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PRASAT NEUROLOGICAL INSTITUTE

Epilepsy and Brain Tumor

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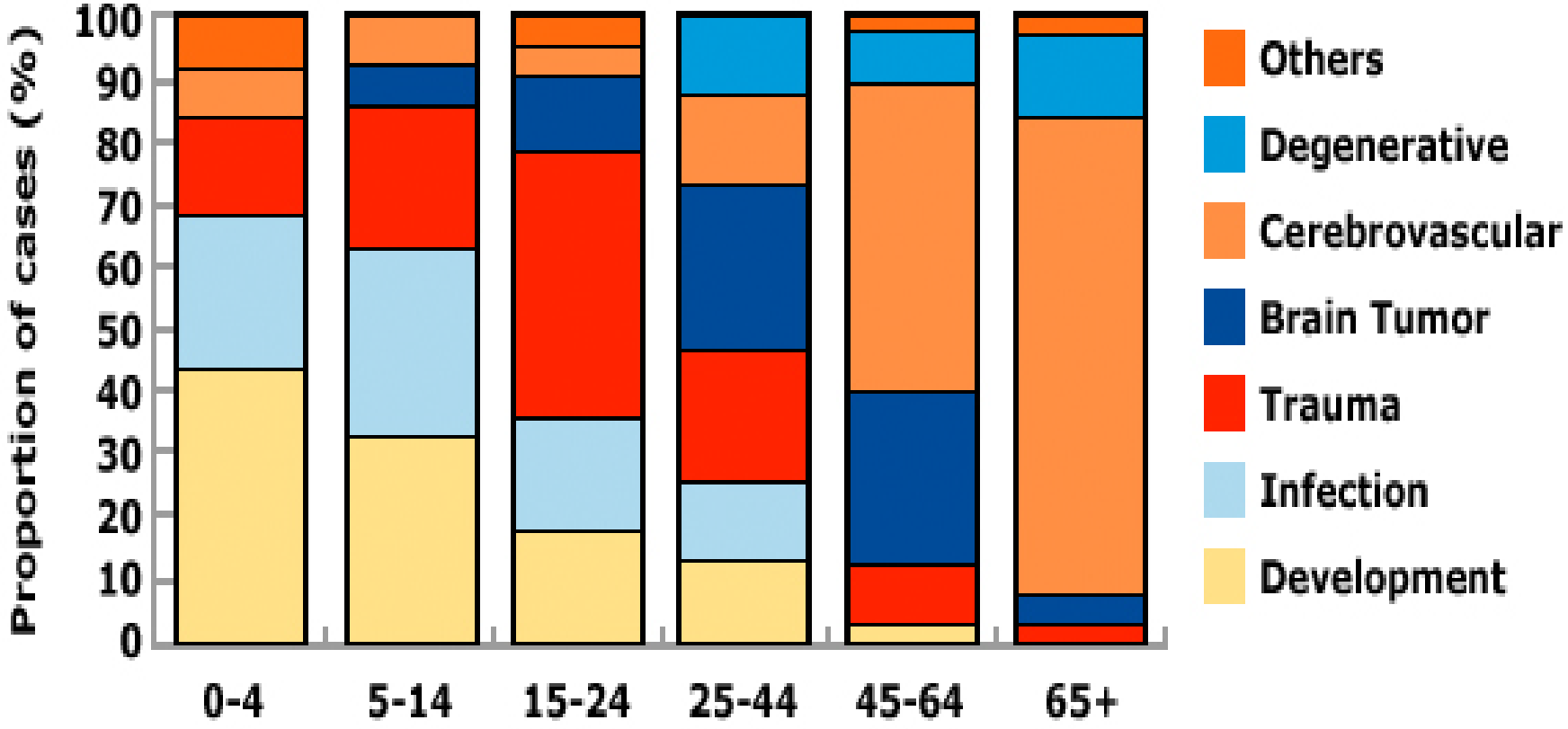
Outline

- Overview
- Pathogenesis：Tumor-> epilepsy

Etiology of Epilepsy , age



Annegers JF. The epidemiology of epilepsy. In: Wyllie E, ed. The treatment of epilepsy: principles and practice. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:165-72.

