Epilepsies Secondary to Defined Mechanisms

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October 13, 2013
Disclosures

• No financial disclosures.

• Will discuss non-FDA approved (off-label) treatments.
Objectives

• Autoimmune Epilepsy
• Brain Tumors and Epilepsy
• Malformations of Cortical Development
• Post-traumatic Epilepsy
• Stroke and Epilepsy
Autoimmune Epilepsy

Sources:
Irani et al, Curr Opin Neurol, 2011
Quek et al, Arch Neurol, 2012
Britton, AES Annual Meeting, 2012
Autoimmune Epilepsy Overview

• These are not zebras!

• Seizures + supporting findings
  – typical presentation is limbic encephalitis
  – strongly suspect in new-onset refractory epilepsy, or new-onset status epilepticus
Supporting Findings

• Clinical signs
  – encephalopathy
  – amnestic syndrome
  – cognitive decline
  – personality changes
  – psych features (e.g., psychosis, catatonia, agitation)
  – movement disorder

• Medical history
  – other autoimmune stigmata (type 1 diabetes, thyroid disease, celiac disease, B12 deficiency)
  – history of cancer (or strong risk factors for cancer)
Workup

- MRI with contrast
  - tends to be normal
  - may show edema or T2 hyperintensity in temporal lobes or limbic structures
- CSF usually normal (incl. oligoclonal bands)
- EEG findings are variable
  - may show focal or generalized seizures
  - may have nonspecific findings
  - “extreme delta brush” in NMDA-R antibody
Adapted from Schmitt et al, Neurology, 2012
Workup

• Divide antibodies into cytoplasmic (onconeural) vs. cell membrane
  – onconeural are more often paraneoplastic
  – cell membrane are more often responsive to immunotherapy

• Cancer screening
  – PET-CT brain and body
  – select cases – testicular ultrasound, colonoscopy, mammogram, prostate or gynecologic exam
## Select Onconeural Antibodies

Adapted from McKeon and Pittock, Acta Neuropathol, 2011.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Associated Cancer</th>
<th>Symptoms (other than seizures / limbic encephalitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANNA-1</td>
<td><strong>Small cell carcinoma</strong></td>
<td>Brainstem encephalitis, autonomic or sensory neuropathy</td>
</tr>
<tr>
<td>Ma1, Ma2</td>
<td><strong>Testicular</strong></td>
<td>Brainstem encephalitis</td>
</tr>
</tbody>
</table>
| CRMP-5   | Small cell carcinoma  
Thymoma | Dementia, personality change, chorea, ataxia, neuropathy |
| Amphiphysin | Small cell carcinoma  
Breast adenocarcinoma | Dementia, myelopathy, neuropathy |
| GAD      | **None**  
Thymoma  
Breast adenocarcinoma | **Stiff-person syndrome**, ataxia, brainstem encephalitis, ophthalmoplegia, parkinsonism, **diabetes (DM-1)** |
## Select Neuronal Membrane Antibodies

![Image](image-url.com)

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<th>Associated Cancer</th>
<th>Symptoms (other than seizures / limbic encephalitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGKC-complex*</td>
<td>None</td>
<td>Executive dysfunction, personality changes, brainstem encephalitis, myoclonus (CJD-like picture), neuropathy, hyponatremia</td>
</tr>
<tr>
<td>NMDA</td>
<td>None</td>
<td>Psychosis, extrapyramidal disorders (e.g., choreoathetosis), dysautonomia</td>
</tr>
<tr>
<td>AMPA</td>
<td>Thymic, Lung, Breast</td>
<td>–</td>
</tr>
<tr>
<td>GABA-B</td>
<td>Neuroendocrine tumors incl. small cell carcinoma</td>
<td>Orolingual dyskinesias</td>
</tr>
</tbody>
</table>

*multiple antibody targets in this complex (LGI-1, CASPR2, Contactin-2)

Adapted from McKeon and Pittock, Acta Neuropathol, 2011.
Two Key Antibodies

• VGKC-complex
  – associated with **hyponatremia**
  – LGI-1 subtype is associated with faciobrachial dystonic seizures (with or without EEG correlate)
  – may mimic CJD

• NMDA-receptor
  – seen with or without **ovarian teratoma**
  – can have choreoathetosis, dysautonomia
Treatment

• No controlled trials, no strong evidence basis
• First line
  – find / treat cancer
  – IV Ig OR IV methylprednisolone daily x3-5 days
  – continue weekly for 6-12 weeks
  – plasma exchange used if severe symptoms
• If successful
  – gradual taper + addition of mycophenolate or azathioprine
• If failed
  – consider cyclophosphamide, rituximab
Brain Tumors and Epilepsy

Sources:
Glantz et al, Neurol, 2000
Wyllie’s Treatment of Epilepsy, 2011
What tumors are epileptogenic?

