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## Summary

Considering the high prevalence of non-convulsive Status epilepticus (NCSE) in emergency admissions of patients with altered mental state and the high proportion of cross-sectional imaging performed in this patient cohort, imaging marker suggesting an epileptic origin of the clinical symptoms and – even more critical – indicating ongoing seizure activity would potentially modify therapeutic decisions and patients outcome. In this article we review the cross-sectional imaging techniques to identify pathophysiological processes related to epileptic activity. We discuss the diagnostic potential of brain perfusion imaging to detect hemodynamic correlates of epileptic activity and structural imaging to identify the sequelae of prolonged epileptic activity e.g. cytotoxic/vasogenic edema, gliosis and brain atrophy.

In the atlas part, we aim to include a number of cases of NCSE with representative imaging findings and discuss the correlation of the findings with the clinical semiology and epilepsy syndrome.

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**Key words:** cerebral perfusion, MRI, CT, epilepsy

## Atlas der zerebralen Bildgebung im nicht-konvulsiven Status epilepticus

Status epilepticus non-convulsivus (NCSE) ist eine häufige und schwierige Diagnose bei Patienten mit Bewusstseinsstörungen auf der Notfallaufnahme. In dieser Patientengruppe wird häufig eine zerebrale Schnittbildgebung durchgeführt. Bildgebende Befunde, die eine epileptische Genese der klinischen Symptome oder sogar Hinweise auf fortbestehende epileptische Aktivität liefern könnten, würden potenziell die therapeutischen Entscheide und die Prognose der Patienten ändern. In diesem Artikel diskutieren wir das Potenzi-

al der Hirnperfusionsmessungen, hämodynamische Korrelate epileptischer Aktivität zu detektieren sowie die Resultate der strukturellen Bildgebung, um die Folgen der prolongierten epileptischen Aktivität (zytotoxisches, vasogenes Ödem sowie Gliose und Atrophie) darzustellen.

**Schlüsselwörter:** Zerebrale Perfusion, MRT, CT, Epilepsie

## Atlas de l'imagerie cérébrale du status épileptique non-convulsif

Le status épileptique non-convulsif (NCSE) est une entité fréquente et cliniquement difficile à détecter chez les patients amenés aux urgences avec des troubles de la conscience. En vue de la fréquence élevée avec laquelle une imagerie cérébrale est effectuée chez ces patients, des signes radiologiques suggérant une origine épileptique des symptômes cliniques et – encore plus précieux – des signes indiqueront une activité épileptique persistante, pourront potentiellement modifier la démarche thérapeutique et le pronostic des patients. Dans cet article nous discuterons le potentiel des mesures de perfusion cérébrale d'identifier des corrélats hémodynamiques d'activité épileptique et les marqueurs de l'imagerie structurale qui sont la conséquence d'activité épileptique prolongée (œdème cytotoxique/vasogénique ainsi que gliose et atrophie).

**Mots clés :** Perfusion cérébrale, IRM, CT, épilepsie

## Introduction

NCSE is defined as a change in behavior and/or mental processes from baseline associated with continuous epileptiform discharges in the electroencephalographic recordings (EEG) in absence of convulsive symptoms [1]. This pragmatic definition encompasses

various subtypes of NCSE with different clinical symptoms, notably regarding the degree of impaired consciousness, different ictal EEG patterns and different etiologies. The current diagnostic criteria of NCSE – additional to the clinical evaluation – are based on visual EEG analysis and response to anti-convulsant medication. It reflects clinical limitations to attribute a rapid and specific diagnostic and prognostic evaluation of the epileptic activity. Currently, major efforts are underway in adapting the classification algorithms of NCSE to identify patients requiring immediate and sustained therapeutical interventions [2].

NCSE has an estimated incidence of 3.5 complex partial Status epilepticus (SE) and 15 other NCSE per year and population of 100,000 and therefore accounts for one quarter of all SE. It occurs in up to 9.3% of patients with altered mental state at emergency admission [3] as well as in about 8% of comatose patients without any clinical sign of ongoing epileptic activity. In unselected cases an associated mortality was reported in up to 18% [4]. Mortality is reported to be mainly dependent on the underlying etiology and age. However, NCSE has been shown to be an independent predictor of high mortality, high morbidity and for the occurrence of refractory SE [5].

