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Review

Imaging modalities to diagnose and localize status epilepticus

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ABSTRACT

Neuroimaging, including computed tomography (CT) and magnetic resonance imaging (MRI) are frequently performed in patients who present with status epilepticus (SE). Here we discuss the role of these neuroimaging modalities in clinical evaluation and seizure localization. Additionally, translational neuroimaging research and advanced imaging technologies, such as perfusion and radionucleotide imaging may also contribute to localization of the seizure onset zone and yield opportunities to better understand the pathophysiology of SE and aid in prognostication.

1. Introduction

Status epilepticus (SE) is one of the most common neurologic emergencies with an overall incidence between 14-40/100,000 people per year [1–5]. There is medical consensus that brain imaging is recommended for all children and adults with new onset localization related seizures or SE [6–9]. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly employed methods to evaluate patients with SE. The aim and utility of imaging studies in SE falls into four overlapping categories: diagnosis, localization, evaluating pathophysiology, and prognostication.

In this review, we will discuss the role of neuroimaging following SE in children and adults. We will discuss the diagnostic yield of CT, typically performed in emergency settings, and MRI.

Typical MRI findings will be reviewed as well as differences between focal and generalized SE. Additionally, localization of focal onset epilepsy is a critical element of diagnosis, management and prognostication. Improved resolution of traditional MRI sequences, as well as advanced MRI techniques and other modalities, are playing an increasing part in localization. Furthermore, advanced neuroimaging may add value to clinical and preclinical studies that seek to understand the pathophysiology of these conditions. Finally, we will review the evidence that neuroimaging may contribute to prognostication beyond identifying an underlying cause of SE.

2. Clinical diagnosis

The most critical role for neuroimaging in clinical practice is to aid in diagnosis and identifying the etiology of SE. Neuroimaging is recommended for all patients presenting with new onset status epilepticus and should be considered in those with known epilepsy with a first episode of SE [7,8,10] (see Table 1). CT scans are the most readily available in emergency department setting and better than structural MRI at detecting blood. CT scans detect abnormalities in 15–33% patients [11–13]. This includes many acute symptomatic causes including hemorrhage, trauma, edema and mass lesions [7,12,14]. Combining CT and MRI there is a slightly higher diagnostic yield, identifying abnormalities in 30–36%. A large portion of this improvement is due to MRI being superior for detecting inflammatory changes or subtle, remote structural abnormalities [12,13]. One prospective study, combining CT and MRI identified CNS infections and cerebral dysgenesis as the most common acute and remote symptomatic causes of SE, respectively [13]. Additionally, obtaining a head CT or MRI may change management. Neuroimaging lead to urgent or emergent interventions in 8.5% of children with new onset SE, while 27% of those were identified by MRI only, including stroke, acute demyelinating encephalomyelitis (ADEM) and menigoencephalitis [12]. This data is similar to earlier studies in which neuroimaging identified an etiology for new onset epilepsy in 8–13% of patients [7,15] with the diagnostic yield increasing to 27.5% if the patient presented with status epilepticus [15]. Acute management changes may be initiated following the discovery of acute symptomatic causes of SE, such as hemorrhage, neoplasm, and cerebral edema. Conversely, common remote symptomatic causes of epilepsy include longstanding structural abnormalities, such as neonatal or other remote brain injuries, and malformations of cortical development including focal cortical dysplasias (see Table 2).

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Table 1
Indications for imaging and recommended MRI sequences for the evaluation of new onset seizures and status epilepticus. Abbreviations: 3D: 3-dimensions, FLAIR: fluid attenuated inversion recovery, DTI: diffusion tensor imaging.

Indications for Imaging [7–9]	Modality
Recommended:	MRI (highest diagnostic yield) or
New onset status epilepticus	CT (most readily available)
Consider:	
1. New onset status with known epilepsy	
2. Subsequent episodes of status with atypical presentation or new deficits	
Recommended MRI Sequences: [8]	
T2 weighted sequences in 2 planes and for children < 24 months, 3 planes or 3D T2	
T1 weighted sequence in 3D, high resolution (1 mm^3 isotropic voxels)	
FLAIR (axial and coronal)	
Fast spin echo 3 mm perpendicular to Hippocampal formation	
Diffusion weighted imaging (DWI) with DTI	
Susceptibility weighted imaging (SWI)	
Arterial spin labeling (ASL)	
T1 with contrast (if clinically indicated)	

Table 2
Common structural etiologies identified on neuroimaging. Acute abnormalities frequently prompt a change in management or surgical intervention. Remote causes may be amenable to further characterization. Abbreviations: IPH: intraparenchymal hemorrhage, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, EDH: epidural hemorrhage, TBI: traumatic brain injury, AVM: Arteriovenous malformation, HIE: hypoxic ischemic encephalopathy, TSC: tuberous sclerosis complex.

Acute symptomatic:	Remote symptomatic:
Ischemic stroke	Neonatal injury: stroke, HIE
Hemorrhage: IPH, SAH, SDH, EDH	Other remote injury, e.g. trauma, infection
Neoplasm	Cortical dysplasia
Cerebral edema: secondary to TBI or metabolic cause	Malformation of cortical development: e.g. polymicrogyria, lissencephaly, heterotopias
AVM	Other Genetic causes: e.g. Sturge Weber, TSC

The frequency of MRI abnormalities attributed to SE alone is around 11% [16], although the exact incidence remains unclear as many studies rely on case series or descriptive approaches. Furthermore, inflammatory, autoimmune, or parainfectious causes of SE are difficult to diagnose, as they may have MRI findings similar to those described with SE alone [17,18].