• Adult-onset
• Lower grade tumors
• Tumors close to cortex or sensitive networks (hippocampal, primary motor)
• Parietal tumors have strongest association with seizures, followed closely by temporal
Tumor pathology and seizures

- Nearly 100% of dysembryoplastic neuroepithelial tumors (DNET) have seizures
- 75-90% of gangliogiomas and astrocytomas
- 30-60% of meningiomas and GBMs
- <20% of primary CNS lymphomas
- Hypothalamic hamartomas – gelastic seizures
Why do tumors cause seizures?

• Peritumoral, non-neoplastic tissue often causes seizures (tumor core often silent, necrotic)

• Genetic factors - for example, LGI1
  – tumor-suppressor gene that is absent in GBM
  – mutation causes autosomal dominant lateral temporal lobe epilepsy (with auditory features)
Treatment

• Must balance tumor treatment goals with epilepsy treatment goals
  – seizure freedom is a goal with operable tumors
  – first-line anticonvulsants fail in 60-70% of patients
• Older drugs can interact with chemo and increase risk of bone marrow suppression
• Valproate may have an intrinsic anti-tumor effect (inhibits histone deacetylase)
Prophylaxis

• **NO strong evidence** that anticonvulsants can prevent first seizure in a known brain tumor

• AAN guidelines **against** their use in patients who never had a seizure

• Can be given for the **first week postop**, but should not be continued
Surgical Evaluation

• Is this “tumor surgery” (curative) or “epilepsy surgery” (palliative)?

• Poor prognostic factors
  – longer epilepsy duration
  – low grade tumor
  – seizure at onset of tumor diagnosis
  – subtotal resection (e.g., positive margins)
Surgical Evaluation

• Imaging alone should not guide surgery
• Assess peritumoral or even distant epileptogenic focus (may need invasive EEG)
• Assess for dual pathology (hippocampal sclerosis and tumor); consider resecting both
• Functional mapping (electrocorticography, fMRI) is important, if tumor is near eloquent cortex
Malformations of Cortical Development

Sources:
Blumke et al, Epilepsia, 2011
Krsek et al, Ann Neurol, Jun 2008
Lerner et al, Epilepsia, Jun 2009
Wyllie’s Treatment of Epilepsy, 2011
Malformations of Cortical Development (MCDs)

• Cortical neurons and glia originate from germinal matrix (must develop AND migrate)

• Any disruption in development = MCDs  
  – normal cells in the wrong place  
  – abnormal cells in the correct place
Polymicrogyria (PMG)

Source: www.germaco.net/pmg_gb.html
Polymicrogyria (PMG)

- Excessive, small convolutions/gyri
- Is a descriptive term, assoc. with many syndromes

- **bilateral perisylvian polymicrogyria syndrome**
  - bihemispheric pre- and post-central PMG
  - oromotor dysfunction (tongue, face, pharyngeal, and speech difficulties)
  - seizures
  - aphasia
Schizencephaly (SCZ)

Source: http://emedicine.medscape.com/article/413051-overview
Schizencephaly (SCZ)

• Parenchymal clefts from lack of cortical development
  – schizencephaly = grey matter along cleft (often PMG)
  – porencephaly = white matter along cleft

• deMorsier syndrome
  – SCZ
  – agenesis of septum pellucidum
  – optic nerve hypoplasia
  – hypopituitarism
Hemimegalencephaly

Source: http://radiopaedia.org/articles/emimegalencephaly
Hemimegalencephaly

• Triad of intractable partial seizures in infancy, hemiparesis, and developmental delay

• Variable pathology, including other MCDs
  – often isolated
  – associated with tuberous sclerosis, neurofibromatosis, linear nevus sebaceous syndrome, hypomelanosis of Ito

• May need functional hemispherectomy
Subcortical Band Heterotopía

Source: radiopaedia.org/articles/band-heterotopia
Subcortical Band Heterotopia

- “Double cortex” or “subcortical laminar heterotopia”

- Associated with DCX gene mutation (X-linked)

- Milder symptoms
  - mild developmental delay
  - seizures often delayed until teenage years
Lissencephaly

Source: http://radiopaedia.org/cases/agyria-pachygyria
Lissencephaly (LIS)

- “Smooth brain”
- Developmental delay, hypotonia, spasticity, seizures (esp. epileptic spasms), and difficulty feeding
- Classical (autosomal) forms
  - deletion of LIS1 gene (17p)
  - LIS more severe anteriorly
- X-linked forms
  - DCX mutation can cause SBH or LIS
  - LIS more severe posteriorly
Doublecortin (DCX)

DCX mutation (Xq22.3-q23)

male offspring: $X^{DY}$

female offspring: $X^{DX}$
Periventricular Nodular Heterotopia (PVNH)

Periventricular Nodular Heterotopia (PVNH)

- Periventricular gray matter (failed migration)

- Bilateral PVNH is associated with the FLNA (filamin A) gene at Xq28 (usu. lethal in males)
# Subependymal Nodules?