Age and the underlying etiology have been repeatedly identified as prevalent prognostic factors in NCSE [6]. According to the Nice guidelines ([www.nice.org.uk/CG020NICEguideline](http://www.nice.org.uk/CG020NICEguideline)) emergency cross-sectional neuroimaging is indicated if the clinical symptoms in the context of an epileptic seizure may be caused by an acute neurologic condition. The etiologies of NCSE most frequently identified by neuroimaging are stroke, intracranial tumor, sinus thrombosis and traumatic contusions [7]. Computed tomography (CT) is widely used in this condition mainly motivated by the broader availability, shorter acquisition time and the ease of patient surveillance. Magnetic Resonance Imaging (MRI) has to be considered as alternative in function of the clinical state of the patient as it is superior to CT in the detection of parenchymal lesions and its methodological superiority to CT to differentiate ongoing pathophysiological processes as vasogenic and cytotoxic edema.

Considering the high prevalence of NCSE in emergency admission in patients with altered mental state [3] and the high proportion of cross-sectional imaging performed in this patient cohort, an imaging marker suggesting an epileptic origin of the clinical symptoms and – even more critical – indicating ongoing seizure activity would potentially modify therapeutic decisions and patients' outcome. In this article we review the potential of cross-sectional imaging techniques to identify pathophysiological processes related to epileptic activity. We discuss the 1) diagnostic potential of brain perfusion imaging to detect hemodynamic correlates of epileptic activity and 2) the structural imaging findings of the sequelae of prolonged epileptic activity e.g. cytotoxic/vasogenic edema, gliosis and brain atrophy.

In the atlas part, we aim to include a number of cases of NCSE with representative imaging findings and discuss the correlation of the findings with the clinical semiology and epilepsy syndrome.

## Hemodynamic correlates

Hemodynamic correlates of epileptic seizures in the brain were first described by W. Penfield in the 1930ths. In the following decades this initial observation has been confirmed in many instances, showing that excessive or hypersynchronous epileptic neuronal activity is accompanied by focal brain hyperperfusion (**Figures 1,4,5**). Important observations have been reported based on ictal and postictal SPECT data, showing that the observed hyperperfusion is temporally confined to seizure activity and tends to normalization or hypoperfusion in the postictal state within 90 seconds [8] (**Figure 2**). A second important observation was the correlation of hemodynamic correlates of seizures to the seizure onset zone, including a spatial distribution of hemodynamic changes within the brain that was concordant with the symptomatic zone of seizure semiology [9]. In mesiotemporal lobe epilepsy (MTLE) the spatial distribution of hemodynamic changes reflects physiological neuronal networks involved in seizure propagation [10]. In addition cortical abnormalities in MTLE were observed in a similar distribution (**Figure 8**) [11]. Two recent studies of our group showed the feasibility and diagnostic value of perfusion computed tomography measurements in the emergency setting to differentiate NCSE from post-ictal state [12, 13]. However, the current retrospective studies allow only limited conclusions about the diagnostic value with respect to an unselected cohort of patients and in the differentiation of alternative etiologies of altered mental state (**Figure 4**). Differential diagnosis of altered mental state is broad and includes various conditions such as trauma, tumor, vascular disease, infection, metabolic and toxic encephalopathies. In a subset of patients these conditions may coincide with epileptic activity fulfilling the diagnostic criteria of NCSE (**Figure 3**). In this case, in addition to the evaluation of the structural brain damage, the rapid assessment of how strongly the ongoing epileptic activity contributes to the altered mental state is of crucial importance for prognosis and therapy. The larger the contribution of epileptic activity to the clinical symptoms, the more successful and necessary is a vigorous treatment with seizure suppressive drugs [14]. Here, brain perfusion measurements have the potential of providing important contribution in the diagnostic workup in patients with suspicion of NCSE.

In recent research activity brain perfusion measurements have been used to characterize different epilepsy syndromes and to report the localization of various clinical seizure semiology [15 - 17] (**Figures 3-5**). The atlas part of this article aims at documenting illustrative

cases discussing hemodynamic correlates of ongoing epileptic activity in patients with altered mental state compared to simple focal NCSE as well as showing typical distribution of perfusion changes in patients with different epilepsy syndromes (Figures 1,5,6).