MRI changes most commonly associated with SE are increased T2 or fluid-attenuated inversion recovery (FLAIR) signal and/or diffusion restriction. Diffusion weighted imaging (DWI) and the corresponding apparent diffusion coefficient (ADC) are imaging modalities that reveal local edema that may be induced by SE. Generalized tonic-clonic seizures may lead to decreased ADC values in cortical and/or subcortical regions. These changes are typically more focal, even when seizures are generalized and frequently correlate with T2 or FLAIR hyperintensities [19–21] (see Fig. 1). Typical subcortical brain regions affected are the basal ganglia, thalamus, particularly the pulvinar, hippocampi, and cerebellum [22–26]. Similarly, focal or unilateral SE, as well as lateralized periodic discharges detected by EEG are associated with focal diffusion restriction and increased T2 or FLAIR signal that may persists for days to weeks [27,28].

In studies and case reports where serial MRIs are performed, the majority of FLAIR and diffusion restriction abnormalities are reversible [19–21,28], A minority of patients, particularly those with prolonged bouts of SE may develop permanent focal brain atrophy and cortical laminar necrosis [20,21,28,29]. Serial MRIs have demonstrated hippocampal signal abnormalities following febrile SE that may be related to the development of hippocampal sclerosis [30,31] and may be associated with developmental hippocampal abnormalities (discussed further below) [32].

Imaging studies of refractory SE requiring a continuous infusion, demonstrate similar patterns of changes with T2 hyperintensities seen in cortex and subcortical nuclei [33]. Case reports and small series of patients following refractory and super refractory status epilepticus, defined as seizures persisting 24 h after initiation of a continuous anesthetic infusion [34,35] demonstrate long standing changes on MRI. These changes include cerebral atrophy, cortical laminar necrosis and mesial temporal sclerosis [29,36–39]. Studies that correlate neuroimaging with pathologic findings have found widespread areas of abnormalities, including the cortex, thalamus and deep grey nuclei as well as hemispheric and crossed cerebellar atrophy [25,26,40–42]. This atrophy may be secondary to energy failure from excitotoxicity or ischemia or a combination of these.

3. Localization

MRI and other imaging modalities frequently reveal focal abnormalities following SE. Seizure localization may even be appreciated in the setting of seemingly generalized seizures, which likely implies focal onset with secondary generalization. This lends itself to further reliance on neuroimaging as a tool to localize seizure onset. Improved seizure localization increases the number of therapeutic options, including surgery. Traditional MRI and more recently, high resolution epilepsy sequences may identify structural etiologies, including chronic lesions (e.g. remote stroke, calcified cysticercosis) and dysplasias [7,12,13]. Diffusion abnormalities are frequently ipsilateral to structural lesions [19,23,24]. Finding concordance between MRI and focal EEG findings increases diagnostic yield [19,43].

Beyond MR imaging, focal epilepsy is associated with perturbations in physiologic measures of brain function, especially metabolism and blood flow, which are typically tightly coupled and may be measured with radionucleotide imaging [44]. Regional measures of metabolism may be ascertained by [18] Fluorodeoxyglucose-positron emission tomography ([18] FDG-PET) and measures of cerebral blood flow (CBF) by [99] ECD or HMPAO (hexamethylpropyleneamine oxime) single-photon emission computed tomography (SPECT). Similarly, advanced MR imaging techniques, such arterial spin labeling (ASL) may be beneficial in localizing a more discrete seizure onset [27]. ASL imaging is a form of MRI that utilizes a radiofrequency pulse to label arterial water allowing the ability to image cerebral blood flow, thus yielding an image with the intensity of the signal corresponding to local perfusion. These imaging techniques may provide value added in the interictal, ictal and post-ictal periods, particularly when comparing the regional metabolism and blood flow between these time points.

In the interictal state the epileptogenic zone is invariably hypometabolic [45], demonstrating diminished uptake of FDG and showing reduced blood flow [46]. Seizures have been long known to be associated with regional increases in cerebral blood to the origin of the ictal event or to regions representing propagation of ictal activity [47–51]. These observations are enhanced when interictal CBF is subtracted form an ictal study. After the ictal event CBF becomes reduced before normalizing [52,53]. In the setting of prolonged seizures, or SE (where it is not practical to obtain an interictal study), SPECT studies in children and adults show increases in CBF that are generally confined to the seizure focus based on concomitant ictal EEG and MRI findings that may show underlying structural abnormalities [54,55]. Unlike in patients with brief seizures, CBF findings in SE may persist for more than 24 h [54] . Several case reports describe similar findings of increased CBF in complex partial SE [56,57], epilepsia partialis continua [58,59], non-convulsive status [60,61], and with lateralized periodic discharges (LPDs) [62,63].

Ictal FDG-PET studies are rare, however 6% of “interictal” FDG- PET studies show regional increases in metabolism [64]. These observations are secondary to focal cortical dysplasias which exhibit evidence of continuous ictal activity during invasive EEG monitoring [64]. FDG-

