ASN ANNUAL MEETING: NEUROIMAGING FOR PRECISION MEDICINE AND HEALTH

NEUROIMAGING IN EPILEPSY

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GK has no financial ties to any EEG or neuroimaging technology companies.
GK has no financial ties to any vasoactive or anti-seizure medication companies.

DISCLAIMER:
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ROLES OF NEUROIMAGING IN EPILEPSY

• Etiological work-up: Identifying a Causal Lesion

• Surgical Planning for Temporal Lobe Epilepsy
  • Semiology guided
  • Ictal PET/SPECT
  • fMRI to avoid post-resection deficits
  • Concordance of multimodality towards surgical planning
The use of fMRI may be considered an option for lateralizing language functions in place of intracarotid amobarbital procedure (IAP) in patients with medial temporal lobe epilepsy (MTLE; Level C), temporal epilepsy in general (Level C), or extratemporal epilepsy (Level C).

For patients with temporal neocortical epilepsy or temporal tumors, the evidence is insufficient (Level U).

fMRI may be considered to predict postsurgical language deficits after anterior temporal lobe resection (Level C).

The use of fMRI may be considered for lateralizing memory functions in place of IAP in patients with MTLE (Level C) but is of unclear utility in other epilepsy types (Level U).

fMRI of verbal memory or language encoding should be considered for predicting verbal memory outcome (Level B).

fMRI using nonverbal memory encoding may be considered for predicting visuospatial memory outcomes (Level C).

Presurgical fMRI could be an adequate alternative to IAP memory testing for predicting verbal memory outcome (Level C).

Clinicians should carefully advise patients of the risks and benefits of fMRI vs IAP during discussions concerning choice of specific modality in each case.
ROLE OF NEUROIMAGING IN FIRST SZ

• A NI study should be done to exclude a structural brain abnormality if the patient's first SZ was clearly not a physiological NES.

• **Brain MRI is preferred over CT** to identify specific lesions such as cortical dysplasias, infarcts, or tumors. Nevertheless, a brain **CT scan is suitable** to exclude a mass lesion, hemorrhage, or large stroke under emergency situations or if an MRI is unavailable or contraindicated.

• One retrospective review of 148 patients: The cause of seizure was established in 48%; a structural lesion was identified by CT in 37% and 11% had metabolic SZs.

• CT findings agreed with the results of neurologic examination in 82% of cases.

• However, structural lesions (including three tumors) were found by CT in 15% with nonfocal findings and in 22% patients with generalized EEG abnormalities.

• **A brain MRI is useful in children presenting with their first SZ** to identify congenital abnormalities such as neuronal migration disorders and AVM. In young to middle-aged adults, common findings are MTS, sequelae of head injury, congenital anomalies, brain tumors, and vascular lesions.

• In the elderly, **MRIs often reveal strokes, cerebral degeneration, or neoplasms.**

• However, up to 50 percent of patients, regardless of age, have normal neuroimaging studies.

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• Adults with an unprovoked first SZ should be informed that their SZ recurrence risk is greatest early within the first 2 years (21%-45%) (Level A), and clinical variables associated with increased risk may include a prior brain insult (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), and a nocturnal SZ (Level B).

• Immediate antiepileptic drug (AED) therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first 2 years (Level B) but may not improve quality of life (Level C).

• Over a longer term (>3 years), immediate AED treatment is unlikely to improve prognosis as measured by sustained seizure remission (Level B).

• Patients should be advised that risk of AED adverse events (AEs) may range from 7% to 31% (Level B) and that these AEs are likely predominantly mild and reversible.

• Clinicians' recommendations whether to initiate immediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the AEs of AED therapy, consider educated patient preferences, and advise that immediate treatment will not improve the long-term prognosis for seizure remission but will reduce seizure risk over the subsequent 2 years.

