Brain tumor-related epilepsy

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Brain tumor related epilepsy (BTRE)

- Scope:
  - Investigation
  - Treatment

Investigation

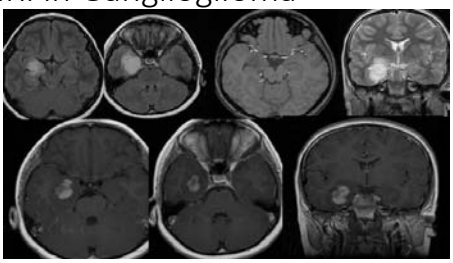
- Neuroimaging
- EEG
- Molecular markers

Neuroimaging

Neuroimaging

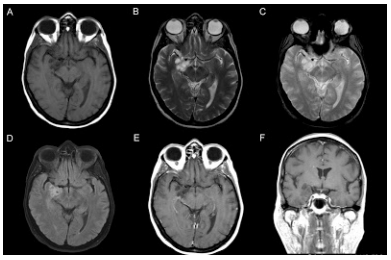
- Brain imaging with contrast: MRI >>> CT
- All patients with a first seizure should undergo an MRI at the time of presentation which may show focal lesions such as tumors
- Imaging characteristics
  - Structure, location
  - Size, shape, density
  - Mass effect, edema
  - Calcification, bleeding
  - Contrast enhancement

MRI in Ganglioglioma



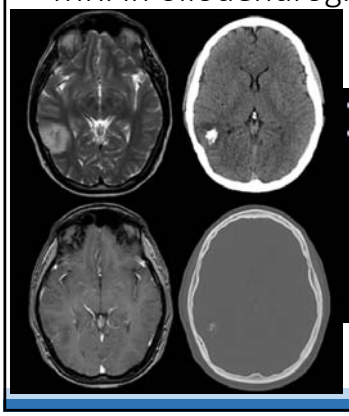
- T1: solid component iso to hypointense
- T1 C+ (Gd): solid component variable contrast enhancement
- T2: hyperintense solid component
  - Variable signal in the cystic component depending on the amount of proteinaceous material or presence of blood products
  - Peritumoral FLAIR/T2 oedema is distinctly uncommon
- T2* (GE/SWI): calcified areas (common) will show blooming signal loss

MRI in dysembryoplastic neuroepithelial tumours (DNET)



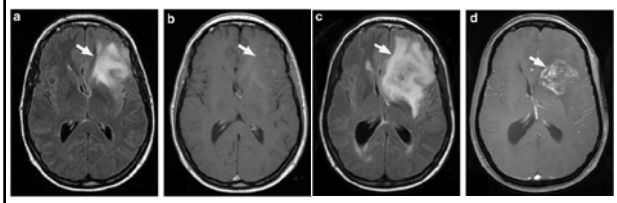
- Typically seen as a cortical lesion with hardly any surrounding vasogenic oedema.
- T1: generally hypointense c.f adjacent brain
- T1 C+ (Gd): may show enhancement in ~20-30% of cases, enhancement may be heterogeneous or a mural nodule
- T2: generally high signal, high signal 'bubbly appearance'
- FLAIR: mixed signal intensity with bright rim sign, partial suppression of some of the "bubbles"
- T2*: calcification relatively frequent, haemosiderin staining uncommon as bleeding into DNETs is only occasional
- DWI: no restricted diffusion, MR spectroscopy: non-specific although lactate may be present

MRI in oliodendroglioma

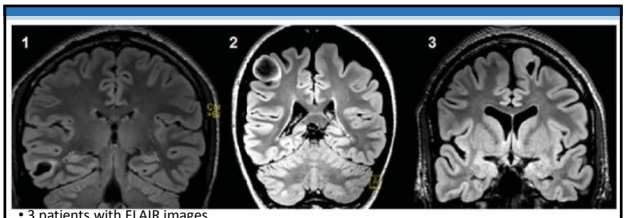


- WHO grade II neoplasm of oligodendrocytes
- Imaging features
  - Cortical/subcortical mass
  - Majority in frontal lobe 65%
  - Calcifications 50%
  - Generally T2 hyperintense
  - Enhancement 50%
  - Cystic components 20%
  - May remodel adjacent calvarium