## Sequelae of epileptic activity

### Cytotoxic edema

Cytotoxic edema is due to a disruption of the cellular metabolism that impairs functioning of the Na<sup>+</sup>/K<sup>+</sup>-ATPase in the glial cell membrane, leading to intracellular retention of sodium and water. In consequence astrocytes and neuronal cells increase intracellular volume and extracellular space is reduced. This elicits a hyperintensity on diffusion weighted images (DWI) and lower apparent diffusion coefficient (ADC) values (Figures 4,5,7). These image properties are believed to reflect a reduction in the diffusibility of extracellular protons [18]. In epilepsy cytotoxic edema is reported in cases of prolonged epileptic brain activity. The observed changes are in large parts reversible (Figure 1) but may as well result in consequent brain volume loss (Figure 9). In acute cerebrovascular disease ADC values below  $6 \times 10^{-6}$  mm<sup>2</sup>/s are considered irreversible, indicating infarction core [19]. The use of ADC values in the acute state of an epileptic condition as a predictive factor of consecutive brain damage is not established. Our observation (unpublished data) suggest that the ADC values in cytotoxic edema of epileptic origin tend to be higher (less severe cytotoxic edema) than in patients during the acute phase of ischemic stroke.

### Vasogenic edema

Vasogenic edema occurs when intravascular proteins and fluids penetrate into the parenchymal extracellular space predominantly in subcortical areas. The vasogenic edema typically results from the breakdown of the blood-brain barrier in inflammation, trauma, tumors or subacute stages of cerebral ischemia. In epilepsy, an increase of fluids in the extracellular space may as well result indirectly from hypersynchronous or excessive neuronal/glial activity [20, 21]. In MRI vasogenic edema is characterized by a hyperintense signal on T2 weighted images, hypointense signal on T1 weighted images and, in a quantified manner, by an increase of ADC values. On diffusion weighted images (DWI) vasogenic edema may also be visualized as increased signal intensity related to the “T2 shine-through effect” from the B0 images [22] (Figures 1,2,5).

### Brain atrophy

Epileptic seizures are not considered to induce neuronal damage in general. Recently analysis of structural brain imaging has identified progressive cortical changes as a function of disease duration, interictal spike and seizure frequency [23 - 25]. The distribution of these changes are concordant to the seizure semiology/epilepsy syndrome to some extent [11]. In status epilepticus non-reversible clinical deficits as well as brain atrophy may occur [26, 27]. Lacking substantiated evidence on the prognostic and diagnostic value it is not established to which extent vasogenic/cytotoxic edema as discussed above may be predictive for consequent focal brain atrophy or gliosis (Figures 8,9).

### Conclusion

Currently major efforts are underway to refine definition and classification of NCSE. The lack of consensus on this topic arises because the EEG expression of NCSE does not exist in isolation, but reflects status epilepticus under the variety of pathologic conditions that occur with age, cerebral development, encephalopathy, and epilepsy syndrome [28, 29] (Figure 7). Well established is the benefit of structural brain imaging documenting etiology and severity of the underlying brain process causing the NCSE. Clinically important may be the consideration, “that the larger the contribution of epileptic activity to the clinical symptoms, the more successful and necessary is a vigorous treatment with seizure suppressive drugs” [14]. In this perspective imaging correlates of epileptic activity and its sequelae, as presented above, may contribute to enhance patients’ diagnostic workup and consequently therapeutic decisions and prognostic outcome. The present review aims to give a comprehensive selection on typical pathological imaging findings correlated to the epileptic activity. These imaging findings develop on top of the underlying pathology causing NCSE and represent pathophysiological changes as typically cortical hyperperfusion in ongoing epileptic activity or sequelae of prolonged epileptic activity as cytotoxic/vasogenic edema. Gliosis and brain atrophy represent the end stage of most likely irreversible brain damage of NCSE. The case series of the atlas part point out to following consideration:

- a) Cortical hyperperfusion, particularly if it exceeds vascular territories (thalamic involvement?) may represent ongoing epileptic activity and, in our opinion, should prompt to an explicit diagnostic workup of NCSE.
- b) Diffusionrestriction and/or T2 hyperintensities – particularly if they a) exceed vascular territories, b) are subtle, c) are restricted to gray matter and d) have a spatial distribution that corresponds to the patients (past) symptoms suggest an epileptic eti-