Krumholtz et al. Neurology. 2015
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NEUROIMAGING
FOR PERIODIC DISCHARGES

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“PLEDS”, “PLEDS+”, “SIRPIDS”, “GPED COMA”, “EPC”, “NCSE”, “BOUNDARY SYNDROMES”…

THE ICTAL-INTERICTAL CONTINUUM…
ELECTROCLINICAL SE…
ELECTRORADIOLOGIC SE…
ELECTROMETABOLIC SE…
ELECTROPERFUSIVE SE…

BACK TO A (BROADER ETIOLOGICALLY-DRIVEN) ECSE AS A SPECTRUM…
The Ictal-Interictal-Injury Continuum

Potential for 2° Neuronal Injury

High

SIRPIDs

Interictal

Low

TW

S-B

GPEDs

PLEDs proper

PLEDs-Plus

EPC

NCS

NCSE

GCSE
Fig. 1. IC treatment algorithm. (a) When deciding whether to treat an IC pattern, the association with clinical events, the presence of risk factors (RF) for seizures, location and type of pattern as well as the response to AED trial and brain injury biomarkers should be considered. (b) To determine aggressiveness of treatment, clinicians should consider hemodynamic status, whether the patient is intubated and other potential complications from anesthetic medications. If the patient is not intubated, a single AED, preferably with low drug-drug interactions and ability to rapidly titrate should be maintained at least 24 h (AED trial). If the AED trial results in clinical improvement or imaging or biomarker studies suggest the possibility of an ictal pattern, AED dosage should be increased or a second AED added (AED treatment). If the patient is intubated, anesthetic medications such as benzodiazepines, barbiturates or propofol can be considered. AMD: acute metabolic disorder, Aw: anesthetic withdrawal, BP: blood pressure, NA: not available, worsening?: worse clinical state or EEG.
Combining brain injured patients from Harvard, Yale and Emory, also explored if higher frequencies were the tipping point for these PDs to be linked to subsequent SZs.

"Plus modifiers", which are superimposed fast activity on top of these PDs, as well as prevalence and laterality of these PDs, more than frequency alone, were associated with subsequent SZs.

Regarded as a new composite signature of seizure-like activity, which to most experts, signals that it may require vigorous treatment (Krish & Bazil JAMA Neurol. 2016).
ROLE OF NEUROIMAGING IN DEFINING ECSE

New views on electro-clinical status epilepticus: does metabolic imaging add to clinical context to clarify the therapeutic significance on the ictal-interictal spectrum?

- There is added diagnostic and prognostic value, as well as clearer therapeutic significance, with the adjunct of lesional and metabolic imaging, when compared to the recent classification of ictal-interictal patterns based solely on periodic epileptiform discharges characteristics, as per the bi-dimensional ictal-interictal continuum (IIC) put forth by Chong & Hirsch in 2005.

From Electroclinical to Electrometabolic Status Epilepticus?
Gregory Kapinos¹ · Jan Claassen²

[CrossMark]
Neurocritical Care

Metabolic Correlates of the Ictal-Interictal Continuum: FDG-PET during Continuous EEG

ROLE OF PHARMACOLOGICAL TESTING IN DEFINING ECSE

Low dose MDZ escalation test:

The problem remains that ECSE heavily relies on the clinical context, as well as on the clinical exam, which, in stuporous patients, is already dismal to begin with, solely due to the underlying acute brain injury.

Neurointensivists have thus devised a pharmacological test to confirm ECSE with a high bar, with previously published eminence-based criteria. (Box 1) But again, there is great limitation in the subjective measurement of clinical and EEG background ameliorations, in brain-injured critically ill patients.
OPERATIONAL DEFINITIONS FOR THE MODALITY-BASED VARIOUS SUBTYPES OF STATUS EPILEPTICUS

• EEG Characteristics for ictal signature: SZ and NCSE

• Clinical context, etiology, underlying lesion

• Pharmacological test for PDs

• Intracranial probing for metabolic trace

• Neuroimaging for metabolic or perfusive status:
  • PET (traditionally, hypermetabolism is compelling)
  • SPECT (recent data suggests that hyper-perfusion is a correlate/surrogate)
  • CTP/MRP (any focal hyperperfusion on imaging may suffice as per Kapinos et al. preliminary data)
WHAT DEFINES ELECTROGRAPHIC STATUS EPILEPTICUS?

• A pattern of >3Hz spike-wave, periodic discharges (PDs), or rhythmic activity. Frequency, amplitude, morphology, and evolution domains are all diagnostically important characteristics

• OR discrete electrographic seizures meeting Young 1996’s criteria, without recovery of EEG background

WHAT DEFINES UNEQUIVOCAL NONCONVULSIVE ELECTROGRAPHIC STATUS EPILEPTICUS?

