbreviations: AED = antiepileptic drug; CBZ = carbamazepine; CLB = clobazam; ICU = intensive care unit; IVlg = IV immunoglobulin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; MDZ = midazolam; PB = phenobarbital; PEX = plasma exchange; PHT = phenytoin; SE = status epilepticus; TPM = topiramate; VPA = valproate.
^a Fever (number of days before neurologic symptoms onset).

The claustrum function has remained obscure for decades. In 1996, its involvement in a case of de novo refractory status was reported for the first time.¹⁶ Only in recent years has the scientific community gained a strong interest in the function of the claustrum, mainly with respect to its role in sensory integration and consciousness.^{17–21}

METHODS Patients and investigations. In a retrospective multicenter study (2010–Dec 2013), information including demographic data, clinical features, diagnostic findings, therapeutic interventions, and clinical outcomes of patients fulfilling the following inclusion criteria were acquired: (1) previously healthy adults (>16 years of age) with refractory SE (failed IV treatment with antiepileptic drugs, requiring general anesthesia)²²; (2) onset of seizures 0–21 days after a febrile illness; and (3) lacking evidence of infectious agents in CSF. Exclusion criteria were a history of seizures (febrile or afebrile), as well as previous or concomitant neurologic disorder. Data were extracted from the participating centers, reviewing clinical charts, EEG (video-EEG) recordings, and MRI (when available). During the study period, 155 cases of refractory SE were observed. Among these, 6 fulfilled our inclusion criteria.

No family history for febrile seizures or epilepsy was reported. No participant had personal or familial history of an immunologic disorder.

All patients were examined for viral and bacterial infections. The following blood and CSF analyses were performed: viral tests including herpes simplex virus 1 and 2, varicella-zoster virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, rubella, parvovirus B19, enterovirus, and mumps. All virologic studies were performed using DNA PCR. The presence of oligoclonal immunoglobulin G bands was checked with isoelectrofocusing, performed with agarose gel support. Antinuclear antibodies, antiphospholipid antibodies, anti-DNA antibodies, anticardiolipin antibodies, anti-extractable nuclear antigen antibodies, and antithyroid antibodies were analyzed with immunoenzymatic tests and indirect immunofluorescent staining.

Thorax-abdomen CT was performed in all patients, showing no occult neoplasm. An extensive blood analysis and testing of classical onconeural antibodies (anti-GAD, anti-Yo, Ri, Hu, anti-Ma2) was negative in all participants.

Standard protocol approvals, registrations, and patient consents. The scientific advisory boards of participating institutions approved the research protocol according to local regulations and consent was obtained from patients or their relatives. This research is reported following Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Literature review. Searches for identification of studies were run in from 1990 to 2014 in MEDLINE and PubMed. Searches were limited from 1990 to the present day since studies carried out previously would necessarily have included participants without MRI. The search keywords were as follows: “AERRPS”; “FIRES”; “NORSE”; “status epilepticus” and “claustrum”; “epilepsy” and “claustrum”; “status epilepticus” and “neuroimaging.” For each citation considered, the abstract was read (when available). The bibliography of each of the retrieved articles was examined to identify relevant references that could have been missed by electronic search. Only peer-reviewed original articles providing images of the claustrum involvement were accepted for inclusion in the review.

Table 2 Investigational data during the acute phase in the reported patients

Patient	CSF		Brain MRI in acute phase				Vigilance	Other negative findings
	Cells, μ L	Oligoclonal bands	EEG	Clastrum	Other brain regions	Days from fever/SE onset		
1	3	Absent	GSW, PD, centroparietal SW	Bilateral	Insular cortex	17/10	Coma (on anesthetic treatment)	LG11, Caspr2, NMDAR, AMPAR, GABA _A , mGlu-R1-R3-R5, POLG1 mutations
2	0	Absent	GSW, PD, centroparietal SW	Bilateral	None	11/4	Coma (on anesthetic treatment)	LG11, Caspr2, NMDAR, AMPAR, GABA _A , mGlu-R3
3	20	Absent	PD, SW with alternating side predominance (left > right)	Bilateral	None	9/3	Coma (on anesthetic treatment)	LG11, Caspr2, NMDAR
4	19	Absent	PD, SW with alternating side predominance (left > right)	Bilateral	None	13/9	Stupor	LG11, Caspr2, NMDAR, VGCC, mGlu-R3
5	23-3	Absent	Multifocal with frontotemporal, occipital SW	Bilateral	Right posterior thalamus	10/3	Coma (on anesthetic treatment)	LG11, Caspr2, NMDAR, AMPAR, GABA _A , mGlu-R3
6	10	Present	Frontotemporal bilateral theta, L or R frontotemporal SW	Bilateral	None	10/4	Coma (on anesthetic treatment)	LG11, Caspr2, VGCC-Ab, NMDAR