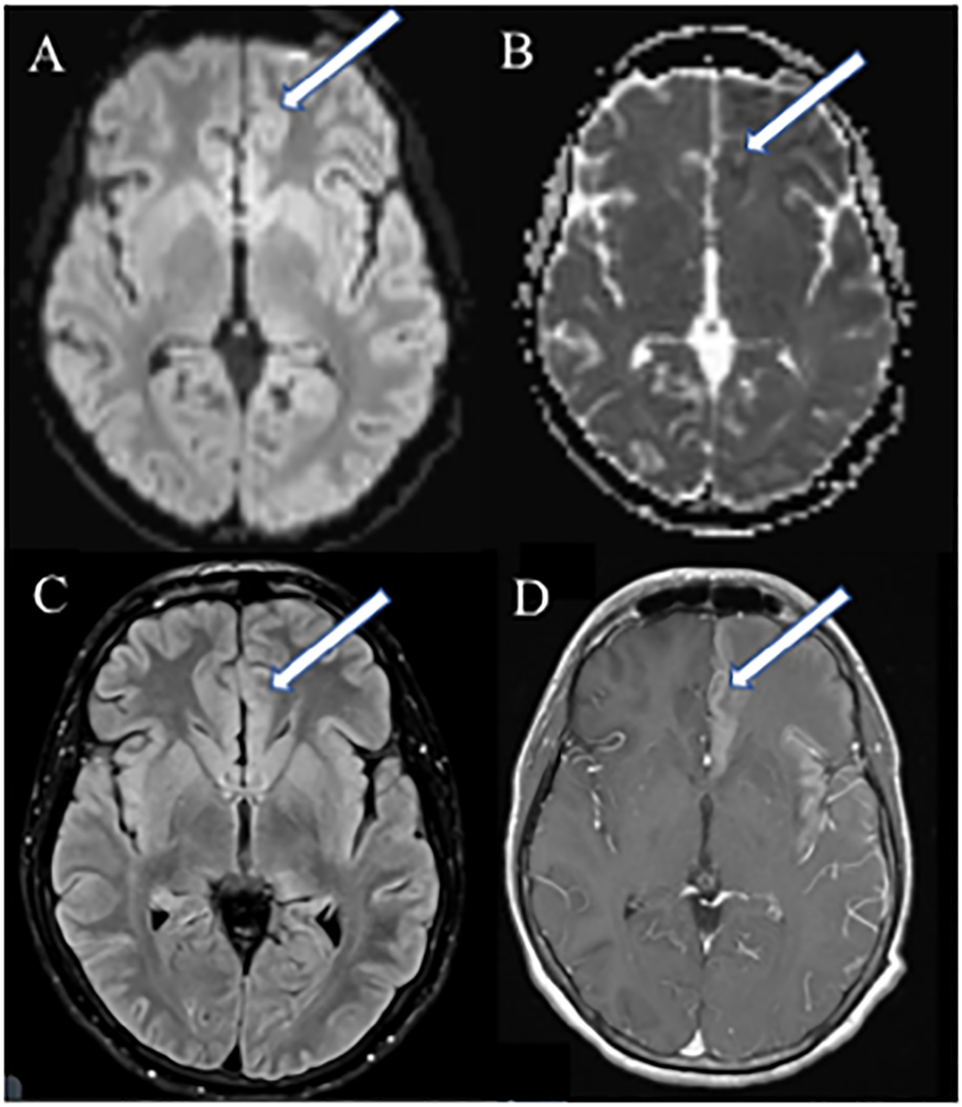

Fig. 1. Common MRI findings due to status epilepticus. DWI (A) sequence reveals increased intensity in the left insular and frontal cortices (white arrows) with corresponding decreased apparent diffusion coefficient (ADC, B). There are similar regions of increased intensity on FLAIR imaging (C) and contrast enhancement (D) implying a component of vasogenic edema. These changes resolved on repeat MRI one week later.

PET performed in children and adults in status commonly show increased glucose ligand uptake that is concordant with the seizure focus [65–67]. These observations have also been made in isolated case reports of refractory status epilepticus [55,68,69] and in PLDs [70].

A recent ASL study of 21 patients with epilepsy found that 71% of subjects had post-ictal hypoperfusion within 90 min following a seizure. Eighty percent of those with hypoperfusion had regional concordance with the suspected seizure onset zone [28]. These findings recapitulate earlier studies by Rowe and colleagues who used SPECT to demonstrate that combining ictal and interictal studies of CBF yielded a correct localization in 72% of patients [46] and postictal SPECT correctly localized the correct temporal lobe in 97% of patients [52].

4. Understanding pathophysiology

Neuroimaging may provide an opportunity to investigate and elucidate the pathophysiology of SE and brain injury. SE results in both vasogenic and cytotoxic cerebral edema. Vasogenic edema occurs with blood brain barrier breakdown and results in T2 hyperintensity without diffusion restriction [71,72], as well as contrast enhancement (see Fig. 1). Conversely, cytotoxic edema describes the intracellular accumulation of fluid that occurs with a failure of cellular metabolism. Brain injury, such as ischemia, leads to ATP-dependent sodium/potassium ($Na+/K+$) membrane pump failure and is visualized as diffusion restriction on MRI [73,74].

The timeline of cellular changes following seizure initiation has been studied extensively in animal models. These preclinical studies suggest a reduction in inhibitory signal and/or persistence of excitatory signal as the cause of prolonged seizures [75–78]. Excess glutamate and decreased gamma-amino butyric acid (GABA) tone leads to oxidative stress and perturbations in cellular metabolism [79–81]. Mitochondrial injury and ultimately ATP-dependent $Na+/K+$ pump failure leads to calcium ion influx and intracellular, cytotoxic edema [82,83]. Additionally, there is evidence for blood brain barrier breakdown leading to vasogenic edema in clinical and preclinical studies [84–87]. The etiology of seizure-induced injury is likely multifactorial, but the relative contributions of intrinsic neuronal factors versus global issues of cerebral perfusion and oxygen delivery remains an important topic of research with neuroimaging playing a key role.