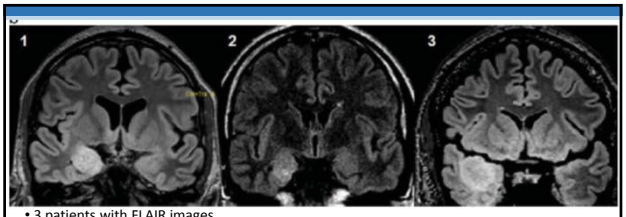
MRI in Glioblastoma maltiforme



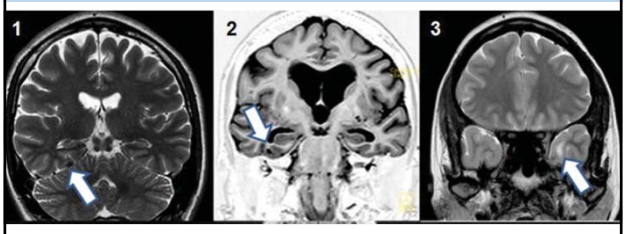
- **T1:** hypo to isointense mass within white matter, central heterogeneous signal (necrosis, intratumoural haemorrhage)
- **T1 C+ (Gd):** enhancement is variable but is almost always present, typically peripheral and irregular with nodular components, usually surrounds necrosis
- **T2/FLAIR:** hyperintense, surrounded by vasogenic oedema, flow voids are occasionally seen
- **GE/SWI:** blood products (or occasionally calcification)



- 3 patients with FLAIR images
  - Liquor-isointense cortical/iuxtacortical "cystic" lesion with hyperintense "rim"-signal
- Radiologist reports DNET or ganglioglioma
- Histopathology:
  - 1: Ganglioglioma WHO I
  - 2: DNET WHO I
  - 3: Angiocentric glioma WHO I ("ANET")



- 3 patients with FLAIR images
  - Hyperintense "mass lesions" or "parenchyma consolidation", no contrast enhancement
- Radiologist report: "likely low-grade glioma"
- Histopathology:
  - 1: Ganglioglioma WHO I
  - 2: DNET WHO I
  - 3: Astrocytoma WHO II

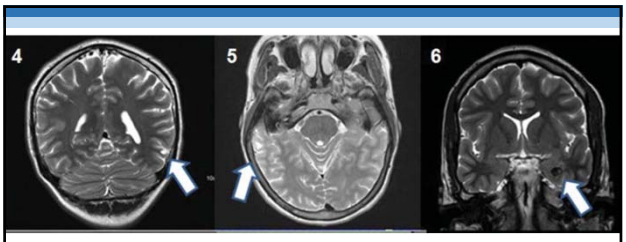


MRI suggests non-tumor

1: Tentorial calcification/ganglioglioma

2: Contusion/ganglioglioma

3: Unspecific white matter lesion/ganglioglioma.