Abbreviations: ADC = apparent diffusion coefficient; AMPAR = antibodies against amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2 = contactin-associated protein-like 2; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; GABA_A, GABA_B = antibodies against the gamma-aminobutyric acid A and B receptor; GSW = generalized spikes and waves; LG11 = antibodies against leucine-rich glioma inactivated protein 1; mGlu-R3 = antibodies against metabotropic glutamate receptor 3; NMDAR = antibodies to N-methyl-D-aspartate receptor; PD = periodic discharges; SE = status epilepticus; SW = spikes and waves; VGCC = antibodies against voltage-gated calcium channel.

RESULTS Clinical data, interventions, and outcomes of the 6 patients are summarized in table 1.

Age at onset was between 17 and 35 years; different ethnicities were represented. Fever, in the context of a flu-like condition, preceded the onset of neurologic symptoms in all patients. Confusion, stupor, sleepiness, and signs of consciousness alteration were the most common symptoms at disease onset, followed after a few days by acute repeated seizures that were uncountable in all but one patient. Seizures consisted in all participants of focal motor/myoclonic events with alternating side involvement and subsequent generalization. In patient 1, a dramatic generalized myoclonus was present through the entire acute phase of the disease. Antiepileptic drugs (AED) failed in every patient to control seizures, with all participants requiring intensive care unit (ICU) admission and treatment with midazolam and propofol. Barbiturate coma with burst-suppression pattern was applied in 4 out of 6 patients for 5–14 days. Corticosteroid IV treatment was used as adjunctive therapy in all patients during the acute early phase, while IV immunoglobulins (IVIg) or plasma exchange (PEX) were used in 4 patients. One patient did not survive the acute phase (patient 3: sepsis during ICU, staying 3 weeks after onset). One of the surviving patients was lost to follow-up since he returned to his home country (patient 5). Four patients are on AED therapy: 3 have active chronic focal epilepsy despite adequate drug regimens and 1 presented seizure clusters for months despite AED polytherapy before epilepsy control.

Brain imaging. During the acute phase of the disorder, brain MRI showed bilateral claustrum involvement in all patients (figure 1): these positive imaging studies were acquired with a time lag of 3–10 days from SE onset (table 2). Notably, in all patients the first MRI study, undertaken in the few days preceding the development of seizures or in the first days (0–2 days) after the onset of refractory SE, was negative. Beyond high signal on fluid-attenuated inversion recovery/T2 and diffusion-weighted images (but with normal apparent diffusion coefficient [ADC]) (figure 2), no other sequences revealed claustrum abnormalities; no contrast enhancement was observed in any case. MRI studies undertaken after SE resolution no longer showed claustrum alterations (figure 2).

We did not observe signal alterations involving the medial temporal lobe, the splenium of corpus callosum, or other brain regions in any patient. MRI studies in the chronic phase were available for 3 patients and showed mild diffuse atrophy in one.

Notably, claustrum alterations were not observed in any other case of SE for which an MRI study was available during the acute phase (104 cases), considering any etiology.

Figure 1 Clastrum sign

(A, B) Axial and coronal fluid-attenuated inversion recovery (FLAIR) images show claustrum hyperintensity (red arrows) during the status epilepticus (SE) in patients 1 and 2, 10 and 4 days from onset, respectively. (C) Axial and coronal T2 images show claustrum hyperintensity (red arrows) during the SE in patient 3, 3 days from onset. (D) Axial FLAIR and axial T2 images show claustrum hyperintensity (red arrows) during the SE in patient 4, 9 days from onset. (E) Axial FLAIR images acquired during SE (left image) and coronal detail (right image) of claustrum hyperintensity in patient 5 (red arrows); note also the posterior thalamus hyperintensity (the patient also experienced visual seizures). (F) Axial FLAIR images show claustrum hyperintensity (red arrows) during the SE in patient 6, 7 days from onset.