The relative contribution of and timing of these types edema in SE may play a role in understanding the pathophysiology and localization of seizure onset. In studies of super refractory SE, there is increased T2

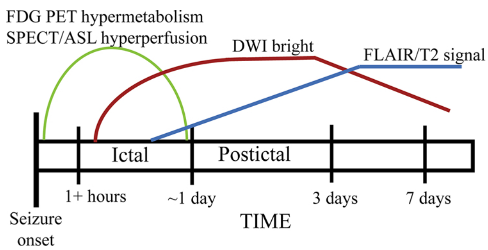

Fig. 2. Timeline of imaging changes in status epilepticus. Imaging findings that may occur during and following SE include: 1. PET hypermetabolism and SPECT or ASL measured hyperperfusion while a seizure is ongoing; 2. an increase in diffusion restriction acutely, that remains elevated for 1–7 days following seizure and gradually decreases; 3. a gradual increase in FLAIR/T2 signal that rises through the post-ictal period and then, typically resolves over days to weeks. Note: timing of imaging changes and relative signal increases vary. PET = positron emission tomography, SPECT = single-photon emission computed tomography, ASL = arterial spin labeling, DWI = diffusion weighted imaging, FLAIR = fluid attenuated inversion recovery.

signal without restricted diffusion, indicative of vasogenic edema [18,33]. This may add evidence to the role of blood brain barrier breakdown and the immunopathophysiology that has been associated with many cases of super refractory SE. The resolution of similar MRI findings has been seen in more typical, non-super refractory cases of SE as well, again supporting the role of vasogenic edema [84,85].

Diffusion restriction that occurs following seizures may be related to postictal ischemia. This has been supported by animal models of SE. In these studies chemically induced seizures lead to an ADC decrease that peaked between 1–2 days after prolonged seizures, with resolution by day 7 [88–90]. Several hypotheses have been proposed to explain pathophysiology of these imaging changes in the postictal state. These theories include decreased excitatory neurotransmitter availability or desensitization, a relative increase in inhibitory transmitters and receptors, and decreased cerebral blood flow [91,92].

In contrast, T2 hyperintensities that occur with diffusion restriction, indicative of cytotoxic edema, leave lasting changes on follow-up MRI [16,29,36,37]. Thus these imaging findings and the presence of cytotoxic edema may be a more ominous sign, implying longer lasting or permanent cellular injury (see Fig. 2).

There is the most evidence for alterations in cerebral perfusion during SE. These studies, utilizing, CT and MRI perfusion and more recently ASL imaging have demonstrated increased perfusion during SE and hypoperfusion in the post-ictal state [27,93,94]. Perfusion based modalities may play a role in investigating the pathophysiology and the relative contribution of blood flow and oxygen delivery to cellular injury in SE and the post-ictal state (see Table 3).

Table 3
Summary of Imaging modalities, findings and interpretation during and following resolution of status epilepticus. Abbreviations: FLAIR: fluid-attenuated inversion recovery, DWI/ADC: diffusion weight imaging/apparent diffusion coefficient, CTP: computed tomography perfusion, SPECT: single-photon emission computed tomography, ASL: arterial spin labeling, PET: positron emission tomography.

Imaging Modality	Imaging Findings	Interpretation
T2/FLAIR MRI	Ictal or Post-ictal: Hyperintensity	Cytotoxic or vasogenic edema
DWI/ADC MRI	Ictal: Diffusion restriction	Cytotoxic edema
Perfusion Imaging (e.g. CTP, SPECT, ASL)	Ictal: Hyperperfusion Post-ictal: Hypoperfusion	Changes in blood flow according to demand
FDG-PET	Ictal: Hypermetabolism Interictal: Hypometabolism	Changes in cellular metabolism during and following SE

5. Prognosis

Finally, neuroimaging has a place in prognostication following repeated seizures or SE. In SE, neuroimaging may play a prognostic role by helping identify the underlying etiology of the seizures and/or by understanding the relative contribution of the seizures themselves on neurologic outcome. Identifying an underlying structural cause of the SE has implications for acute management, mortality and neurologic outcomes, depending on the abnormality identified and its acuity [12,15,65,95].

To address the independent contribution of SE to neuroimaging findings and prognosis, prospective neuroimaging studies would be ideal. These are logistically challenging and it is rarely feasible to obtain baseline images on individuals before they present with SE. Clinical and preclinical studies have generally found transient signal changes on conventional MRI sequences [88–90]. As an exception, some studies in animals and humans have identified longer lasting structural abnormalities in the setting of presumed cytotoxic edema with T2 hyperintensities and diffusion restriction. Volumetric analysis of the hippocampus 21 days after pilocarpine induced seizures in a rat model correlated with the degree of T2 and ADC change on day 2 following SE [88] . Similarly, increased T2 signal and diffusion restriction in humans may lead to permanent cellular injury based on the lasting changes visualized on follow-up MRI [16,29,36,38]. Thus, certain early MRI changes may predict decreased structural volumes later on.

The role of SE in long term structural changes has been investigated the most with regards to the relationship between febrile SE and mesial temporal sclerosis (MTS) [30]. Serial MRIs of 11 toddlers presenting with febrile SE found 5 of them with evidence of hippocampal sclerosis when scanned an average of 9 months later [31]. In addition, it was appreciated in a group of immunosuppressed patients that human herpesvirus 6 was associated with increased T2 signal and increased FDG-PET uptake in the hippocampus who had a clinical syndrome including epilepsy and follow-up MRI or autopsy in a subset revealed MTS [96]. Furthermore, longitudinal volumetric imaging has revealed hippocampal asymmetries months after febrile status epilepticus [97] and found a correlation between amygdala and hippocampal volumes with a history of prolonged febrile seizures in patients with existing temporal lobe epilepsy [98].