EPILEPSY AND BRAIN TUMORS

- CNS neoplasms are the cause of

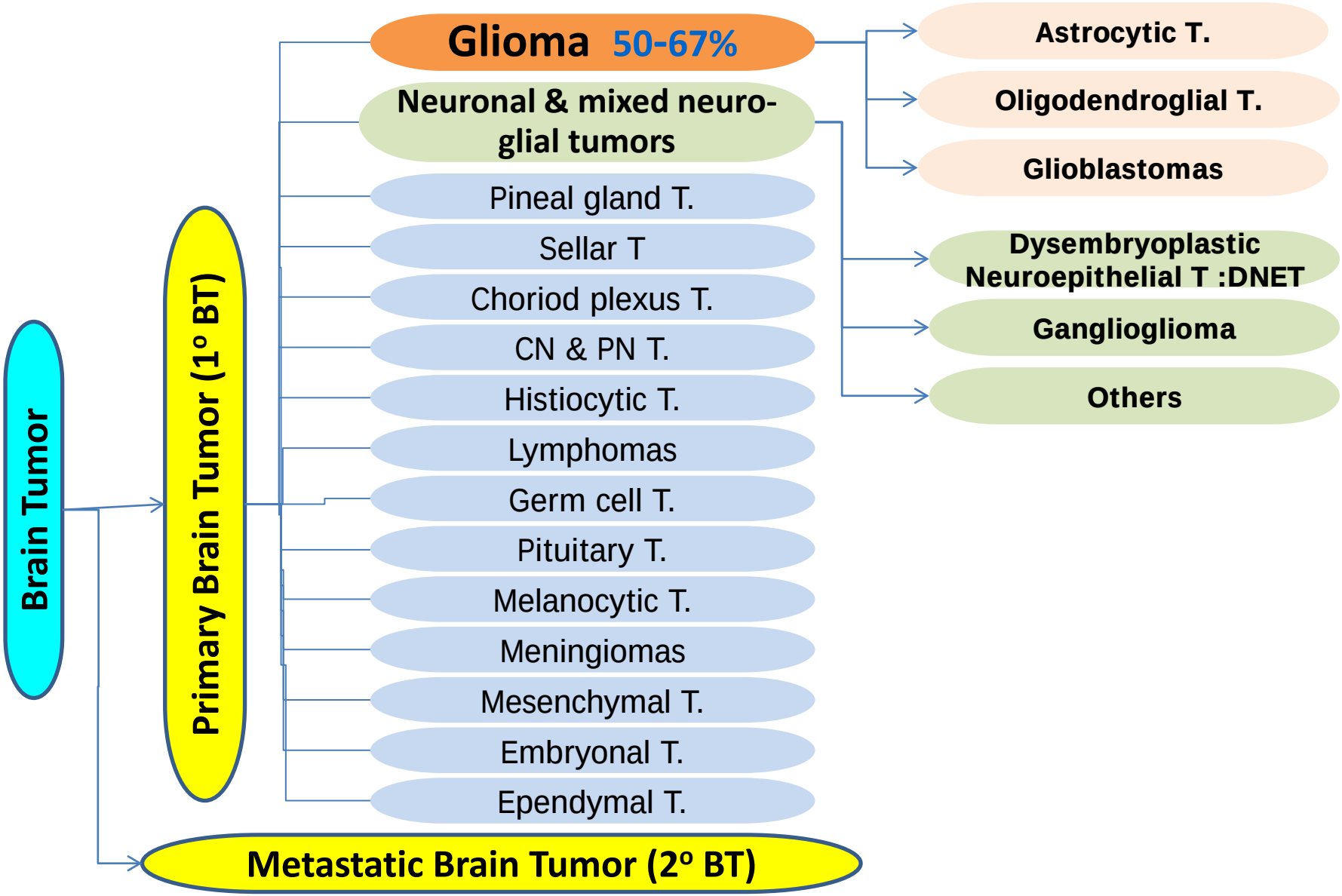
  (*van Breeman MS, et al 2007)*

  ≈ 10–15% of adult-onset epilepsy

  ≈ 0.2–6.0% of childhood-onset epilepsy

- Seizure is the most common **presenting symptom** of brain tumor *(Lynam LM, et al 2007)*
  - 38% of primary CNS tumors
  - 20% of secondary CNS tumors

Brain Tumor Classification



Brain Tumor Grade

- “low grade” (WHO grade I or II)
- “high grade” (WHO grade III or IV).