Other investigational data. EEG during the acute phase showed multifocal spikes and sharp waves over frontocentral regions in the majority, with periodic lateralized discharges (figure e-1 on the *Neurology*[®] Web site at Neurology.org). Seizures arose independently from the 2 hemispheres with secondary generalization in every patient.

All patients had negative multiple neural antibodies testing, including antibodies to NMDA receptor, leucine-rich glioma inactivated protein 1, and contactin-associated protein-like 2 (previously attributed to voltage-gated K channels) (table 2).²³ One participant (patient 1) had additional negative testing for CSF and serum antibodies against γ -aminobutyric acid-A receptor (GABA_A), responsible for the recently described acute autoimmune encephalopathy with refractory seizures/SE.²⁴ This patient was also screened for mitochondrial disorders. The most common mutations in the *POLG* gene p.A467T, p.W748S, and p.G848S were tested and were negative²⁵; muscle biopsy did not show specific alterations,

and no respiratory chain defects were observed on muscle tissue specimens.

Literature review. Overall, 16 cases were included in the review (14 studies, reported in table 3). The online supplementary references (e1–e53) report 53 studies on neuroimaging changes during SE, which did not show any case with claustrum involvement. The patient age range was 6–65 years (8 female). Fever, in the context of a flu-like condition, preceded the onset of neurologic symptoms in 15 out of 16. Drowsiness, confusion, and seizures were the presenting symptoms after a fever episode. In the acute phase, seizures configured a SE in all cases, with a predominance of focal motor and secondarily generalized seizures. In 7 cases, benzodiazepines and AED were successful in controlling SE, while in 8 patients the SE was considered refractory or super-refractory, with need for drug-induced coma.²² One patient died in SE.²⁶ MRI studies showing bilateral claustrum alterations were acquired during the SE

Figure 2 Typical temporal sequence of MRI alterations

(A) Normal MRI (fluid-attenuated inversion recovery [FLAIR] sequences) before the fully developed status epilepticus (SE) (left); bilateral hyperintensity of the claustrum in FLAIR imaging during status epilepticus (central image); normal appearance of the claustrum after the resolution of the status (right image). Images refer to patient 2. (B, C) Diffusion-weighted imaging (DWI) (left) and apparent diffusion coefficient (ADC) (right) images of patients 3 and 6 show high signal in the region of the claustrum in DWI with normal ADC. The same pattern was observed in other patients. DWI sequences were not acquired in patient 1.

acute phase in stuporous/unconscious patients, with a time lag of 3–20 days from SE onset. MRI alterations in the acute phase consisted in every patient of hyperintense appearance of the claustrum on T2-weighted images. No case showed contrast enhancement. In 2 cases, ADC maps were reported, with no evidence of decreased diffusion, as in our cases.^{27,28} In 5 cases, medial temporal lobe hyperintensities were also present.^{26,27,29–31}

Follow-up MRIs were reported for 11 out of 16 patients showing normal findings or mild atrophy. In the MRI studies undertaken after SE resolution, the claustrum alterations were always reversed.

Clinical follow-up data were available for 10 patients. Eight out of 10 developed chronic focal epilepsy despite AED treatment.

The neuropathologic examination in the patient who died during SE showed marked astrocytic reaction in the Sommer sector and end folium of both hippocampi and in the claustrum bilaterally. No signs of encephalitis or global hypoxic-ischemic changes were observed.²⁶

A presumed etiology was lacking in 13 out of 16 cases. Herpes simplex virus 1 encephalitis, mumps encephalitis, and voltage-gated potassium channel antibodies-related encephalitis were the presumed causes for 3 patients. In 7 patients (children or adolescents), the authors considered the condition as belonging to the acute encephalitis with refractory, repetitive partial seizures/FIRES spectrum.

DISCUSSION We report clinical, EEG, and brain imaging findings of a homogeneous group of 6 adult patients who developed a new-onset refractory or super-refractory SE starting a few days after a febrile illness and showing a striking claustrum alteration, mainly bilaterally. We ascertained through an extensive literature review that at least 16 other cases have been described from 1996 to the present. Some of these cases were observed in children and were attributed to FIRES.^{7,32} Claustrum involvement in febrile-related new-onset SE is probably more frequent than has been reported. Indeed, even for the cases included in the review, several of the imaging findings were not identified as claustrum alterations, but rather as peri-insular or external capsule lesions.^{27,33,34} For these reasons, multicentric studies are needed to evaluate the actual claustrum involvement in both children and adults with febrile-related new-onset SE.