More recently, the Consequences of Prolonged Febrile Seizures in Childhood Study (FEBSTAT) a multicenter collaboration was developed to identify the relationship between febrile SE and subsequent MTS and temporal lobe epilepsy. This group sought to compare imaging findings of children with febrile SE with simple febrile seizures. They compared the brain MRIs of 199 children with febrile SE to 96 children with their first simple febrile seizure. The group identified more acute hippocampal abnormalities, including increased T2 signal in febrile SE compared with controls. Additionally, there were more developmental abnormalities of the hippocampus, including malrotation, occurring in 10.5% of SE patients versus 2.2% of controls. Extratemporal imaging abnormalities were not different between the two groups [32]. With continued follow-up the FEBSTAT study will be able to further address the contribution of developmental and acute hippocampal abnormalities on subsequent evolution of hippocampal atrophy and on the development of temporal lobe epilepsy.

6. Conclusion

Neuroimaging is a critical component of the evaluation of status epilepticus. It provides diagnostic value in many cases and in some prompts emergent interventions that would not have been appreciated otherwise. Serial neuroimaging may allow for better assessments of brain injury over time and improve our understanding of the pathophysiology, including the timing and relative contributions of impairments in cellular metabolism, changes in cerebral blood flow and blood brain barrier breakdown. With better understanding of the underlying process we gain insights into the pathogenesis of SE in different disease states while also aiding in targeted interventions and prognostication. Finally, of equal importance is the ability of MRI and other advanced imaging techniques to provide seizure onset localization that is the first step in consideration for surgical approaches to treat underlying epilepsy and in rare cases persistent status.

Existing recommendations on the indications and timing for neuroimaging in SE rely heavily on expert opinion. We have described here data supporting the diagnostic value of neuroimaging that has established it as a standard of care in new onset SE. However, knowledge gaps remain. The impact of neuroimaging findings on the type and escalation of anti-epileptic therapies has not been described. Additionally, there is limited prospective data about the prognostic value of neuroimaging, which is in part related to the heterogeneity of etiologies. Further investigation of SE based on etiology and neuroimaging findings may facilitate future targeted therapies and a better understanding of prognosis. The FEBSTAT study is an important step forward to fill this void.

Disclosures

RMG and WDG: Have no relevant disclosures.