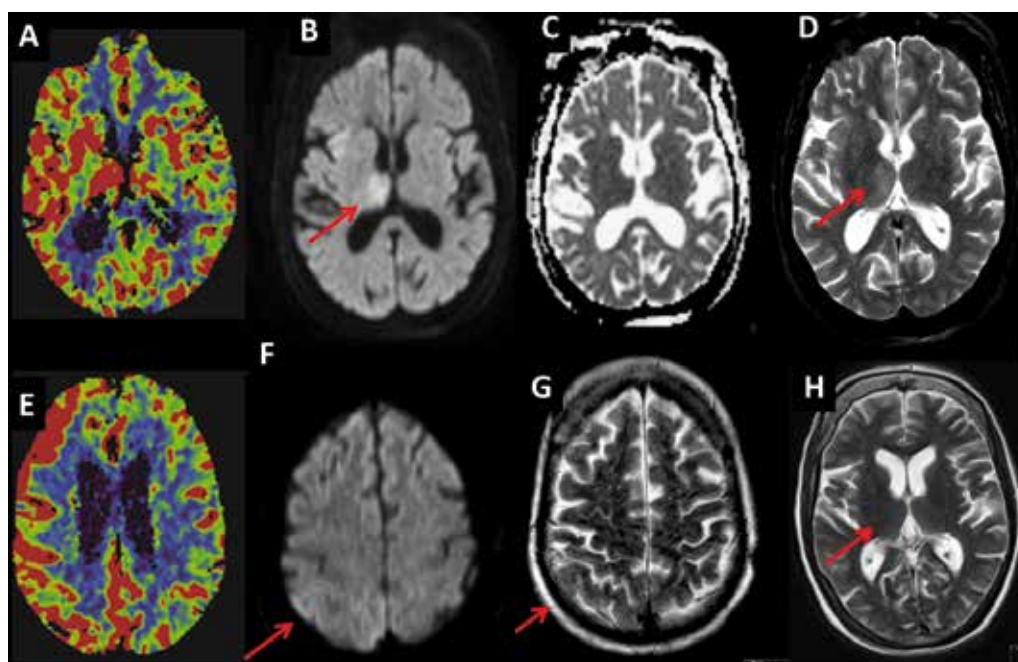


Figure 1: 59 year old female with structural epilepsy, during drug withdrawal occurrence of a complex focal SE with clonic movements of left face, shoulder and proximal arm and psychomotor slowing. A-G MRI at 4 days of ongoing focal SE under multiple antiepileptic drugs, A- Hyperperfusion of the right hemisphere including right basal ganglia and right thalamus, B/C- DWI hyperintensity right thalamus; ADC isointens to the contralateral hemispheres representing a mixed cytotoxic and vasogenic edema, D- T2w hyperintensity of the right thalamus (vasogenic edema), E- Hyperperfusion of the right hemisphere fronto-parieto-occipital, F- DWI hyperintensity of the right parieto-occipital cortex, ADC isointensity representing a mixed cytotoxic and vasogenic edema, G- T2w hyperintensity of the right parieto-occipital cortex (vasogenic edema), H- 2 weeks after successful treatment of focal SE – T2w isointensity of thalamic tissue representing (at least in part) reversible structural changes.