Our observations are important for several reasons. First, this imaging sign seems to be associated with a very aggressive form of SE, with focal motor seizures and myoclonus, often requiring ICU admission and anesthetic drugs. Indeed, considering our patient group and the previously observed cases, refractory or super-refractory SE cases were observed in 14 out of 22 patients (64%), and chronic epilepsy was reported in 12 out of 14 cases for which follow-up was available/possible (85%). Second, no definite

Table 3 Findings in reports describing claustrum damage in patients with new-onset status epilepticus

Reference/ year	Name given to the condition	No. of patients	Age, y, sex	Presenting symptoms	Fever (days before onset)	Presumed etiology	Seizure semiology	Evolution of SE	MRI from SE onset (d)	Immunotherapy	Outcome/epilepsy
33/1994	None	1	7, M	Lethargy	Yes (7)	HSV1 (herpes stomatitis the week before)	Focal motor	Refractory	11	None	Behavioral impairment; chronic epilepsy
16/1996	None	1	12, F	Dizziness, fatigue	Yes (14)	None	Focal motor	Responsive	7	Steroids	Normal life; no epilepsy
26/2001	None	1	35, M	Seizures, stupor	Yes (4)	None	Focal motor	Super-refractory	13	None	Death
29/2006	Acute encephalopathy with refractory SE	1	12, F	Fluctuation of vigilance	Yes (7)	None	Focal motor	Super-refractory	20	None	Severe cognitive deficit; chronic epilepsy
30/2006	Nonherpetic limbic encephalopathy	1	8, M	Seizures	Yes (und.)	None	Und.	Responsive	Und.	Und.	Und.
32/2007	AERRPS	1 ^a	10, M	Fluctuation of vigilance	Yes (6)	None	Focal motor	Super-refractory	11	Steroids, IVIg	Mild cognitive deficit; no epilepsy
7/2011	FIRES	3 ^a	6-14, 3 M, 1 F	Confusion, stupor, agitation	Yes (4-8)	None	Focal motor	Responsive in 3; refractory in 1	Und.	Steroids, IVIg in 3 out of 4	Mild to severe cognitive deficit; chronic epilepsy
27/2011	None	1	39, F	Lethargy	Yes (4)	None	Focal motor	Super-refractory	14	None	Normal life; chronic epilepsy
35/2011	None	1	21, M	Seizures	Yes (7)	Mumps (PCR serum)	Focal motor	Refractory	7	None	Und.
39/2013	FIRES	1	19, F	Seizures	Yes (7)	None	Focal motor	Responsive	3	Steroids	Normal life; no epilepsy
31/2014	None	1	65, F	Fluctuation of vigilance	Und.	Ab anti-VGKC	Focal motor	Responsive	3	Steroids	Memory loss; epilepsy outcome not reported
34/2014	Possible FIRES	1	14, M	Drowsiness, confusion	Yes (10)	None	Focal occipital	Responsive	10	Steroids, IVIg	Normal life; chronic epilepsy
40/2014	None	1 ^a	22, F	Und.	Und.	None	Focal motor	Refractory	7	Und.	Und.
28/2014	None	1	28, F	Seizures, stupor	Yes (7)	None	Und.	Refractory	20	None	Und.

Abbreviations: Ab = antibodies; AERRPS = acute encephalitis with refractory, repetitive partial seizures; FIRES = febrile infection-related epilepsy syndrome; HSV = herpes simplex virus; IVIg = IV immunoglobulin; SE = status epilepticus; Und. = undetermined; VGKC = voltage-gated potassium channel.

^a Cases extracted from group studies.

etiology was ascertained, with the exception of 3 patients.^{31,33,35} Considering the striking homogeneity of the observed cases, it seems highly probable that an unknown but specific etiology accounts for febrile-related SE with claustrum hyperintensity. From this point of view, the literature review and the reported cases allow us to affirm that claustrum involvement was not observed in the context of refractory SE secondary to acute structural brain damage or to other specific SE etiologies. Importantly, no other case with claustrum involvement was observed in our cohort of SE cases observed during the 4-year study period across the different participating centers (104 cases with MRI peri-SE, post-SE). Moreover, we screened 56 publications on peri-ictal imaging changes in SE and only 3 cases were identified, notably all fulfilling our inclusion criteria. It seems therefore unlikely that claustrum lesions represent a consequence of refractory SE *per se*.