References

[1] Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol 2006;5(September 9):769–79.
[2] Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Neurology 2006;368(July 9531):222–9.
[3] Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology 1998;50(March 3):735–41.
[4] Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care 2014;20(June 3):476–83. Springer US.
[5] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46(April4):1029–35.
[6] Neuroimaging CO. Recommendations for neuroimaging of patients with epilepsy. Commission on neuroimaging of the international league against epilepsy. Epilepsia 1997;38(November 11):1255–6.
[7] Riviello JJ, Ashwal S, Hirtz D, Glauser T, Ballaban-Gil K, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2006;67:1542–50. Lippincott Williams & Wilkins.
[8] Gaillard WD, Chiron C, Helen Cross J, Simon Harvey A, Kuzniecky R, Hertz-Pannier L, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 2009;50(September 9):2147–53.
[9] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. 2012. p. 3–23.
[10] Freilich ER, Schreiber JM, Zelleke T, Gaillard WD. Pediatric status epilepticus. Curr Opin Pediatr 2014;26(December 6):655–61.
[11] Maytal J, Krauss JM, Novak G, Nagelberg J, Patel M. The role of brain computed tomography in evaluating children with new onset of seizures in the emergency department. epilepsia 2000;41(August 8):950–4.
[12] Lyons TW, Johnson KB, Michelson KA, Nigrovic LE, Loddenkemper T, Prabhu SP, et al. Yield of emergent neuroimaging in children with new-onset seizure and status epilepticus. Seizure: Eur J Epilepsy 2016;1(February 35):4–10. BEA Trading Ltd.
[13] Singh RK, Stephens S, Berl MM, Chang T, Brown K, Vezina LG, et al. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology 2010;23;74(February 8):636–42. Lippincott Williams & Wilkins.
[14] Earnest MP, Feldman H, Marx JA, Harris JA, Biletch M, Sullivan LP. Intracranial lesions shown by CT scans in 259 cases of first alcohol-related seizures. Neurology 1988;38(October 10):1561–5.
[15] Berg AT, Testa FM, Levy SR, Shinnar S. Neuroimaging in children with newly diagnosed epilepsy: a community-based study. Pediatrics 2000;106(September 3):527–32.
[16] Milligan TA, Zamani A, Bromfield E. Frequency and patterns of MRI abnormalities due to status epilepticus. Seizure 2009;18(March 2):104–8.
[17] Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC, et al. New-onset refractory status epilepticus. Neurology 2015;2;85(November 18):1604–13.
[18] Meletti S, Giovannini G, d'Orsi G, Toran L, Monti G, Guha R, et al. New-onset refractory status epilepticus with claustrum damage: definition of the clinical and neuroimaging features. Front Neurol 2017;27;8(March Suppl. 6):735–9.
[19] Canas N, Breia P, Soares P, Saraiva P, Calado S, Jordão C, et al. The electroclinical-imagiological spectrum and long-term outcome of transient periictal MRI abnormalities. Epilepsy Res. Elsevier B.V. 2010;1;91(October 2-3):240–52.
[20] Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. Neurology 1999;23;52(March 5):1021–7.
[21] Kim JA, Chung JI, Yoon PH, Kim DI, Chung TS, Kim EJ, et al. Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: periictal diffusion-weighted imaging. AJNR Am J Neuroradiol 2001;22(June 6):1149–60.
[22] Nakae Y, Kudo Y, Yamamoto R, Dobashi Y, Kawabata Y, Ikeda S, et al. Relationship between cortex and pulvinar abnormalities on diffusion-weighted imaging in status epilepticus. J Neurol 2015;31;263(October 1):127–32. Springer Berlin Heidelberg.
[23] Chatzikonstantinou A, Gass A, Förster A, Hennerici MG, Szabo K. Features of acute DWI abnormalities related to status epilepticus. Epilepsy Res Elsevier B.V 2011;1;97(November 1-2):45–51.
[24] Katramados AM, Burdette D, Patel SC, Schultz LR, Gaddam S, Mitsias PD. Periictal diffusion abnormalities of the thalamus in partial status epilepticus. Epilepsia 2009;27;50(January 2):265–75.
[25] Samaniego EA, Stuckert E, Fischbein N, Wijman CAC. Crossed cerebellar diaschisis in status epilepticus. Neurocrit Care 2009;5;12(December 1):88–90.
[26] Massaro AM. Teaching neuroimages:crossed cerebellar diaschisis in hemispheric status epilepticus. Neurol Am Acad Neurol 2012;13;79(November 20). e182–2.
[27] Gaxiola-Valdez I, Singh S, Perera T, Sandy S, Li E, et al. Seizure onset zone localization using postictal hypoperfusion detected by arterial spin labelling MRI. Brain 2017;28;140(September 11):2895–911.
[28] Huang Y-C, Weng H-H, Tsai Y-T, Huang Y-C, Hsiao M-C, Wu C-Y, et al. Periictal magnetic resonance imaging in status epilepticus. Epilepsy Res 2009;86(September 1):72–81.
[29] Donaire A. Cortical laminar necrosis related to prolonged focal status epilepticus. J Neurol Neurosurg Psychiatr 2006;1;77(January 1):104–6.
[30] Nohria V, Lee N, Tien RD, Heinz ER, Smith JS, DeLong GR, et al. Magnetic resonance imaging evidence of hippocampal sclerosis in progression: a case report. Epilepsia 1994;35(November 6):1332–6.
[31] Provenzale JM, Barboriak DP, VanLandingham K, Macfall J, Delong D, Lewis DV. Hippocampal MRI signal hyperintensity after febrile status epilepticus is predictive of subsequent mesial temporal sclerosis. AJR Am J Roentgenol 2008;190(April 4):976–83.
[32] Shinnar S, Bello JA, Chan S, Hesdorffer DC, Lewis DV, Macfall J, et al. MRI abnormalities following febrile status epilepticus in children: the FEBSTAT study. Neurology 2012;28;79(August 9):871–7.
[33] Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001;42(November 11):1461–7.
[34] Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;28;135(July 8):2314–28.
[35] Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;5;134(October 10):2802–18.
[36] Doherty CP, Cole AJ, Grant PE, Fischman A, Dooling E, Hoch DB, et al. Multimodal longitudinal imaging of focal status epilepticus. Can J Neurol Sci 2016;16;31(February 02):276–81. Cambridge University Press.
[37] Sirven JI, Zimmerman RS, Carter JL, Drazkowski JF, Larson JS. MRI changes in status epilepticus. Neurology 2003;10;60(June 11):1866.
[38] Chevret L, Husson B, Nguefack S, Nehlig A, Bouilleret V. Prolonged refractory status epilepticus with early and persistent restricted hippocampal signal MRI abnormality. J Neurol 2008;22;255(January 1):112–6.
[39] Bauer G, Gotwald T, Dobesberger J, Embacher N, Felber S, Bauer R, et al. Transient and permanent magnetic resonance imaging abnormalities after complex partial status epilepticus. Epilepsy Behav 2006;8(May 3):666–71.
[40] Men S, Lee DH, Barron JR, Muñoz DG. Selective neuronal necrosis associated with status epilepticus: MR findings. AJNR Am J Neuroradiol 2000;21(November 10):1837–40.
[41] Nixon J, Bateman D, Moss T. An MRI and neuropathological study of a case of fatal status epilepticus. Seizure 2001;10(December 8):588–91.
[42] Teixeira RA, Li LM, Santos SLM, Zanardi VA, Guerreiro CAM, Cendes F. Crossed cerebellar atrophy in patients with precocious destructive brain insults. Arch Neurol 2002;59(May 5):843–7.
[43] Rennebaum F, Kassubek J, Pinkhardt E, Hübers A, Ludolph AC, Schocke M, et al. Status epilepticus: clinical characteristics and EEG patterns associated with and without MRI diffusion restriction in 69 patients. Epilepsy Res. Elsevier B.V 2016;1(February 120):55–64.
[44] Gaillard WD, Fazilat S, White S, Malow B, Sato S, Reeves P, et al. Interictal metabolism and blood flow are uncoupled in temporal lobe cortex of patients with complex partial epilepsy. Neurol Am Acad Neurol 1995;1;45(October 10):1841–7.
[45] Theodore WH, Gaillard WD, Sato S, Kufta C, Leiderman D. Positron emission tomographic measurement of cerebral blood flow and temporal lobectomy. Ann Neurol 1994;36(August 2):241–4. Wiley Subscription Services, Inc., A Wiley Company.
[46] Rowe CC, Berkovic SF, Sia STB, Austin M, McKay WJ, Kalnins RM, et al. Localization of epileptic foci with postictal single photon emission computed tomography. Ann Neurol 1989;26(November 5):660–8. Wiley Subscription Services, Inc., A Wiley Company.
[47] Harvey AS, Hopkins IJ, SBowe JM, Cook DJ, Shield LK, Berkovic SF. Frontal lobe epilepsy: Clinical seizure characteristics and localization with ictal 99mTc-HMPAO SPECT. Neurol Am Acad Neurol 1993;1;43(October 10). 1966–6.
[48] Harvey AS, Bowe JM, Hopkins IJ, Shield LK, Cook DJ, Berkovic SF. Ictal 99mTc-HMPAO single photon emission computed tomography in children with temporal

