Disclosure

None
Learning Objectives

• Summarize most essential facts relating tumor type to the clinical manifestations of epilepsy.
• Summarize the most critical implications of tumor type on epilepsy treatment.
Learning Objectives

• Summarize most essential facts relating tumor type to the clinical manifestations of epilepsy.
• Summarize the most critical implications of tumor type on epilepsy treatment.
Fact 1:

Tumor type is one of the main determinants of the risk of epilepsy (Jehi, 2010)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Seizure frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysembryoplastic neuroepithelial tumor (4,16)</td>
<td>100</td>
</tr>
<tr>
<td>Ganglioglioma (3)</td>
<td>80–90</td>
</tr>
<tr>
<td>Low-grade astrocytoma (3)</td>
<td>75</td>
</tr>
<tr>
<td>Meningioma (8)</td>
<td>27–60</td>
</tr>
<tr>
<td>Glioblastoma multiforme (3)</td>
<td>29–50</td>
</tr>
<tr>
<td>Primary CNS lymphoma (3,7)</td>
<td>10–20</td>
</tr>
</tbody>
</table>
Fact 2:

Timing of seizures in relation to diagnosis - rather than tumor type - determines seizure characteristics (Hildebrand, 2005)

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First manifestation (n = 158)</th>
<th>Present evaluation (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only focal (n = 63)</td>
<td>With generalization (n = 79)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>28(^*)</td>
<td>45(^*)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>22(^*)</td>
<td>20(^*)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>6(^*)</td>
<td>6(^*)</td>
</tr>
<tr>
<td>Gliomatosis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

40% Focal  50% GTC  75% Focal  20% GTC
Fact 3:

Tumor type is one of the main determinants of the risk of associated epileptic pathology

Dual Pathology

Developmental brain tumors: DNET and gangliogliomas

- 25%-70% Malformation of cortical development
  (Frater, 2000; Morris, 1996; Jehi, 2008)

- Hippocampal sclerosis (Prayson, 2008)
What is behind the “facts”? 
Tumor type:  (Lyons, 2007)

• Necrosis
• Endothelial proliferation
• Mitosis
• Tissue infiltration
Low grade  
High grade
Tumor type: (Lyons, 2007)

- Necrosis
- Endothelial proliferation
- Mitosis
- Tissue infiltration

\[
\begin{align*}
&\text{Mechanisms of Epilepsy!} \\
&\text{Determinants of excitability}
\end{align*}
\]
Fact 1:
Tumor type is one of the main determinants of the risk of epilepsy (Jehi, 2010)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Seizure frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysembryoplastic neuroepithelial tumor (4,16)</td>
<td>100</td>
</tr>
<tr>
<td>Ganglioglioma (3)</td>
<td>80–90</td>
</tr>
<tr>
<td>Low-grade astrocytoma (3)</td>
<td>75</td>
</tr>
<tr>
<td>Meningioma (8)</td>
<td>27–60</td>
</tr>
<tr>
<td>Glioblastoma multiforme (3)</td>
<td>29–50</td>
</tr>
<tr>
<td>Primary CNS lymphoma (3,7)</td>
<td>10–20</td>
</tr>
</tbody>
</table>
Fact 1:
Tumor type is one of the main determinants of the risk of epilepsy (Jehi, 2010)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Seizure frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysembryoplastic neuroepithelial tumor (4,16)</td>
<td>100</td>
</tr>
<tr>
<td>Ganglioglioma (3)</td>
<td>80–90</td>
</tr>
<tr>
<td>Low-grade astrocytoma (3)</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Seizure frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme</td>
<td>29–50</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>10–20</td>
</tr>
</tbody>
</table>
Fact 2:

Timing of seizures in relation to diagnosis - rather than tumor type - determines seizure characteristics (Hildebrand, 2005)

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First manifestation (n = 158)</th>
<th>Present evaluation (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only focal (n = 63)</td>
<td>With generalization (n = 79)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>28*</td>
<td>45*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>22*</td>
<td>20*</td>
</tr>
<tr>
<td>Grade 4</td>
<td>6*</td>
<td>6*</td>
</tr>
<tr>
<td>Gliomatosis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

40% Focal 50% GTC 75% Focal 20% GTC

American Epilepsy Society | Annual Meeting 2012
Fact 3:

Tumor type is one of the main determinants of the risk of associated epileptic pathology

**Dual Pathology**

Developmental brain tumors: DNET and gangliogliomas

- 25%-70% Malformation of cortical development
  (Frater, 2000; Morris, 1996; Jehi, 2008)

- Hippocampal sclerosis (Prayson, 2008)
Association with hippocampal sclerosis

Consideration particularly with long standing epilepsy
Association with MCD  

(Jehi, 2010, from Wyllie's textbook of the Treatment of the epilepsies)
Fact 4:

• In general, risk of developing intractability is at least 50% when tumor is the etiology.

• Twice as high as the risk of intractability with other causes of epilepsy.
Impact on Clinical Care and Practice

- Recognize high risk of seizures in all patients with brain tumors.
- Recognize that adequate epilepsy control requires adequate treatment of the tumor.
- Consider early surgery
- Tumor surgery is NOT the same as epilepsy surgery.
Thank you!
Peritumoral Changes and Epileptogenesis

December 2, 1012

Steve Chung, MD
Professor of Neurology
Barrow Neurological Institute
Disclosure

• Received research grants: Barrow foundation, Esai, GSK, Lundbeck, Medtronics, Neuronex, SK Life Science, Supernus, Sunovion, UCB Pharma, Upsher-Smith, Valeant

• Member of speaker’s bureau: GSK, Lundbeck, UCB Pharma

• Consulting/Advisory Board: Esai, Lundbeck, UCB Pharma, Upsher-Smith
Learning Objectives

• What causes seizures in brain tumor patients?
• Understand the various peritumoral changes that contribute to seizures
Does size, grade, or location matter?

- High-grade gliomas are less often associated with seizures (30-40%), and smaller tumors are more likely present with seizures\(^1\)
- Low grade glioneuronal tumors (i.e. gangliogliomas and DNETs) are more often associated with seizures (80-100%)\(^2\)
- Seizures are more likely to occur if tumors are in mesial temporal and insular structures

Are tumor-related seizures due to peritumoral changes rather than the tumor itself?

\(^1\) Lee JW. Arch Neurol. 2010; 67(3)
\(^2\) Prayson RA. Am J Surg Pathol 2010; 34
Are seizures caused by the tumor or peritumoral tissue?

• Intrinsic epileptogenicity of brain tumors is supported by the presence of hyperexcitable neuronal components within the tumor\(^1\)
  • i.e. Dysplastic neurons and giant cells of cortical tubers
    (Alteration of glutamate and GABA receptor expressions)\(^2\)

• Also, the dysplastic and disorganized peritumoral region may cause epileptogenesis via Distorsion and Infiltration.

\(^1\)Ferrier et al. Epilepsia. 2006
Changes in peritumoral tissue 

by high-grade tumors

• Rapid growth causes tissue damage (Distortion)$^1$
  • Necrosis
  • Hemosiderin deposition
  • Peritumoral edema
• High-grade tumors present less frequently with seizures
  • i.e. in GBM, 30-50%$^2$

$^1$Riva et al. Neurol Sci. 2005
$^2$Moots et al. Arch Neurol. 1995
Changes in peritumoral tissue

*Initial thoughts*

- Penfield in 1940: Seizures are due to impaired vascularization and peritumoral ischemic changes\(^1\)
- Echlin in 1959 proposed partial isolation or denervation hypersensitivity theory\(^2\)

\(^1\)Penfield. *Arch Neurol Psych* 1940
\(^2\)Echlin. *Clin Neurophysiol* 1959
\(^1,2\)Beaumont. *Acta Neurochir* 2000
Changes in peritumoral tissue

*Altered living environment*

- Peritumoral regions face altered biochemical and hormonal profile, vascular organization, axonal collaterals and neosynaptogenesis.
- May explain why low-grade tumors cause seizures more frequently

---

1 Lee JW. Arch Neurol. 2010; 67(3)  
2 Prayson RA. Am J Surg Pathol 2010; 34
Changes in peritumoral tissue

*Altered living environment (1)*

- Ion changes may cause hyperexcitability\(^1\)
  - Decreased extracellular Mg\(^{2+}\)
  - Increased extracellular Fe\(^{3+}\)
- pH changes may cause hyperexcitability\(^2, 3\)
  - Peritumoral cortex is significantly alkaline
  - Altered carbonic acid levels
  - ↑Alkalinity blocks membrane K\(^+\) conductance
  - pH increase causes reduced GABA levels and activates NMDA receptors