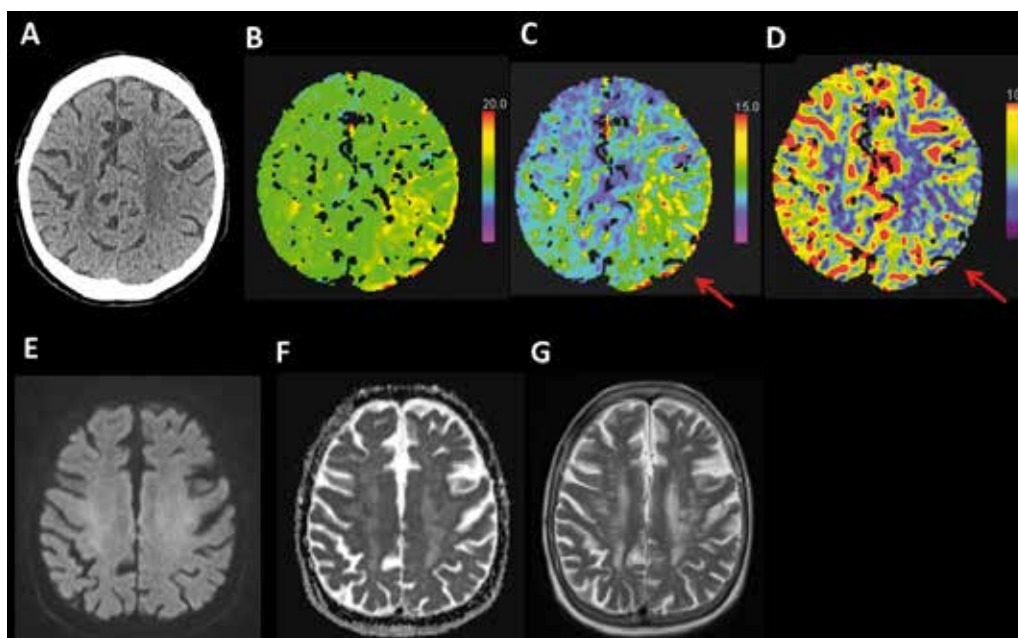


Figure 2: 91 year old female in postictal state after prolonged generalized tonic-clonic seizure with acute hemiparesis on the right for 3h, GCS 7. EEG showed slowing on the left hemisphere. A- CT nativ without abnormality, B-D hypoperfusion of the left parietal hemisphere with B- prolonged TTP (time to peak), C- prolonged TTD (time to drain), and D- decreased CBF (cerebral blood flow). E-G follow-up MRI one day later: no diffusion restriction, leukencephalopathic changes within the white matter. Postictal hypoperfusion is observed particularly in patients with postictal focal deficits (Todd's paresis or aphasia). Perfusion changes are most easily seen on maps of contrast transition times (TTD, mean transit time (MTT) or TTP). We note a diffuse cortico-subcortical pattern and a spatial distribution not corresponding to vascular territories.

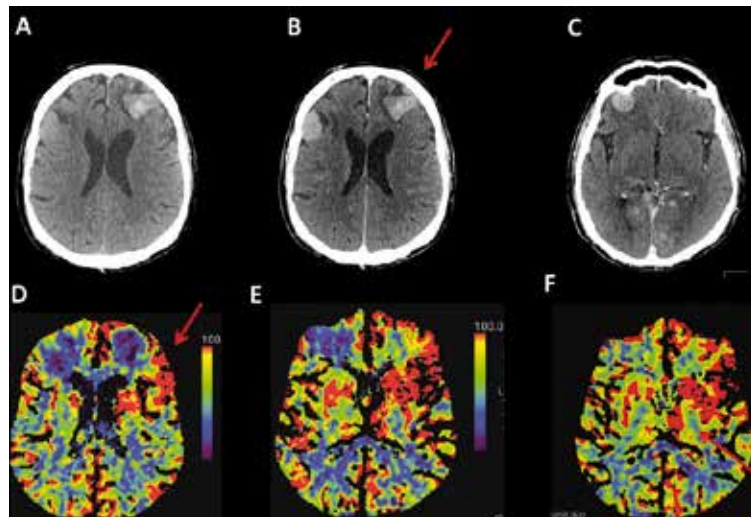


Figure 3: 67 year old male, malignant melanoma, cerebral metastasis, no reaction to speech since 2 hours, spasticity on the right, anisokoria of pupils, clinical diagnosis of NCSE. A- CT unenhanced B/C and after contrast showing multiple metastasis and hemorrhage in one metastasis left frontal, D-F hyperperfusion of the left Insula and left frontal lobe, left thalamus and basal ganglia. Complex situation, in spite of multiple intracranial metastasis with acute hemorrhage frontal left, perfusion imaging detects hyperperfusion in a cortical distribution involving basal ganglia associated to ongoing epileptic activity. The hyperperfusion is distinct from tumor related hyperperfusion by its distribution and intensity in this case.