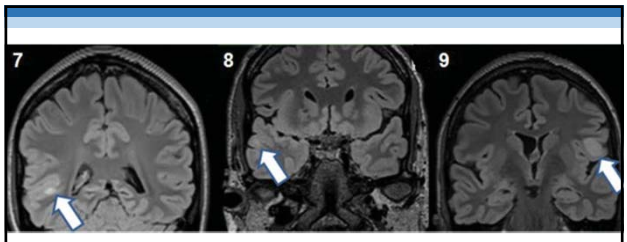


MRI suggests non-tumor

4: Contusion/DNT

5: Contusion/ganglioglioma

6: Cavernous hemangioma/ganglioglioma



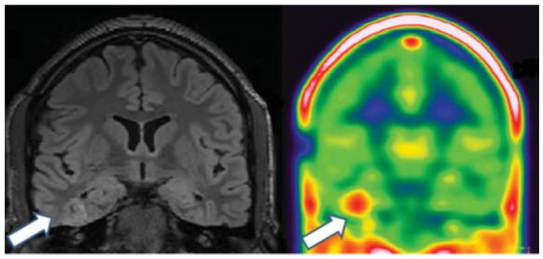
MRI suggests non-tumor

7: Focal cortical dysplasia (FCD)/ganglioglioma

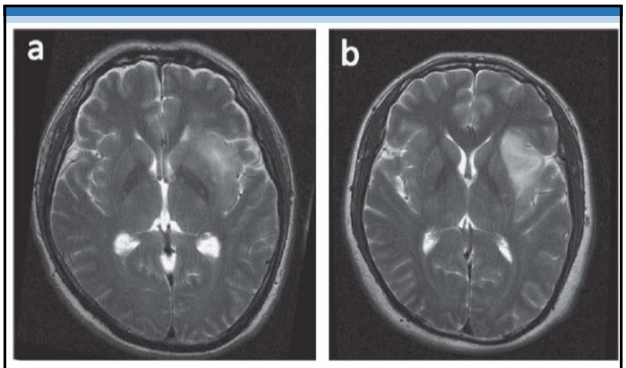
8: No lesion/ganglioglioma

9: FCD/isomorphic astrocytoma (INET)

Patient male, age 22, seizures since age 15: Right temporo-basal lesion of unknown classification



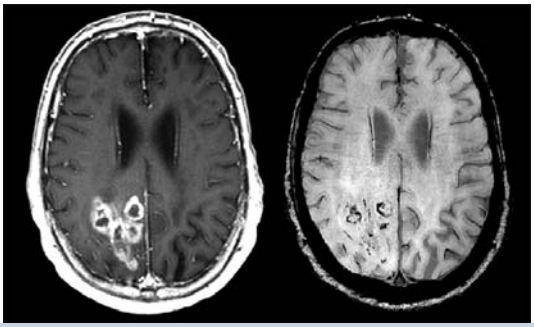
F18Ethyl-Tyrosine-PET demonstrates significant uptake at lesion site indicating a neoplasm
Histology: Ganglioglioma WHO I



Astrocytoma (WHO grade II)

Case A: presented with 2^0 GTC
Case B: presented with only headache

Recurrent seizures despite multiple AEDs



Electroencephalography (EEG)

The role of EEG in the evaluation

- To localize the epileptogenic focus
- To determine risk for recurrent seizures
- Guide decision for antiepileptic drug therapy
- EEG mapping: to identify individuals in which the lesion may not be the primary epileptogenic focus

Invasive EEG recording

- Peg electrode, subdural grid, strip electrode, depth electrode
- Used in about 10% of patients undergoing epilepsy surgery for tumor-related epilepsy
- Extratemporal lobe epilepsy needed in case the lesion is close to eloquent cortex
  - To help to confine the surgical resection by defining functional borders

Intraoperative EEG

- Performed in some centers
- Some studies
  - No significant difference in terms of seizure outcome between BTRE patients with and without intraoperative EEG
    - Comment: monitored electrocorticography mainly in more severe cases → complicated result
  - 2-stage surgery with intracranial EEG before tumor surgery improved seizure outcomes in patients with primary brain tumors
- Conclusion needs to be confirmed by a larger prospective study

Molecular markers

Several molecular markers have been identified in brain tumors in recent years

Isocitrate dehydrogenase 1/2 (IDH1/2) mutations, 1p/19q codeletion and MGMT promoter methylation

- Clinical importance for patient's prognosis have been confirmed in many studies
- IDH 1/2 mutations
  - Common in diffuse low-grade gliomas
  - Associated with seizures as the initial Symptom
  - A predictor of epileptogenicity
- A conflicting data
  - Not confirm the relation between molecular markers (1p19q codeletion, p53 expression and isocitrate dehydrogenase 1 expression) and seizure in low-grade gliomas