\(^1\)Singh R. *Epilepsia* 1990
\(^2\)Okada Y. *J Neurosurg* 1992
\(^3\)Tang C. *Proc Natl Acad Sci* 1990
Changes in peritumoral tissue

*Altered living environment (2)*

- Changes in amino acid concentration
  - Inhibition of glutamate transporters (GLAST, GLT1, EAAC1) $\rightarrow$ extra cellular glutamate level increase$^1$
  - Altered GABA level and GABAnergic transmission$^2$
  - Increased level of polyamines (Spermine, spermidine, putrescine)$^3$
  - Enzymatic changes (i.e Glutamine synthetase↑)

- These changes may be a cause or a consequence of seizures

$^1$Rothstein J. *Neuron* 1996
$^2$Haglund N. *J Neurosurg* 1992
$^3$Sessa A. *Cancer Lett* 1994
Changes in peritumoral tissue

*Altered living environment (3): IL-1β*

- Immune mediated changes occur in peritumoral region\(^1\)
- Elevated IL-1β level in brain tumor\(^2\)
  - Elevated IL-1β in acute/chronic seizure models
  - Proconvulsive effects of IL-1β \(^3\)
    - Augments nitric oxide formation
    - Directly inhibits GABA\(_A\)
    - Increases NMDA receptor function
    - Inhibits K\(^+\) efflux

\(^1\)Soliven B. *J Neurochem* 1992
\(^2\)Nowak M. *Epilepsia* 2009
\(^3\)Li G. *Seizure* 2011
Changes in peritumoral tissue

*Altered living environment (4): TNFα, BBB*

- Up-regulation of TNFα mRNA after seizures and in subjects with CNS tumors (in animal)\(^1\)
- TNFα may play a dichotomous role\(^2\)
  - TNFα activates p55: proconvulsant effect
  - TNFα activates p75: anticonvulsant effect
- Cytokines cause enhanced BBB permeability\(^3\)

---

\(^1\)Godlevsky L. *Pol J Pharmacol* 2002
\(^2\)Li G. *Seizure* 2011
\(^3\)Marchi N. *Epilepsia* 2007
Summary: Peritumoral tissue and Epileptogenesis

• Aberrant neuronal/glial neosynapses
• Disturbed balance of excitatory/inhibitory inputs
• Membrane instability and altered neurotransmitter concentrations
• Cytokine/TNF mediated membrane excitability
• Disruption of the blood-brain-barrier
Panel Flash Session:
How genetic & biochemical alterations in brain tumors contribute to epileptogenesis

December 2\textsuperscript{nd}, 2012

Joon H. Uhm, MD FRCPC
Departments of Neurology & Oncology
Mayo Clinic, Rochester, MN
<table>
<thead>
<tr>
<th>Name of Commercial Interests</th>
<th>Type of Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Disclosures

American Epilepsy Society  | Annual Meeting 2012
Learning Objectives

Snapshot of

• The key genetic alterations in gliomas
• The mechanisms by which these genetic alterations lead to epileptogenic changes in the peritumoral microenvironment
Genetic & biochemical alterations in glioma

Signal transduction
- EGFR
- PI3K
- PTEN
- AKT
- mTOR

Gene induction
- PTEN
- AKT
- mTOR

Cell cycling
- G1/S
- CDK4
- Rb
- P16

Effector functions
- Protease
- Integrin
- vEGF
- Proteolysis
- Invasion
- Motility

Proliferation
- G1
- G2
- S

Proliferation
- Proliferation
- Angiogenesis

Blood vessels
- Blood vessels
Genetic & biochemical alterations in glioma

Signal transduction

Gene induction

Cell cycling

Effector functions

Protease

Integrin

vEGF

Proteolysis

Invasion

Motility

Blood vessels

Angiogenesis

G1

G1/S Checkpoint

CDK4

GO

M

G1

G2

S

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª

ª
How do tumor-derived ‘pollutants’ promote epileptogenesis?

More detailed discussion in session to follow...