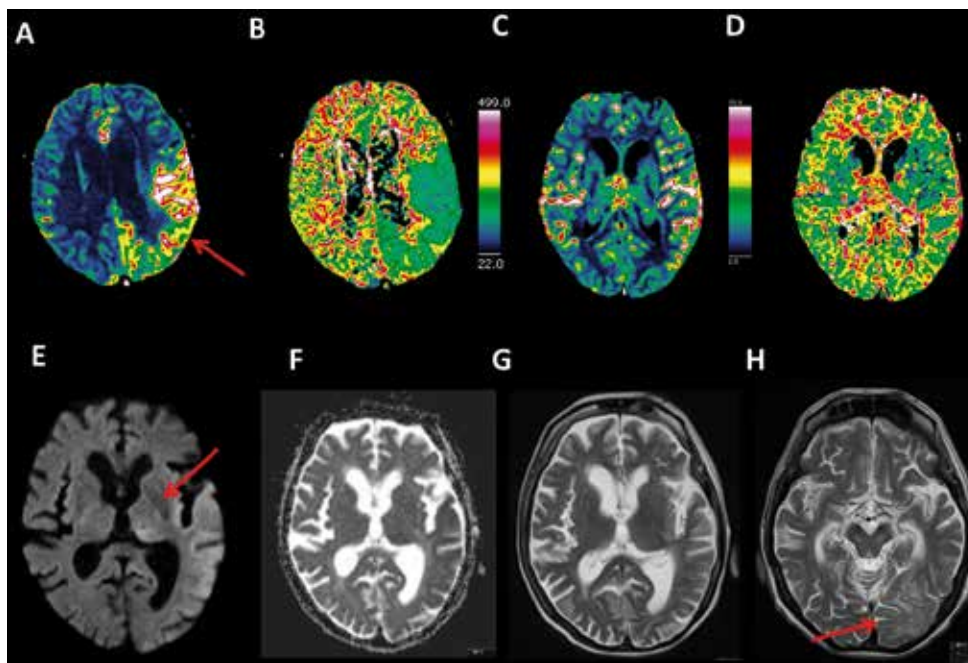


Figure 4: 67 year old male with acute sensorimotor aphasia and hemiparesis on the right since 2 hours, EEG documents left seizure activity with temporal dominance leading to an electroclinical diagnosis of NCSE. A-D increased CBF of the left hemisphere temporo-parieto-occipital (A,C) and MTT shortening (B,D), E-G cytotoxic edema temporo-parieto-occipital and pulvinar thalamus, H- follow-up MRI: vasogenic edema left occipital. Patient with inaugural NCSE without documented preceding generalized tonic-clonic seizure. Here, hyperperfusion without territorial distribution initiated the EEG-based diagnosis of NCSE.

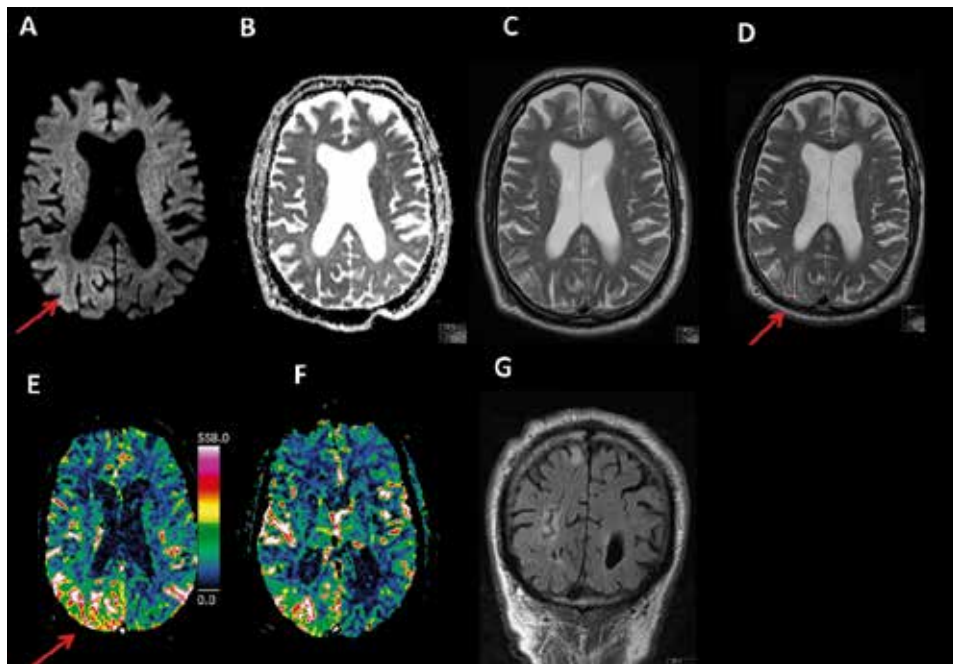


Figure 5: 74 year old male with hemianopsia to the right and ataxia, and intermittent cloni of the left foot correlating to rhythmic discharges on EEG. No altered mental state. A-D cytotoxic edema in the occipital lobe on the right, E-F hyperperfusion in the right occipital and temporal lobe, no thalamic involvement evident G- one week later T2w hyperintensity (vasogenic edema/gliosis) in the cortex of the right occipital lobe.

In patient without impaired consciousness (vigilance) no thalamic cytotoxic edema or perfusion changes were visible