Skardelly et al

Other markers

- Expression of BRAF V600E mutations in glioneuronal tumors
  - Associated with a worse postoperative seizure outcome
- Overexpression of nuclear protein Ki-67
  - Found to be a poor prognostic factor for seizure control in low-grade glioma patients
- High RINT1 expression
  - Represent a risk factor for low-grade glioma (LGG) -related seizures
  - Associated with seizure outcomes
- Low expression of very large G-protein-coupled receptor-1 (VLGR) 1 and dysregulation of miR-128 expression
  - Associated with epilepsy in low-grade gliomas
- Low Ki-67 expression and EGFR amplification
  - Correlated with preoperative seizures in anaplastic gliomas

Treatment

Treatment

- Varies according to the type of tumor
- Multidisciplinary approach
  - Surgical treatment and/or radiological treatment (mainstay of the treatment)
  - Medical (chemotherapy and AEDs)

Surgical treatment

Step approach for surgical management of patients with tumor-related epilepsy

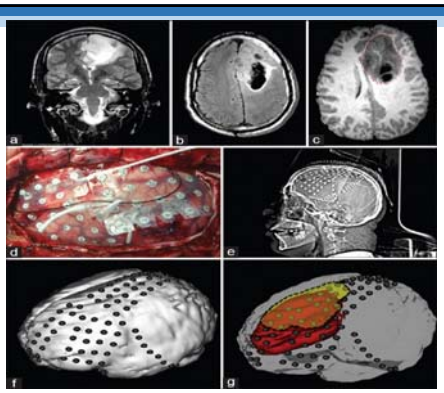
- 1) Attempting to localize the seizure focus with routine scalp EEG
- 2) When scalp EEG is insufficient, the use of invasive EEG (iEEG) mapping is recommended
  - Bilateral ictal discharges
  - Excessive artifacts
  - Localization disagreement between imaging, scalp EEG& neuropsychological tests
  - Involvement of the eloquent cortex
  - Lateralizing of the dominant epileptogenic temporal lobe

Step approach for surgical management of patients with tumor-related epilepsy

- 3) Electrocorticography (ECoG) uses subdural or depth electrodes
  - To record activity directly from the brain intraoperatively for short periods of time or extraoperatively for hours to days
- 4) Stereoencephalography (SEEG)
  - To use multiple depth electrodes to record activity within the brain
- 5) Surgery may then proceed to remove the tumor and the associated seizure foci
  - Use of ECoG or an awake craniotomy if the area involves the eloquent cortex

How much resection is required?

- A systematic review: seizure free
  - Gross total tumor resection : 87%
  - Subtotal tumor resection: 55%
- limited and expanded resections
  - Presumption: neurons surrounding the tumor constitute the epileptogenic zone, removing the tumor alone may not guarantee a good outcome in seizure control
  - For most surgical series involving pediatric patients
    - Lesionectomy alone yielded very good results
  - For studies on adult patients
    - Gross total resection or even extended lesionectomy could greatly improve seizure prognosis



The epileptogenic zone determined by long-term extraoperative intracranial EEG recording is shown in yellow, and overlaps only partially with the tumor and extends beyond the tumor margin in an eccentric manner

Mesial temporal lobe surgery: decision making

- Lesions located in “non-dominant” temporal lobe
  - With a long duration of epilepsy characterized by frequent and disabling seizures
  - Mesial structures should also be resected if they are involved or in close relation with the tumor
- Lesions located in “dominant” temporal lobe
  - If the mesial structures are not involved and properly functioning
  - They should not be included in resection

Outcome evaluation: Engel classification

- Class I: seizure free or free of disabling seizures
- Class II, rare seizures per year (less than three seizure days)
- Class III, effective (seizure decreased by at least 80%)
- Class IV, no improvement