Grading of selected CNS tumors according to the 2016 CNS WHO

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III

Other astrocytic tumours

Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I

d ganglioglioma I
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I
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I

Seizure frequency based on Tumor type

Lancet Neurol 2007 421-430

Tumor type	Seizure frequency%	% of primary brain tumors
DNET	92-100	0.8-5
Ganglioglioma	80-90	0.3-3
Low-grade glioma	60-85	15
Meningioma	27-41	36.4
GBM	29-49	15.1
Metastatic Lesions	14-35	-
Primary CNS Lymphoma	10	2-4

Neuronal tumors have a higher incidence of seizures. Due to-> population of neurons could be epileptogenic within the tumor whereas in the glial tumors the seizure focus is generally in the peritumoral brain tissue

Seizures & Tumor Pathology

- Slow-growing, infiltrative tumors : DNET & LGG
  - Highest risk Sz 75%-100% in adults and children.
- Meningiomas and high-grade astrocytomas,
  - Less common in children compared with adults
  - 30%-60% incidence of Sz in adults and children.
- Seizures in 20-40% of pts brain metastases,
  - in 67% with melanoma, in 48% with lung cancer,
  - In 33% with CA breast , in 55% with unknown CA

Maschio M., 2012

Developmental brain & Tumor

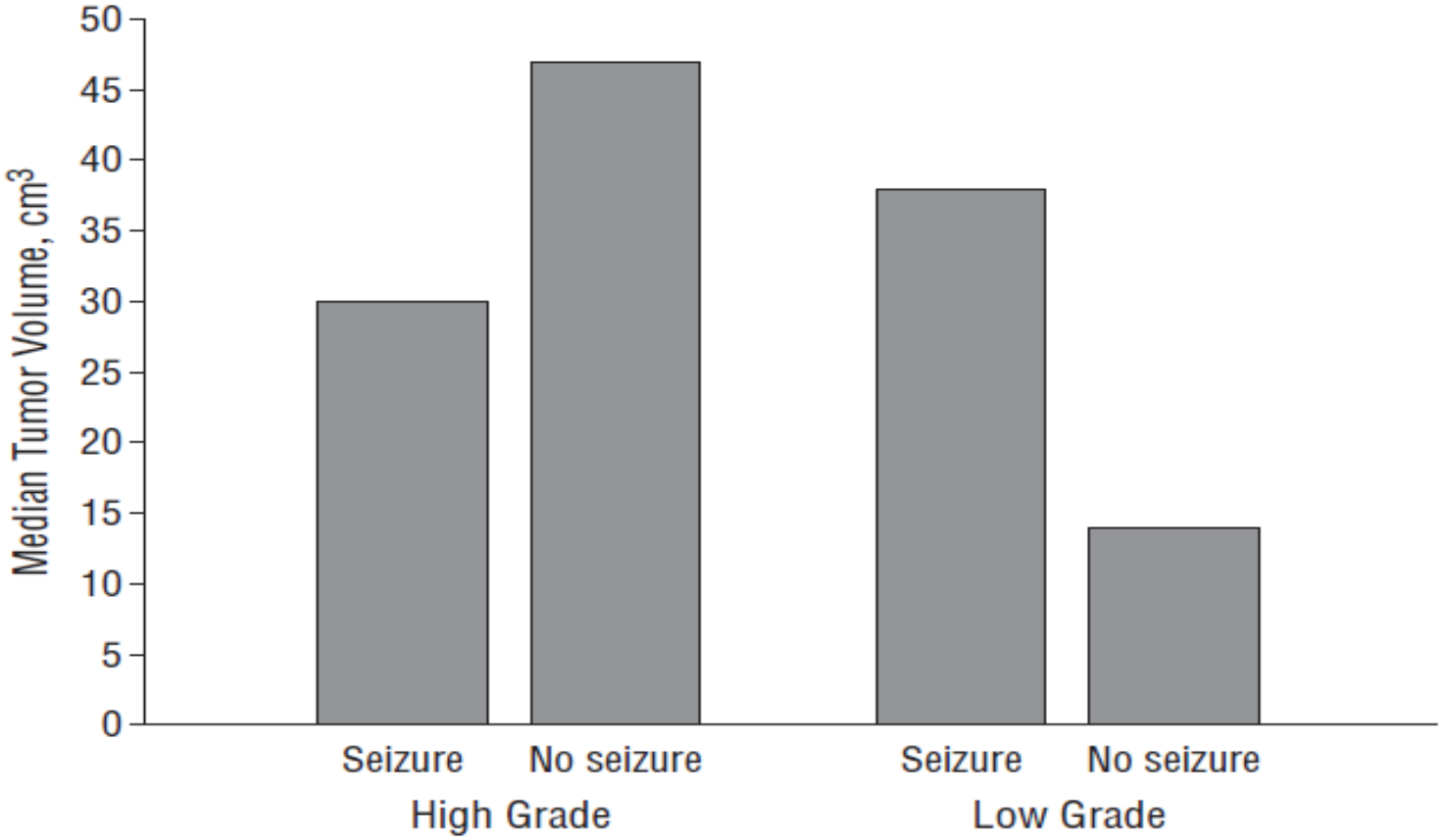
Table I. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