This retrospective uncontrolled study prevents us from making inferences about analysis of outcomes in relation to treatments. However, immunomodulatory treatment could have been relevant to outcomes.^{12,13} Notably, in the reported 6 patients, the 4 who received early IVIg/PEX (beyond IV steroids) had a good outcome also concerning cognitive aspects, while the 2 patients who did not receive such treatment died or had severe cognitive deficits. This observation, together with the reversibility of the claustrum lesions, the preceding febrile illness, and the absence of any detectable infectious agent, supports a role of inflammation-mediated mechanisms as relevant in the determination of SE and encephalopathy in the presented cases.¹⁵ The neuropathologic findings in one previously reported patient who died during SE showing evidence of only reactive gliosis without signs of encephalitis support this hypothesis.²⁶

Our findings underscore the key role of claustrum dysfunction in the pathophysiology of this form of refractory or super-refractory SE. Indeed, the time course of the MRI alterations suggests that the SE was strictly time-related to claustrum dysfunction/damage. Of course, it is not possible to affirm if claustrum damage is the initial event leading to ictogenesis and SE, or if conversely it is the consequence of this peculiar form of febrile-related SE. Fever, seizures, or both could be relevant to induce claustrum alterations. However, we suggest that claustrum could have a relevant role in the maintenance of this very aggressive form of refractory SE.

Experimental evidence in animal models indicates that some subcortical structures and circuits act as critical modulators of seizure propagation and maintenance.³⁶ In recent years, the concept that during focal seizure activity specific cortical-subcortical

circuits can be critical in sustaining epileptic activity and ictogenesis has been supported by functional brain imaging studies.³⁷ Notably, however, few observations pointed attention to the claustrum within this framework, even in animal models.³⁸ This can be explained by the paucity of clinical data about claustrum involvement in epilepsy and by the unknown functions of this thin layer of gray matter. Recent advances in neuroanatomy and physiology indicate this subcortical region as a highly relevant hub center in neural synchronization of several (and distant) cortical areas, and, as a consequence, a structure involved in integration of conscious perception.^{17–21} Considering these physiologic properties of the claustrum, this structure could also be a key region in promoting the propagation and synchronization of abnormal epileptic activity from several cortical regions. To this point, 2 properties of claustral neurons are relevant. First, claustrum-cortical fibers connect the claustrum with several cortical areas, including the prefrontal, pre-postcentral, posterior parietal, orbitofrontal, and medial temporal cortex.^{20,21} Second, the claustrum is constituted by densely packed and tightly interconnected GABAergic interneurons.^{17,18} Therefore, the claustrum can potentially bind together and modulate neural activities (epileptic activity in our case) from and to widespread cortical areas.

Interestingly, a recent EEG/fMRI study in patients with focal drug-resistant epilepsies found a common brain region with increased hemodynamic responses in relation to interictal epileptiform discharges, regardless of the localization of interictal and ictal activity.³⁷ This region was close to the frontal piriform cortex, and its Talairach coordinates suggest that it corresponds to the claustrum. Notably, GABA_A receptor binding (measured by flumazenil PET) was reduced in patients with more frequent seizures.

Even though this report is a hypothesis-generating study of preliminary nature, our findings suggest that the claustrum could be an attractive new target for epilepsy and SE therapy that deserves to be explored in future studies. Future prospective studies are needed to delineate the specificity of this imaging biomarker, its pathogenetic role in refractory SE, and the etiology of the condition.

AUTHOR CONTRIBUTIONS

Stefano Meletti: design and conceptualization of the study, interpretation of the data, drafting and revising the manuscript. Jana Slonkova, Iva Mareckova, Nicola Specchio: data collection, interpretation of the data, drafting and revising the manuscript. Giulia Monti, Giada Giovannini, Nicola Pietrafusa: data collection, drafting and revising the manuscript. Petr Hon, Vaclav Marcian, Petr Krupa, Dagmar Berankova, Annalisa Chiari, Michal Bar: analysis and interpretation of data, revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

S. Meletti received research grant support from the Ministry of Health (MOH), from the non-profit organization CarisMo Foundation, and has received personal compensation as a scientific advisory board member for UCB and Eisai. J. Slonkova, I. Mareckova, G. Monti, N. Specchio, P. Hon, G. Giovannini, V. Marcian, A. Chiari, P. Krupa, N. Pietrafusa, D. Berankova, and M. Bar report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received February 5, 2015. Accepted in final form June 8, 2015.

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