Surgical outcome in DNETs, GGs, LGG

- The rates of seizure freedom: DNET 68-83% , GGs 70–85%, LGG 65-71%
- Good prognostic factors
  - A shorter duration of epilepsy (less than 1 year)
  - Gross total resection
  - Early resection
  - Younger age
  - Calcification on MRI
- Poor outcome
  - Preoperative secondarily generalized seizures
  - preoperative epilepsy and parietal and insular locations
- Not significant difference: temporal versus extratemporal tumors

Surgical Rx: Glioblastoma

- An aggressive tumor
- Seizure freedom rates following resection: ~ 77%
- Seizure recurrence is generally associated with progression of the glioblastoma

Antitumor treatment

Antitumor treatment

- Chemotherapy and radiotherapy may improve seizure control, even not improve MRI or survival
- Standard treatment for glioblastoma
  - Tumor resection followed by external beam radiation therapy (RT) with concomitant and adjuvant chemotherapy
- LGG: these Rx improve seizure control
- DNET: No role

Medical treatment

Antiepileptic agents

Antiepileptic treatment

- An essential part of the seizure control
- Initiate AEDs following a first seizure related to a tumor
- Monotherapy
  - Safer therapeutic window, increased compliance, cost effective
- Combination therapy
  - If monotherapy fail control

Effectiveness of AEDs in brain tumor related epilepsies

- Traditional AEDs: no randomized clinical trials
- Newer AEDs
  - OXC monotherapy: 62.9% patients seizure-free
  - TPM monotherapy: 55.6% patients seizure-free
  - LEV (mono & poly-therapy): 47.4-88% patients seizure-free
  - LCM (one add-on tudy): 42.9% patients seizure free
  - GBP, pregabalin (PGB), tiagabine (TGB), and zonisamide (ZNS) in add-on: responder rate from 27.4-100%

Drug interaction with chemotherapy

- Hepatic cytochrome P 450 inducer or inhibitor
  - Corticosteroid
  - Chemotherapeutic agents
    - Nitrosoureas, paclitaxel, cyclophosphamide, etoposide, topotecan, irinotecan, thiotepa, Adriamycin, methotrexate

Drug interaction with chemotherapy

- Avoid:
  - Enzyme-inducing drugs particularly in glioblastoma patients because of the risk of interaction with chemotherapeutics
- Newer AEDs
  - Levetiracetam (LEV), lamotrigine (LTG), topiramate (TPX), gabapentin (GBP), and pregabalin (PGB)
  - Fewer or lack of significant drug–drug interactions with chemotherapy agents

AED	CYP Metabolism	Hepatic Enzymes Affected	CTDs Lowered by AEDs
Carbamazepine	1A2, 2C8, 2C9, 3A4	↑1A2, 2C9, 2C19, 3A families	↓MTX, VCR, PTX, 9-AC, VM26
Ethosuxamide	3A4, 2B, 2E1	-	-
Lamotrigine	-	↑UGT	-
Levetiracetam	-	-	-
Phenobarbital	2C9, 2C19, 2E1,3A4	↑1A2, 2B, 2C, 3A, UGT	↓CP, IFF, TTP, NU, MTX, VCR, PTX, 9-AC, VM26, DOX, PCZ, TMX, CS
Phenytoin	2C8, 2C9, 2C19	↑1A2, 2B, 2C, 3A, UGT ↓2C9	↓BUS, MTX, VCR, PTX, TPT, IRI, 9-AC, VM26, CS, DEX
Topiramate	-	↑β-oxidation ↓2C19	-
Valproate	2C9, 2C19, 2E1	↓2C9, 2C19, 3A4, UGT, epoxide hydrolase	-