FCD Type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)	
FCD Type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)	
FCD Type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIIb)	Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc)	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId)

Epilepsia, 52(1):158–174, 2011

- ≈ half of pts DNET and epilepsy have cortical dysplasia associated with the tumor *(Chang et al., 2010).*

Seizure and Tumor Volume



High-grade tumors presenting with seizures are likely to be **smaller** than those presenting with other symptoms

Lee et al., 2010

Seizure and Location of Tumor

- Higher seizure frequency associated with
  - **Supratentorial** tumors
  - Located in **the cortex** and **superficially**
- Higher epileptogenic supratentorial tumors in
  - **Fronto-temporal** region (80%) and **fronto-parietal** region (71%).
- Epileptogenic infratentorially localized tumors in about 2.5% of cases

Evaluation of Sz in a Pt with a Known Tumor

Possible causes of seizure in children with brain tumors

Tumor progression	Hyponatremia (SIADH, CSW)
Tumor relapse	Hypernatremia (DI)
Secondary malignant neoplasm	Hypoglycemia
PRES	CNS/Shunt infection
Toxic encephalopathy	Cerebrovascular accidents
Subtherapeutic AED levels	Epilepsy unrelated to tumor

AED, antiepileptic drug; CNS, cerebrospinal fluid; DI, diabetes insipidus; PRES, posterior reversible encephalopathy syndrome; SIADH, syndrome of inappropriate antidiuretic hormone.

Well EM., et al *2012*

Late-Onset Seizures

- Late effects from brain tumors and their treatment defined as **5 years after diagnosis** in cancer survivors
- Packer, 2003 reported seizure :
  - 25% long-term survivors of childhood BT
  - 6.5% had first seizure > 5 years after diagnosis
- Radiation therapy (RT)
  - at doses > 30 Gy to any cortical segment - 2-fold increase in risk
  - Seizures more likely in younger children

Semin Pediatr Neurol 2012 ; 19:3-8

Brain Tumor-related Epilepsy Pharmacological Resistance.