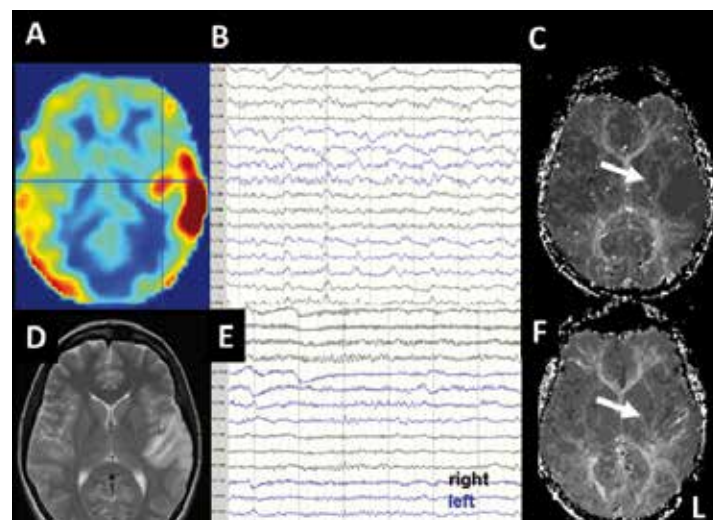


Figure 6: 31 year old female with MELAS syndrome. For 24 hours rushing on the right side. A-D MRI at admission A- hyperperfusion latero-temporal left (measured by arterial spin labeling), B- EEG showing left hemispheric periodic sharp transients, C- TTP map confirms hyperperfusion, D- T2-weighted images with acute lesion temporal left, E-F EEG and MRI 7 days later, NCSE successfully treated, E- EEG without evidence of ongoing epileptic activity F- TTP map showing normalization of brain perfusion. In Case 6 acoustic hallucination as ictal semiology has been confined to the contralateral temporal lobe including the primary auditory cortex and illustrates the potential of perfusion imaging to provide pathophysiological insights into clinical symptoms independent to their underlying etiology.

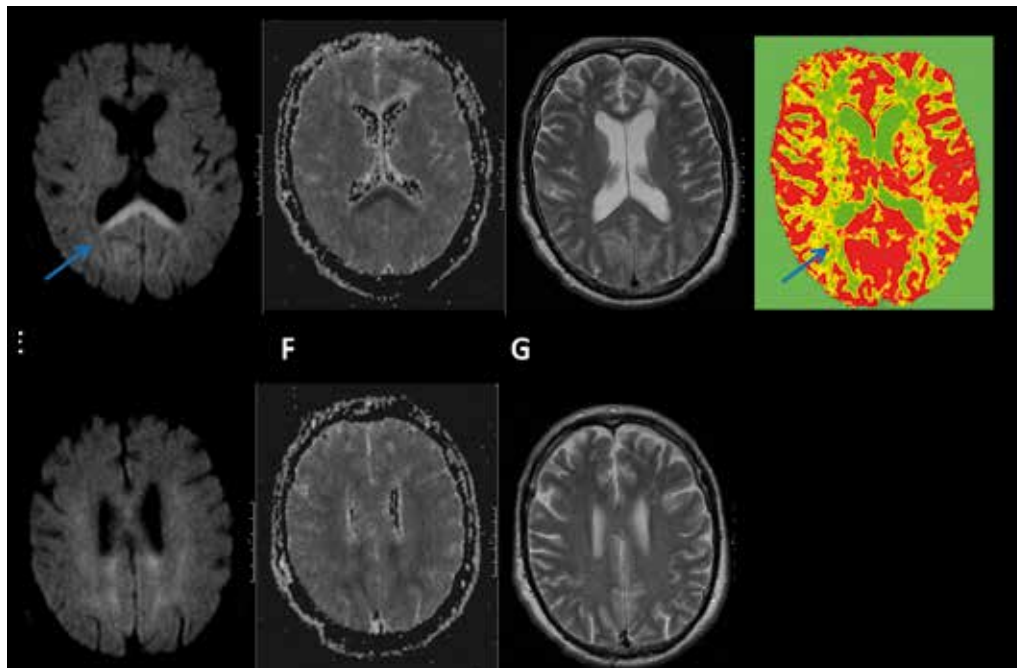


Figure 7: 59 year old male with status post myocardial infarct and resuscitation 6 days before MRI with postanoxic (myoclonic) SE, A-C cytotoxic edema in splenium corporis callosi (arrow), D- hyperperfusion bilateral in the cuneus, temporal on the left, and in the corpus callosum (arrow) , E-G cytotoxic edema bilateral mainly in the periventricular white matter, (C/G) Example of a pattern of cytotoxic edema predominant in the white matter tracts correlating to the underlying pathology of cerebral hypoxia due to cardiac arrest. Cross-sectional imaging discloses a diffuse pattern of hyperperfusion including corpus callosum unusual to all other cases reported here. Postanoxic SE is harboring a poor prognosis in a relevant portion of patients. Cross-sectional imaging play a role together with clinical and electrophysiological parameters to estimate prognosis of the underlying pathology (see article from Rossetti and Hänggi et al. in this issue). The experience with perfusion imaging as isolated parameter of epileptic activity is yet limited and to the authors conviction no comment or suggestion can be made at this stage.