MTX = Methotrexate, VCR = Vincristine, PTX = Paclitaxel, 9-AC = 9-aminocamptothecin, VM26 = Teniposide, CP = Cyclophosphamide, IFF = Ifosfamide, TTP = Thiotepa, NU = Nitrosoureas, DOX = Doxorubicin, PCZ = Procarbazine, TMX = Tamoxifen, CS = Corticosteroids, BUS = Busulfan, TPT = Topotecan, IRI = Irinotecan, DEX = Dexamethasone, AED = antiepileptic drug, CYP = cytochrome P, CTDs = cytotoxic drugs, UGT = UDP-glucuronosyltransferase, CYP = cytochrome P450

CT			AEDs
Gemcitabine Mechlorathamine Oxaliplatin Pemetrexed Rituximab			No interactions expected
Bleomycine Capecitabine Carboplatin Citarabine Fluorouracile			PHT
Anastrozole Cisplatin Ciclofosfamide Dacarbazine Docetaxel Doxorubicine Epirubicine Erlotinib	Etoposide Exemestane Gefitinib Irinotecan Ixabepilone Letrozole Metotrexate Paclitaxel Procarbazine	Sorafenib Sunitinib Tamoxifen Temsirolimus Toremifene Vinca Alkaloid Vormostat	PHT CBZ PB PRM VPA
Vormostat			TPM LEV metabolite

Adverse event of AEDs

- More frequent in patients with tumor-related epilepsy than in the rest of the epileptic population
  - 24% AE with tumor
  - 0.5-12% AE without tumor
- Newer AEDs
  - Lower side effect profiles

AEDs with potential antitumoral effects

- Cause for refractory epilepsy
  - Overexpression of proteins (P-glycoprotein, MRP1, MRP5) leading to multidrug resistance
  - These proteins act at the level of the blood–brain barrier to actively transport lipophilic drugs (like many AEDs) through the capillary endothelium
- VPA & LEV
  - May not be substrates for these proteins
  - May be Better efficacy

Possible antitumor effect: VPA

- An in vitro action (inhibition) on hystone deacetylase
  - Induce growth arrest
  - Promotion of apoptosis, reduction of cell differentiation, suppression colony-forming efficiency & tumorigenicity
  - Induced autophagy in glioma cells
- One retrospective study
  - An advantage with regard to survival rate in patients treated with VPA and temozolomide
  - Suggesting a possible synergy between VPA and the CT
- Several studies: improve survival of patients with glioblastoma
  - VPA = first line in Glioblstoma
- Caution: thrombocytopenia

Possible antitumor effect

- An antitumor effect of levetiracetam through O-6 methylguanine-DNA methyltransferase (MGMT) has been suggested
- Seizure treatment with VPA or with the combination of VPA and levetiracetam
  - 52% on VPA
  - 59% on VPA + LEV

AEDs in Brain tumor without seizure

- Prophylactic antiepileptic therapy
  - Lack of efficacy in preventing seizures
  - Potential serious side effects
  - Prophylactic use of AEDs should not be considered
  - Should suspend the AEDs within 1 week following surgery

The Guidelines of the American Academy of Neurology 2000

Conclusion

Conclusion (1)

- Seizures are the onset symptom in 20-40% of patients, while a further 20-45% of patients will present them during the course of the disease
- Brain tumors (both primary and metastasis) are the second most common cause of focal intractable epilepsy in epilepsy surgery series, with the greatest proportion related to DNETs and GGs
- The pathogenesis of tumor-related epilepsy remains poorly understood
- The presence of epilepsy in brain tumor is considered the most important risk factor for long-term disability and related with refractory to antiepileptic treatment

Conclusion (2)

- BTRE requires a unique and multidisciplinary approach from neurology, neurosurgery and neurooncology
- Early surgical intervention improves seizure outcomes in individuals with medically refractory epilepsy, especially in patients with a single lesion that is epileptogenic
- New generation drugs are preferred because of lower interactions to chemotherapy and cause fewer side effects
- Prophylactic AED treatment to prevent seizure in brain tumor is not recommended

Thank you