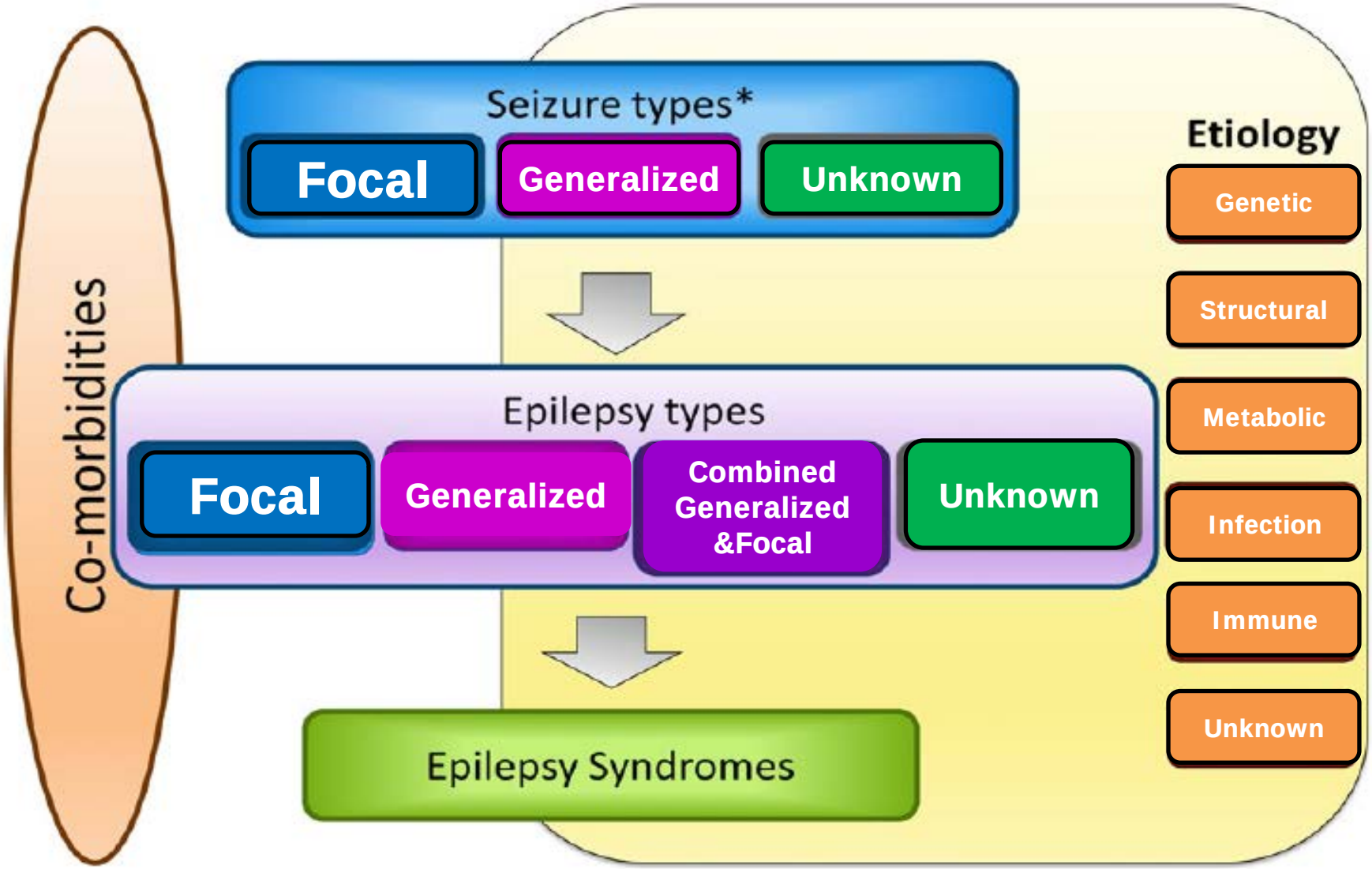
- Complete seizure control was achieved in only 12.6% patients with a brain tumor

  (Hildebrand et al., 2005)

- In 15–58% of cases of low-grade glioma, the epilepsy appears to be intractable

  (Duffau et al., 2002)

Classification of the Epilepsies



Scheffer IE, et al Epilepsia, 58(4):512–521, 2017

ILAE 2017 Classsification of seizure types (expanded version)

Focal Onset

Aware

Impaired Awareness

Motor Onset
- Automatisms
- Atonic
- Clonic
- Epileptic spasms
- Hyperkinetic
- Myoclonic
- tonic

Non-motor Onset
- Autonomic
- Behavior arrest
- Cognitive
- Emotional
- Sensory

Focal to bilateral tonic-clonic

Generalized Onset

Motor
- Tonic-clonic
- Clonic
- Tonic
- Myoclonic
- Myoclonic-tonic-clonic
- Myoclonic-atonic
- Atonic
- Epileptic spasms