<table>
<thead>
<tr>
<th>Tuberous Sclerosis</th>
<th>Periventricular Nodular Heterotopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>smaller</td>
<td>larger</td>
</tr>
<tr>
<td>less in number</td>
<td>more in number, often bilateral</td>
</tr>
<tr>
<td>heterogeneous</td>
<td>homogeneous</td>
</tr>
<tr>
<td>calcified</td>
<td>not calcified</td>
</tr>
<tr>
<td>white matter intensity on MRI</td>
<td>gray matter intensity on MRI</td>
</tr>
</tbody>
</table>
Focal Cortical Dysplasia (FCD)

• Typically has refractory partial seizures
• Typical MRI findings
  – blurred gray-white junction
  – cortical thickening
  – “transmantle sign”: abnormal T2 signal extending from cortex to the superolateral margin of the lateral ventricle

Source: Blumcke et al, Epilepsia, 2011
FCD types and prognosis

• Proposed classification system (ILAE task force*)
  – type I – abnormal cortical lamination/layering
  – type II – dysmorphic neurons (+ balloon cells in Type IIb)
  – type III – associated lesions (e.g., hippocampal sclerosis, tumors, vascular malformations)

• “Milder” type often has normal MRI (may be found on interictal PET or SPECT)

• “Severe” pathology (Type IIb) may have better prognosis – easier to find on MRI and resect

Source: Lerner et al, Epilepsia, Jun. 2009

*Source: Blumcke et al, Epilepsia, 2011
Post-traumatic Epilepsy

Sources:
Chang and Lowenstein, Neurol, 2003
Schierhout and Roberts, Cochrane review, 2010
Wyllie’s Treatment of Epilepsy, 2011
Early Seizures After Head Trauma

• Early seizures = within first week

• 10% will develop late seizures (multivariate analysis has shown that early seizures are predictive but not an independent risk factor)

• Early status has higher risk for late seizures
Early Seizures After Head Trauma

• Strong evidence for prophylaxis in adults with severe brain injury for the first week only
  – Cochrane review – NNT is 10
  – AAN recommendations – phenytoin x 1 week

• No evidence that prevention of early seizures prevents late seizures / epilepsy
Late Seizures After Head Trauma

• Late seizures = epilepsy

• Only one unprovoked late seizure necessary for diagnosis (recurrence risk is 86% in 2 yrs)

• 70-80% develop epilepsy within 2 years

• Risk declines after that, but epilepsy can start > 15 years later
Severity of Head Trauma

• Early seizures PLUS moderate/severe trauma

• Mild: LOC < 30 min, no skull fracture

• Moderate: LOC 0.5-24 hrs, no parenchymal injury

• Severe: LOC > 24 hrs, contusion, ICH, or dural penetration
Mild Head Trauma

• May have higher association with psychogenic non-epileptic events (PNES)

• Head trauma is a risk factor for both epilepsy and PNES (and PTSD)
Workup

• Imaging may be misleading
  – vulnerable networks are preferentially injured (hippocampus, temporal and frontal poles)
  – epileptogenic focus may be distant from original injury site

• EEG may be misleading
  – in first month after injury, may not predict development of epilepsy / late seizures
  – presence of interictal epileptiform discharges may confound a diagnosis of PNES
Treatment considerations

• Seizure-free rates lower (25-40%)

• Hippocampal sclerosis can be post-traumatic, esp. if trauma occurred before 5 years of age

• Seizure-free rates lower after temporal lobectomy, but chances of class I outcome is still up to 60%
Stroke and Epilepsy

Source:
Wyllie’s Treatment of Epilepsy, 2011
Pediatric Stroke

• Neonatal stroke
  – Usually large vessel arterial disease
  – Up to 80% have seizure as presenting symptom

• Childhood stroke
  – Usually small vessel arterial disease
  – Up to 30% have seizure as presenting symptom

• Epilepsy risk is approximately 15-25%
Adult Stroke

• Post-stroke seizures: 7-11% incidence
  – Acute symptomatic seizures (within 24 hrs)
  – Early seizure (within 1 week)
  – Late seizure / epilepsy (after 1 week)

• Post-stroke epilepsy: 2-4% prevalence
  – High recurrence after first late seizure (50-70%)
  – Consider treatment after first late seizure
Predictors of Post-stroke Epilepsy

- Cortical location
- Stroke severity (exam / NIHSS)
- Hemorrhage

- PLEDs/LPDs may be predictive (uncommon)
- Focal slowing is not predictive
References


Self-Assessment Questions
1. A 55 year old man presents with a one month history of progressive cognitive decline and episodes of unresponsiveness. Despite treatment with multiple anticonvulsants, he becomes comatose. On exam, he is noted to have myoclonic jerks. Labs reveal hyponatremia. Which serum antibody is most likely to be positive in his condition?