lobe epilepsy. Epilepsia 1993;34(September 5):869–77. Blackwell Publishing Ltd.
[49] Vera P, Kaminska A, Cieuta C, Hollo A, Stiévenart JL, Gardin I, et al. Use of subtraction ictal SPECT co-registered to MRI for optimizing the localization of seizure foci in children. J Nucl Med 1999;40(May 5):786–92.
[50] Kaminska A, Chiron C, Ville D, Dellatolas G, Hollo A, Cieuta C, et al. Ictal SPECT in children with epilepsy: comparison with intracranial EEG and relation to post-surgical outcome. Brain 2003;1;126(January 1):248–60.
[51] O'Brien TJ, So EL, Mullan BP, Hauser MF, Brinkmann BH, Bohnen NI, et al. Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. Neurol Am Acad Neurol 1998;1;50(February 2):445–54.
[52] Rowe CC, Berkovic SF, Austin MC, McKay WJ, Bladin PF. Patterns of postictal cerebral blood flow in temporal lobe epilepsy: qualitative and quantitative analysis. Neurology 1991;41(July 7):1096–103.
[53] Newton MR, Berkovic SF, Austin MC, Rowe CC, McKay WJ, Bladin PF. Postictal switch in blood flow distribution and temporal lobe seizures. J Neurol Neurosurg Psychiatry 1992;1;55(October 10):891–4. BMJ Publishing Group Ltd.
[54] Tatum WO, Alavi A, Stecker MM. Technetium-99m-HMPAO SPECT in partial status epilepticus. J Nucl Med 1994;35(July 7):1087–94.
[55] Bhatia S, Ahmad F, Miller I, Ragheb J, Morrison G, Jayakar P, et al. Surgical treatment of refractory status epilepticus in children: clinical article. J Neurosurg Pediatr 2013;12(October 4):360–6.
[56] Bauer J, Stefan H, Huk WJ, Feistel H, Hilz MJ, Brinkmann HG, et al. CT, MRI and SPECT neuroimaging in status epilepticus with simple partial and complex partial seizures: case report. J Neurol 1989;236(July 5):296–9. Springer-Verlag.
[57] Ali II, Pirzada NA, Vaughn BV. Periodic lateralized epileptiform discharges after complex partial status epilepticus associated with increased focal cerebral blood flow. J Clin Neurophysiol 2001;18(November 6):565–9.
[58] Matthews R, Franceschi D, Xia W, Cabahug C, Schuman G, Bernstein R, et al. Parietal lobe epileptic focus identified on spect-mri fusion imaging in a case of epilepsia Partialis Continua. Clin Nucl Med 2006;31(December 12):826–8.
[59] Sztriha L, Pávics L, Ambrus E. Epilepsia partialis continua: follow-up with 99mTc-HMPAO-SPECT. Neuropediatrics 1994;25(October 5):250–4. © Georg Thieme Verlag KG Stuttgart·New York.
[60] Ohe Y, Hayashi T, Deguchi I, Fukuoka T, Maruyama H, Kato Y, et al. A case of nonconvulsive status epilepticus with a reversible contralateral cerebellar lesion: temporal changes in magnetic resonance imaging and single-photon emission computed tomography finding. J Stroke Cerebrovasc Dis 2013;22(November 8). e639–42.
[61] Kutluay E, Beattie J, Passaro EA, Edwards JC, Minecan D, Milling C, et al. Diagnostic and localizing value of ictal SPECT in patients with nonconvulsive status epilepticus. Epilepsy Behav 2005;6(March 2):212–7.
[62] Handforth A, Cheng JT, Mandelkern MA, Treiman DM. Markedly increased mesiotemporal lobe metabolism in a case with PLEDs: further evidence that PLEDs are a manifestation of partial status epilepticus. Epilepsia 1994;35(July 4):876–81.
[63] Assal F, Papazyan JP, Slosman DO, Jallon P, Goerres GW. SPECT in periodic lateralized epileptiform discharges (PLEDs): a form of partial status epilepticus? Seizure 2001;10(June 4):260–4.
[64] Bansal L, Miller I, Hyslop A, Bhatia S, Duchowny M, Jayakar P. PET hypermetabolism in medically resistant childhood epilepsy: Incidence, associations, and surgical outcome. Epilepsia 2016;18;57(January 3):436–44.
[65] Alexopoulos A, Lachhwani DK, Gupta A, Kotagal P, Harrison AM, Bingaman W, et al. Resective surgery to treat refractory status epilepticus in children with focal epileptogenesis. Neurol Am Acad Neurol 2005;8;64(February 3):567–70.
[66] Struck AF, Westover MB, Hall LT, Deck GM, Cole AJ, Rosenthal ES. Metabolic correlates of the Ictal-Interictal Continuum: FDG-PET during continuous EEG. Neurocrit Care. 2016;11;24(May 3):324–31. Springer US.
[67] Siclari F, Prior JO, Rossetti AO. Ictal cerebral positron emission tomography (PET) in focal status epilepticus. Epilepsy Res 2013;105(August 3):356–61.
[68] Nardetto L, Zoccarato M, Santelli L, Tiberio I, Cecchin D, Giometto B. 18F-FDG PET/MRI in cryptogenic new-onset refractory status epilepticus: a potential marker of disease location, activity and prognosis? J Neurol Sci 2017;15(October 381):100–2.
[69] Stayman A, Abou-Khalil B. FDG-PET in the diagnosis of complex partial status epilepticus originating from the frontal lobe. Epilepsy Behav 2011;20(April 4):721–4.
[70] Tatum WO, Stecker MM. Serial FDG-PET scans in a patient with partial status epilepticus. Epilepsia 1995;36(February 2):214–5.
[71] Schaefer PW, Buonanno FS, Gonzalez RG, Schwamm LH. Diffusion-weighted imaging discriminates between cytotoxic and vasogenic edema in a patient with Eclampsia. Stroke 1997;1;28(May 5):1082–5.