Non-motor Absence
- Typical
- Atypical
- Eyelid myoclonia

Unknown Onset

Motor
- Tonic-clonic
- Epileptic spasms

Non-motor
- Behavior arrest

Unclassified

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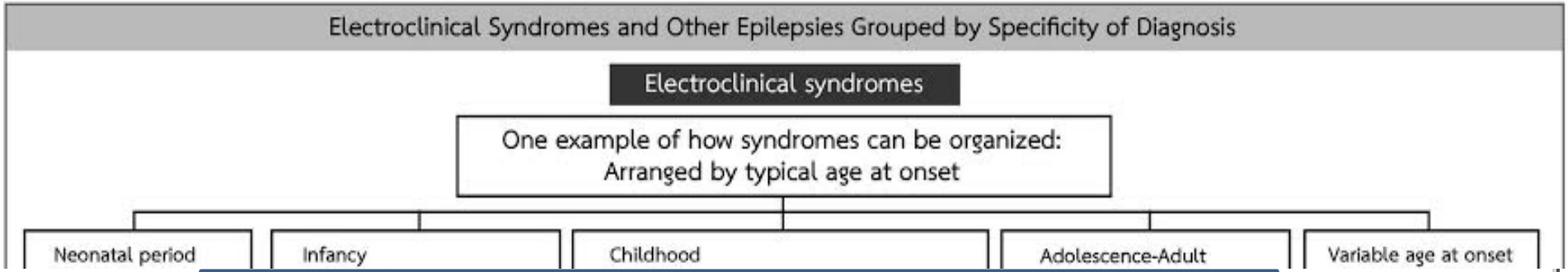
Revised Terminology for Organization of Seizures and Epilepsies 2010



Non-syndromic epilepsies

- **Epilepsies attributed to organized by structural-metabolic causes**
  - **Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)**
  - **Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc)**
  - **Tumor, infection, trauma, angioma, antenataland perinatal insults, stroke , etc**

Epilepsies of unknown cause

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Symptomatology

- Focal onset seizure type
- Seizure semiology depends on
  - Tumor location or adjacent abnormal brain (Primary epileptogenic)
  - Secondary epileptogenic

Secondary epileptogenesis

- Occur in up to **one-third** of brain tumor patients where the epileptogenic focus does not correspond to the tumor location.
- Can be seen in low-grade brain tumors in the temporal lobe which have associated **hippocampal sclerosis**

Pathogenesis of tumor-related epilepsy

- Cellular mechanisms - > epileptogenesis **: NOT CLEAR**
- Two theories of pathogenesis

1. Tumor origin

  - Tumor itself may excrete molecules that could make the tumor tissue epileptogenic, or it could change the peri-tumoral microenvironment and turn this into an epileptogenic zone

2. Peri-tumor

  - Tumor mechanically compresses the surrounding normal tissue, which eventually becomes epileptogenic after suffering from ischemia and hypoxia.

- Both processes could potentially cause 2^{o}changes
  - In neurotransmitters and their receptors, metabolic changes, and inflammatory responses, eventually leading to epileptic seizures.

Seizure 21 (2012) 153–159

Schematic of observed mechanisms underlying the

HISTOLOGY

- ECoG studies-> epileptiform activity is associated with a *high neuronal density* within the lesion (Ferrier et al., 2006).
- Glial tumor: abrupt tissue damage leading to necrosis and haemosiderin deposition and to oedema (Riva, 2005).

LOCATION

Proximity to cortical gray matter ≈ associated with epilepsy

HISTOLOGY preferred location

- Most GLIONEURONAL tumors occur in the temporal,

- LGG tend to grow in2'functional areas near, but rarely within, primary eloquent parts of the brain

- OLIGODENDROGLIAL tumors more likely located in frontal lobe

Tumor histology associated with the lobe during brain development

Duffau and Capelle 2004

Table 2 Molecular (or proposed) targets of known potential relevance to tumour associated epilepsy