- Patients without known epileptic encephalopathy varying from mild to coma.
- EEG is indispensable for the diagnosis:
  - A pattern of >2.5Hz for any type of periodic discharges (PDs),
  - OR <2.5Hz or rhythmic delta activity AND a spatial-temporal evolution of the pattern with onset increments, evolution then decrementing termination.
- NCSE can be difficult to discern because of the lack of interictal background for salient contrast with the ictal activity.

WHAT DEFINES ELECTRO-CLINICAL STATUS EPILEPTICUS?

• An ictal-interictal continuum (IIC) pattern temporally associated with clonic (even if subtle myoclonic) activity

• OR an IIC pattern following a single seizure in association with persistent encephalopathy

• OR Frequent or continuous EEG abnormalities (spikes, sharp-waves, rhythmic slow activity, PLEDs, BIPEDs, GPEDs, triphasic waves) in patients whose EEGs showed no previous similar abnormalities, in the context of acute cerebral damage (e.g., anoxic brain damage, infection, trauma).

• Ideally, this IIC pattern should be associated with both clinical and EEG improvement following short-acting anti-seizure medication to definitely satisfy NCSE (pharmacotherapy should be as an ex juvantibus punctual trial to decide on the need for treatment -see below- rather than prolonged anti-seizure treatment, as it becomes a self-fulfilling prophecy for ECSE)

All prior references +
NOTION OF ELECTRO-PHARMACOLOGICAL STATUS EPILEPTICUS:

• Benzodiazepine trial: sequential small doses of rapidly acting, short-duration benzodiazepines are administered (e.g. midazolam 0.5 mg increments up to 2mg total maximum).

• ECSE is confirmed ex juvantibus when all 3 criteria are met:
  • 1) effacement of the IIC EEG pattern; and
  • 2) appearance of previously absent normal EEG background; and
  • 3) improvement in responsiveness or consciousness.

• If EEG improves, but the patient does not, the result is equivocal (IIC pattern was a mere sequela, not actively altering the patient, or benzodiazepine triggered profound sedation)

Claassen J. How I treat patients with EEG patterns on the ictal-interictal continuum in the neuro ICU. Neurocrit Care. 2009 Dec;11(3):437-44.
NOTION OF ELECTRO-METABOLIC STATUS EPILEPTICUS:

• PDs collocalizing with focal hypermetabolism on PET are behaving like NCSE and deserve treatment


NOTION OF ELECTRO-PERFUSIVE STATUS EPILEPTICUS:

• PDs collocalizing with focal hyperperfusion on perfusion imaging (especially SPECT) are behaving like NCSE and deserve treatment

References on following page...
List of studies using regular/conventional “luminar-perfusive” imaging (MRP/ASL or CTP):

• Kapinos et al. in progress…

NOTION OF ELECTRO-ETIOLOGIC STATUS EPILEPTICUS:

• Back to the context primacy: the underlying brain disease, syndromal entity (with matching epilepsy or boundary condition) and the presence of a lesion visible on imaging are the most significant factors predicting subsequent seizures and influencing the prognosis (and thus, the need for dedicated treatment)

Not only “full blown seizures” but also "near-seizures" alter the brain utilization of oxygen and behave like SZs, representing ongoing secondary brain injury.

It was unsure if PDs that are not considered SZs, but are nearing them on a IIC, especially because of higher intrinsic frequency, would be also responsible for low pbtO2, likely responsible for subsequent brain damage.

Dr. Claassen not only linked these PDs to low pbtO2, but also revealed a time-locked association, insinuating causality.

Frequency >2Hz seems to be the tipping point.
Not only seizures but also these periodic discharges were deleterious, as proven by time-locked alteration of neuronal metabolism.
MRP in LPDs for decision to treat

Perfusion MRI can impact treatment decision in ictal-interictal continuum


• “pMRI was useful in distinguishing ictal from interictal LPDs”

• “Findings of pMRI In the first patient, hyperperfusion in the area showing LPDs was considered an indication that the LPDs were ictal, and aggressive treatment led to clinical improvement.”

• “The second patient had no asymmetry on pMRI and therefore we did not escalate antiepileptic therapy, and the LPDs resolved spontaneously over the next few days.”

• “pMRI offers several advantages over other techniques such as SPECT.”

• “It does not expose the patient to radiation, and newer techniques like arterial spin labeling can even obviate the need for intravenous contrast.”