[72] Barzó P, Marmarou A, Fatouros P, Hayasaki K, Corwin F. Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging. J Neurosurg 1997;87(December 6):900–7.
[73] Simard JM, Kent TA, Chen M, Tarasov KV, Gerzanich V. Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. Lancet Neurol 2007;6(March 3):258–68.
[74] Stadnik TW, Demaerel P, Luypaert RR, Chaskis C, Van Rompaey KL, et al. Imaging tutorial: differential diagnosis of bright lesions on diffusion-weighted MR images. Radiographics 2003;23(January 1). e7–e7.
[75] Goodkin HP, Joshi S, Mtchedlishvili Z, Brar J, Kapur J. Subunit-specific trafficking of GABAA receptors during status Epilepticus. J Neurosci 2008;5;28(March 10):2527–38.
[76] Seinfeld S, Goodkin HP, Shinnar S. Status Epilepticus. Cold Spring Harb Perspect Med 2016;1;6(March 3). a022830–13.
[77] Goodkin HP. Status Epilepticus increases the intracellular accumulation of GABAA receptors. J Neurosci Soc Neurosci 2005;8;25(June 23):5511–20.
[78] Rajasekaran K, Todorovic M, Kapur J. Calcium-permeable AMPA receptors are expressed in a rodent model of status epilepticus. Ann Neurol 2012;23;72(July 1):91–102. Wiley Subscription Services, Inc., A Wiley Company.
[79] Schubert D, Piasecki D. Oxidative glutamate toxicity can be a component of the excitotoxicity cascade. J Neurosci 2001;1;21(October 19):7455–62.
[80] Murphy TH, Miyamoto M, Sastre A, Schnaar RL, Coyle JT. Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress. Neuron 1989;2(June 6):1547–58.
[81] Aoyama K, Watabe M, Nakaki T. Regulation of neuronal glutathione synthesis. J Pharmacol Sci 2008;108(3):227–38.
[82] Griffiths T, Evans MC, Meldrum BS. Intracellular sites of early calcium accumulation in the rat hippocampus during status epilepticus. Neurosci Lett 1982;30;30(June 3):329–34.
[83] Griffiths T, Evans MC, Meldrum BS. Status epilepticus: the reversibility of calcium loading and acute neuronal pathological changes in the rat hippocampus. Neuroscience 1984;12(June 2):557–67.
[84] Yaffe K, Ferriero D, Barkovich AJ, Rowley H. Reversible MRI abnormalities following seizures. Neurology 1995;45(January 1):104–8.
[85] Hong K-S, Cho Y-J, Lee SK, Jeong S-W, Kim WK, Oh EJ. Diffusion changes suggesting predominant vasogenic oedema during partial status epilepticus. Seizure 2004;13(July 5):317–21.
[86] Nitsch C, Klatzo I. Regional patterns of blood-brain barrier breakdown during epileptiform seizures induced by various convulsive agents. J Neurol Sci 1983;59(June 3):305–22.
[87] Sammaritano M, Andermann F, Melanson D, Pappius HM, Camfield P, Aicardi J, et al. Prolonged focal cerebral edema associated with partial status Epilepticus. epilepsia 1985;26(August 4):334–9. Blackwell Publishing Ltd.
[88] Choy M, Cheung KK, Thomas DL, Gadian DG, Lythgoe MF, Scott RC. Quantitative MRI predicts status epilepticus-induced hippocampal injury in the lithium–pilocarpine rat model. Epilepsy Res 2010;88(February 2-3):221–30.
[89] Fabene PF, Marzola P, Sbarbati A, Bentivoglio M. Magnetic resonance imaging of changes elicited by status epilepticus in the rat brain: diffusion-weighted and T2-weighted images, regional blood volume maps, and direct correlation with tissue and cell damage. NeuroImage 2003;18(February 2):375–89.
[90] Wang Y, Majors A, Najm I, Xue M, Comair Y, Modic M, et al. Postictal alteration of sodium content and apparent diffusion coefficient in epileptic rat brain induced by Kainic acid. Epilepsia 1996;37(October 10):1000–6. Blackwell Publishing Ltd.
[91] Fisher RS, Schachter SC. The postictal state: a neglected entity in the management of epilepsy. Epilepsy Behav 2000;1(February 1):52–9.
[92] Koepp MJ, Diehl B, Woermann FG. Functional neuroimaging in the postictal state. Epilepsy Behav 2010;19(October 2):127–30.
[93] Mathews MS, Smith WS, Wintermark M, Dillon WP, Binder DK. Local cortical hypoperfusion imaged with CT perfusion during postictal Todd's paresis. Neuroradiology 2008;16;50(February 5):397–401. 2nd ed. Springer-Verlag.
[94] Rupprecht S, Schwab M, Fitzek C, Witte OW, Terborg C, Hagemann G. Hemispheric hypoperfusion in postictal paresis mimics early brain ischemia. Epilepsy Res 2010;89(May 2-3):355–9.
[95] Neligan A, Shorvon SD. Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. Arch Neurol Am Med Assoc 2010;67(August 8):931–40.
[96] Wainwright MS, Martin PL, Morse RP, Lacaze M, Provenzale JM, Coleman RE, et al. Human herpesvirus 6 limbic encephalitis after stem cell transplantation. Ann Neurol 2001;50(5):612–9.
[97] Scott RC. Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. Brain 2003;1;126(November11):2551–7.
[98] Cendes F, Andermann F, Dubeau F, Gloor P, Evans A, et al. Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. Neurol. Am Acad Neurol 2011;23;76(May 21). 1845–5.