Target	Suggested relevance in (tumour type)	Location	Potential antiepileptic drug
Glutamate receptors changes			
mGluR	GG, glioma	Tumour/ peritumoral	–
AMPA receptors	GG	Tumour	PB, TPM
Kainate receptors	Astrocytoma	Peritumoral	TPM
NMDA receptors	GN	Tumour	FMT
GABA receptors	GG, glioma	Tumour	PB, BZD, FBM, TPM, propofol
Ion level changes			
Fe^{3+}	Glioma	Peritumoral (extracellular)	–
Mg^{2+}	Glioma	Peritumoral (extracellular)	–
Ca^{2+}	Glioma	Peritumoral (extracellular)	–
Na^{2+}	Glioma	Peritumoral (extracellular)	–
Voltage-gated ion channels			
Sodium channels	Glioma	Tumour	PHT, CBZ, TPM, LTG, OCBZ, FBM, VPA, ZNS
Chloride channels			
NKCC1	GG, glioma	Tumour, peritumoral	–
KCC2	GG, glioma	Tumour, peritumoral	–
Potassium channels	GG, glioma	Tumour	(LEV), (TPM) retigabine
Inflammatory interleukines			
IL-1β	GG	Tumour/ peritumoral	LEV
Synaptic vesicle proteins			
SV2A	GN, glioma	Tumour/ peritumoral	LEV
Gap junctions (connexins)			
CX32	GN, oligodendroglioma	Tumour/ peritumoral	–
CX34	GN, astrocytomas	Tumour/ peritumoral	–
Enzym changes			
Adenosine kinase	Glioma	Tumour/Peritumoral	–
Amino acids			
Glutamate	Glioma	Peritumoral (extracellular)	–
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Enzym changes	Glioma	Peritumoral	Vigabatrin, TPM, ZNS, PHT
PH changes	GN, glioma, meningeoma	Peritumoral	TPM, ZNS
Pi3K-mTOR pathway	GG, glioma	Tumour	–

Brain 2012: 135; 1002–1016

BZD = benzodiazepines; CBZ = carbamazepine; FMT = felbamate; GBP = gabapentin; GG = ganglioglioma; GN = glioneuronal tumours; LEV = levetiracetam; LTG = lamotrigine; OCBZ = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TGB = tiagabine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

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RECEPTORS Changes

- Both GLIOMAS & GG express specific glutamate receptor subtypes : both ionotropic & metabotropic receptors (Aronica et al., 2001b; Maas et al., 2001; Samadani et al., 2007).

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Mg^{2+}	Glioma	moral (extracellular)	–
Ca^{2+}	Glioma	al (extracellular)	–
Na^{2+}			
Voltage-gated ion chanr			
Sodium channels			
Chloride channels			
NKCC1			
KCC2			
Potassium channels			
Inflammatory interleukin			
IL-1β			
Synaptic vesicle proteins			
SV2A			
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Receptor changes *(Aronica et al., 2001b)*

- PERITUMORAL ASTROCYTES express ↑amount of **kainate receptors** -> downregulate GABAergic inhibition : may predispose to epilepsy.
- Multiple **metabotropic glutamate receptors** are overexpressed in the peritumoral cortex

Table 2 Molecular (or proposed) t ntial relevance to tumour associated epilepsy

Target

Glutamate receptor
mGluR
AMPA receptors
Kainate receptors
NMDA receptors
GABA receptors
Ion level changes
Fe^{3+}
Mg^{2+}
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Na^{2+}
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Extracelluar IONIC CHANGES

- Macro- or microhaemorrhage -> neuronal membrane injury -> ↑Extracellular iron (Fe3+) ->change memb AP of neuron *(Shamji, 2009)*
- Mg2+ and Ca2+ probably released from oedema and haemorrhage. ↓Extracellular Mg2+ -> spontaneous epileptiform discharges *(Schaller and Ruegg, 2003).*

Voltage-gated Ion channels

- ↑ voltage-gated **Na channels** in tumor cells-> can generate AP. *(Patt et al.,1996; Labrakakis et al., 1997)*
- ↑**Na–K-Cl cotransporter** (NKCC1) expression & ↓ **K-Cl cotransporter** (KCC2) reported in glioneuronal tumors *(Aronica et al., 2007a, 2008).* -> epileptogenicity in GG by modulation of GABA R *(Yamada et al., 2004).*

Table 2 Molecular (or proposed) targets of known potential relevance to tumour associated epilepsy

- Brain tumors often show a **prominent immune response.**
- Upregulation of **inflammatory interleukins (such as IL-1B)** in GG, have been suggested to play a role in epileptogenicity (Aronica et al.,2008; Vezzani et al., 2011).
- Inflammation activates a cascade of proinflammatory cytokines & induces alterations in the BBB may lead to epilepsy.

