Brain tumor-related epilepsy

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Brain tumor related epilepsy (BTRE)

• Scope:
  • Investigation
  • Treatment

Investigation

• Neuroimaging
• EEG
• Molecular markers

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 is to hypointense
• T2 C+: (Gd): solid component variable contrast enhancement
• T2:hyperintense solid component
  • Variable signal in the cystic component depending on the amount of proteinousous material or presence of blood products
  • Peritumoral FLAIR/T2 edema is distinctly uncommon
• T1* (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 mottled halo.
- T2: high signal, 'bubbly appearance'
- T2*: calcification relatively frequent, haemosiderin staining uncommon as bleeding into DNETs is only occasional.
- DWI: no restricted diffusion.

MRI in oligodendroglioma

- WHO grades II neoplasm of oligodendrocytes
- Imaging features:
  - Cortical/centronuclear mass
  - Majorly frontal lobe 65%
  - Calcification 50%
  - Gd enhancement 50%
  - Cystic component 30%
- May remold adjacent calcification.

MRI in Glioblastoma multiforme

- T1: Hypo to isointense mass within white matter, central heterogeneous signal (necrosis, intratumoral 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.
- DWI: bloood products (or occasionally calcification).

MRI suggests non-tumor

- 1: Tentorial calcification/glioblastoma
- 2: Contusion/glioblastoma
- 3: Unspecified white matter lesion/glioblastoma.
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 2nd 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

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

- 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

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

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

- 3) Electroencephalography (EEG) 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) Stereoecephalography (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 focus
  - Use of ECoG or an awake craniotomy if the area involves the eloquent cortex
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
  - 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

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 study): 42.9% patients seizure free
  - GBP, pregabaline (PGB), tiagabine (TGB), and zonisamide (ZNS) in add-on: responder rate from 27.4-100%

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

Drug interaction with chemotherapy

- Hepatic cytochrome P 450 inducer or inhibitor
  - Corticosteroid
  - Chemotherapeutic agents
    - Nitrosoureas, paclitaxel, cyclophosphamide, etoposide, topotecan, irinotecan, thiotaeta, 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
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 histone deacetylase
  - Induce growth arrest
  - Promotion of apoptosis, reduction of cell differentiation, suppression colony-forming efficiency & tumorigenesis
  - 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 Glioblastoma
  - 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 (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