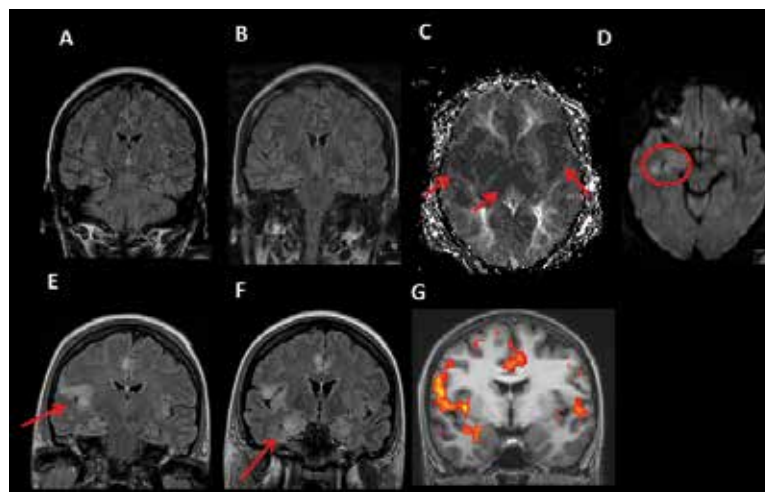
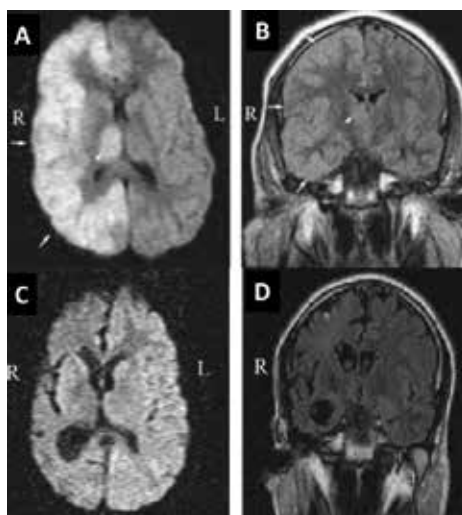


Figure 8: 43 year old female, recurrent secondary generalized seizures for 2 days of unknown etiology, previously influenza symptomatology, at admission convulsive drug resistant status epilepticus, waxing and waning evolution with right hemispheric dominance of epileptic activity on EEG. A-D MRI at admission, unspecific white matter lesions, right dominant diffuse hyperperfusion (TTP), DWI restriction right hippocampus, E-F follow-up MRI: increasing gliosis/vasogenic edema bilateral in the hippocampus, the insula, fronto-basal and cingulum on FLAIR images, G- interictal hemodynamic correlates of MTLE (data from [11]). The distribution of the gliotic changes in drug resistant SE (no etiology of epilepsy disclosed on autopsy) and the interictal hemodynamic changes in MTLE are closely related, endorsing the notion that interictal epileptic activity involves identical neuronal networks as seizure activity.



**Figure 9:** MRI 5 days after the onset of SE illustrates acute brain injury. A- Restricted diffusion in the entire right hemisphere (arrows) and the right thalamus (arrowhead), sparing the deep white matter and basal ganglia, B- Coronal FLAIR shows increased signals in the gray matter of the right cerebral cortex (arrows) and the right thalamus (arrowhead), C-D MRI 6 months later following prolonged complex focal SE reveals advanced brain atrophy limited to the right hemisphere, C- Diffusion weighted image, D- Coronal FLAIR image.

Prolonged epileptic activity may result in irreversible brain damage documented on cross-sectional imaging by gliosis (case 8) evolving to brain atrophy in case 9.

**Fig. 9.** Reprinted adopted from *Epilepsy & Behavior*, Vol 11/ Edition 2, L. Korngut et al. Irreversible brain injury following status epilepticus, 235-240. Copyright (2007), with permission from Elsevier

ology of at least part of the clinical symptoms. The cytotoxic and vasogenic edema of epileptic origin are frequently found to be reversible.

- c) Gliosis and brain atrophy with cortical predominance can represent final stages of NCSE. Prognostic factors predicting irreversible brain damage due to epileptic activity need to be further studied. Focal atrophy due to NCSE may be considered in the diagnostic workup of cortical dementia.
- d) Cross-sectional imaging results presented here suggest an absence or less prominent involvement of thalamic structures in epileptic activity in patients with NCSE without altered mental state (**Figures 5,6**). These results are compatible with the current concepts of generalization and network inhibition of epileptic activity [28].
- e) Further prospective studies are warranted to elucidate the diagnostic value of cross-sectional imaging. The current observations are promising in respect of a potential role in diagnostic workup and in the understanding of the pathophysiological processes of NCSE.

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