KCC2		Tumour, peritumoral	–
Potassium chann…	…glioma	Tumour	(LEV), (TPM) retigabine
Inflammatory …eukines			
IL-1β	GG	Tumour/ peritumoral	LEV
Synaptic vesicle proteins			
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Na^{2+}	Glior		
Voltage-gated ion channels			
Sodium channels	Glior		ZNS
Chloride channels			
NKCC1	GG,		
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•Dysplastic glial cells in GLIOMA express **synaptic vesicle proteins SV2A** ->dysfunction-> calcium accumulation during repeated AP generation -> may epileptogenesis. (De Groot et al., 2010)

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GAP JUNCTION

Disturbed intercellular communication between glial cells->epileptogenic through gap junction channels: **CONNEXINS**

(Aronica et al., 2001a)

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Gap junctions (conne			
CX32			
CX34	GN, a	Tumour/ peritumoral	
Enzym changes			
Adenosine kinase		Tumour/Peritumoral	–
Amino acids			
Glutamate	Glioma	Peritumoral (extracellular)	–
GABA	Glioma	Peritumoral (extracellular)	VPA, LTG, GBP, vigabatrin, TGB
Enzym changes	Glioma	Peritumoral	Vigabatrin, TPM, ZNS, PHT
PH changes	GN, glioma, meningeoma	Peritumoral	TPM, ZNS
Pi3K-mTOR pathway	GG, glioma	Tumour	–

↑extracellular **GLUTAMATE** found in peritumoral brain parenchyma of patients with epilepsy compared to non-tumour patients with epilepsy
(de Groot and Sontheimer, 2010).

Brain 2012: 135; 1002–1016

BZD = benzodiazepines; CBZ = carbamazepine; FMT = felbamate; GBP = gabapentin; GG = ganglioglioma; GN = glioneuronal tumours; LEV = levetiracetam; LTG = lamotrigine; OCBZ = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TGB = tiagabine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

Table 2 Molecular (or proposed) targets of known potential relevance to tumour associated epilepsy

Target	Suggested relevance in	Location	Potential antiepileptic drug
Glutam			
mGlu			
AMP			
Kaina			
NMD			
GABA			
Ion leve			
Fe^{3+}			
Mg^{2+}			
Ca^{2+}			
Na^{2+}			
Voltage			
Sodiu			
Chlor			
N			
K			
Potas			
Inflamm			
IL-1β			
Synaptic vesicle proteins			
SV2A		Tumour/ peritumoral	LEV
Gap junctions (connexins)			
CX32		Tumour/ peritumoral	–
CX34		Tumour/ peritumoral	–
Enzym changes			
Adenosine kinase		Tumour/Peritumoral	–
Amino acids			
Glutamate	ioma	Peritumoral (extracellular)	–
GABA	Glioma	Peritumoral (extracellular)	VPA, LTG, GBP, vigabatrin, TGB
Enzym changes	Glioma	Peritumoral	Vigabatrin, TPM, ZNS, PHT
PH changes	GN, glioma, meningeoma	Peritumoral	TPM, ZNS
Pi3K-mTOR pathway	GG, glioma	Tumour	–

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Genetic & Molecular pathways

- In **GG**, several components of **Pi3K-mTOR** signalling pathways are activated (Boer 2010). -> epileptogenesis , target of mTOR inhibitors
- In **GLIOBLASTOMA** and **LGG,** the pi3K-mTOR pathway plays a role in the development of the tumors (McBride 2010; Sunayama 2010)
- Pi3K-mTOR pathway **Common genetic pathways for tumor-associated epilepsy &glioma** (Berntsson 2009).

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REVIEW ARTICLE

Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment

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Review

The pathogenesis of tumor-related epilepsy and its implications for clinical treatment

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