A. N-methyl-D-aspartate receptor antibody  
B. LGI1 antibody (voltage-gated potassium channel complex)  
C. Glutamic acid decarboxylase antibody  
D. Anti-amphiphysin antibody
2. A 35 year old woman without a history of epilepsy is hospitalized with confusion and psychosis. EEG reveals very frequent partial seizures, which do not stop despite four anticonvulsants. She is noted to have choreiform movements on examination. Which test is most likely to provide a specific diagnosis in her case?

A. PET-CT of abdomen and pelvis
B. LGI1 antibody (voltage-gated potassium channel complex)
C. MRI of the brain with contrast
D. Continuous EEG monitoring
3. Certain factors are associated with higher epileptogenicity in brain tumors. Which of the following factors is NOT likely to be associated with higher epileptogenicity?

A. Adult onset of brain tumor
B. Tumor situated near the hippocampus
C. Tumor situated near primary motor cortex
D. High grade tumor pathology
4. Which of these tumor types is most likely to be associated with seizures?

A. Primary CNS Lymphoma  
B. Dysembryoplastic Neuroepithelial Tumor  
C. Meningioma  
D. Astrocytoma
5. A patient with a brain tumor has never had a seizure and is requesting anticonvulsant prophylaxis when being admitted for his surgical resection. The most appropriate response is:

A. Anticonvulsant prophylaxis is not recommended before the first seizure, and it is also not recommended perioperatively.
B. Anticonvulsant prophylaxis is not recommended before the first seizure, but it is recommended for the first six months postoperatively.
C. Anticonvulsant prophylaxis is not recommended before the first seizure, but it is recommended for the first one week postoperatively.
D. Anticonvulsant prophylaxis is recommended before the first seizure, and it is also should be continued indefinitely postoperatively.
6. A 4 year old boy has severe oral and facial dysfunction since birth, associated with difficulty feeding. He has intractable partial epilepsy with bihemispheric epileptiform discharges on EEG. His MRI is shown below. What is his diagnosis?

A. Polymicrogyria
B. Lissencephaly
C. Schizencephaly
D. Pachygyria
7. An 8 year old boy has history of epilepsy and partial blindness. He has a history of events where he feels palpitations, lightheaded, falls down and passes out for 30-45 seconds. An EEG during the event reveals generalized slow activity. MRI shows clefts in the cortical tissue, lined with grey matter. What is the most appropriate test to order in this patient?

A. Video-EEG  
B. Tilt-table testing  
C. 24-hour cardiac rhythm monitoring  
D. Serum cortisol level
8. A 6 month old boy has epileptic spasms, hypotonia, and difficulty feeding. His MRI reveals lissencephaly. Which genetic mutation is also known to be responsible for a milder phenotype, especially in girls?

A. LIS1 on chromosome 17
B. DCX (doublecortin) on the X chromosome
C. FLNA (filamin A) on the X chromosome
D. TSC2 (tuberin) on chromosome 16
9. A 16 year old girl with intractable partial epilepsy has a brain MRI which reveals periventricular (subependymal) lesions. Which of the following features is more likely to suggest periventricular nodular heterotopia, rather than the subependymal nodules of tuberous sclerosis?

A. Unilateral lesion
B. Calcified lesion
C. Homogenous lesion
D. White matter intensity lesion
10. Which of the following statements is NOT true regarding early seizures after traumatic brain injury?

A. Early seizures occur within the first week after injury
B. Early seizures may be associated with increased occurrence of late seizures / epilepsy
C. Early status epilepticus may be associated with increased occurrence of late seizures / epilepsy
D. Early seizures should be treated in order to lower the risk of late seizures / epilepsy
11. Which of the following statements is true regarding seizures after traumatic brain injury?

A. Prophylaxis of seizures should continue for one month after severe brain injury
B. Risk of epilepsy decreases with time after the injury, especially after the first two years
C. At least two late seizures are necessary to diagnose post-traumatic epilepsy and consider treatment
D. A history of mild head trauma and abnormal EEG should warrant anticonvulsant treatment
12. Which of the following statements is true regarding seizures after stroke?

A. Neonatal strokes are more likely to present with focal neurologic deficits rather than seizures
B. Adult onset stroke is more likely to lead to epilepsy as compared to pediatric stroke
C. At least two late seizures are necessary to diagnose post-stroke epilepsy and consider treatment
D. Focal slowing on EEG is not predictive of epilepsy after stroke
Answers

1. B
2. A
3. D
4. B
5. C
6. A
7. D
8. B
9. C
10. D
11. B
12. D