Optimizing Therapy of Seizures in Stroke Patients

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Post-stroke Epilepsy

• Stroke is the leading cause of symptomatic epilepsy in adults
• One-third of newly diagnosed seizures among the elderly
• About 3% to 5% of stroke patients will suffer a remote seizure, 54% to 66% of whom will develop epilepsy
• Post-stroke epilepsy* may represent up to 11% of all adult epilepsies

*2 or more unprovoked seizures occurring ≥1 week after the stroke
Challenging Issues

• Correctly identifying post-stroke seizure
• Precisely assessing the risk for development of another seizure after a first episode
• Balancing the impact of seizures and anti-epileptic drugs (AEDs) on outcome
• Deciding on the most appropriate AED when needed
The diagnosis of post-stroke seizure

- Poor interobserver agreement
- 63% of such seizures are not recognized by the patients themselves
- Negative motor signs might mimic TIA but might also reflect subclinical ischemia
- Epileptiform EEG abnormalities in stroke patients appears unlikely to facilitate the diagnosis
  - Epileptiform discharge in 17% of patients with stroke
  -- 2% of them eventually suffered a seizure
Risk factors for post-stroke epilepsy

• *Stroke subtype*
  - Early Sz (ES) :
    Hemorrhagic strokes, cerebral vein thrombosis, and subarachnoid hemorrhage >> ischemic stroke
  - Late Sz (LS) : not clear
    2.6% vs 3.8% for hemorrhagic vs ischemic strokes
    12.8% vs 2.7% for hemorrhagic vs ischemic strokes
    5% and 26.6% for cerebral vein thrombosis
  - Recurrent Sz
    7% for subarachnoid hemorrhage
Risk factors for post-stroke epilepsy

- **Stroke location**
  - Cortical location: the most consistent independent predictor of ES (a twofold higher risk than Subcortical)
  - 2.6% to 3.5% of lacunar infarctions
  - Less clear whether cortical location of stroke is a risk factor for LS or epilepsy
  - The lobar location: not a consistent predictor
  - Preserved islands of cortical tissue – risk factor
Risk factors for post-stroke epilepsy

- **Stroke severity**
  - Scandinavian Stroke Scale score below 30 predicted the risk for remote epilepsy with a 4.9 odds ratio
  - Uncertain whether it truly represents an independent risk factor for ES

- **Early and late seizures**
  - ES within 1W after stroke:
    - higher risk for LS or Epilepsy
  - 54-66% of LS \(\rightarrow\) Epilepsy
Impact of post-stroke seizures on outcome

- Higher mortality rate in stroke patients with ES - confounding effects of stroke severity and location
- Other series failed to replicate these findings
- In hemorrhagic stroke, ES was associated with a worsening of the NIH stroke scale and an increase in midline shift on serial CT scan
- Both single and recurrent seizures were associated with a more severe deficit at 1 month after stroke
- Epilepsy: an independent predictor of poor functional recovery at 12 months after SAH
Impact of post-stroke seizures on outcome

• Overall, a majority of studies suggest that LS and recurrent seizures hamper longterm neurologic outcome after stroke

• Sz in elderly people might represent the initial manifestation of otherwise occult CVD
  - patients with a first Sz occurring after the age of 60 and no past history of stroke:
    -- 2.89 relative hazard of suffering a subsequent stroke (95% CI 2.45–3.41; \( p = 0.0001 \))
Treatment Issues

- No available guideline for the primary prevention of seizures related to Stroke
  - prophylactic AED therapy should not be used in stroke patients

- The treatment of post-stroke seizure and epilepsy
  - should AED treatment be initiated after a first post-stroke seizure?
  - which AEDs are the most appropriate for stroke patients?
Several stroke related issues

• The potential dual impact of AEDs on stroke outcome, regardless of seizure occurrence
  - neuroprotective properties and/or altered recovery after cerebral infarction
• The risk for a second seizure that might worsen the functional outcome of patients not treated after a first post-stroke seizure
• Co-medications, mean age
• greater likelihood of achieving seizure control with AEDs compared with other forms of epilepsy
The potential dual impact of AEDs on stroke outcome

- Neuroprotective properties: controversies
  - PHT, BDZ, LTG, TGB, ZNS, LEV, TPM in animal
  - No data have yet confirmed in human subjects

- Old AEDs (except CBZ): negatively influence functional outcome in stroke patients
  - PHT for the primary prevention of Sz in patients with SAH: poor neurologic and cognitive outcome

- Harmful impact >> Hopeful impact
Potential risk of withholding treatment after a first post-stroke seizure

- The risk of a second Sz after a first Sz
  - LS: 54% to 66%
  - ES: below 43%
  - similar to that of general population untreated
  - withholding treatment until the second seizure does not appear to be harmful

- The impact of post-stroke seizures on outcome
  - uncertain, but the possibility that ES & LS might increase mortality rate or lead to SE
  - AED treatment: individualized
Factors influencing the type and dosage of AED

- 4 major issues relate to the choice of AED
  - some drugs to alter post-stroke recovery
  - the interaction between AEDs and anticoagulants and antiplatelet agents
  - the likelihood of achieving seizure control
  - the general problem of AEDs in the elderly
Factors influencing the type and dosage of AED

- PHT & BDZ might hamper functional outcome
- Old AEDs interact with Warfarin, Salicylic acid
- New AEDs do not demonstrate significant interaction
- AEDs are more likely to achieve seizure control in post-stroke epilepsy than in other epilepsy
  - 81% Sz free for 30 Ms with GBP only
  - the choice of AED type and dosage should not necessarily aim at providing maximal efficacy
- Elderly patients are more likely to become seizure free with low doses of AED & more prone to AEs
ILAE Treatment Guideline
Epilepsia, 2006

• ILAE treatment guideline (Epilepsia, 2006)
  - LTG and GBP were the only two AEDs for first-line monotherapy in elderly adults with partial onset seizures (compared to immediate-release form of CBZ)

• The LAM 40089 Study Group
  - No significant difference was observed between LTG and sustained-release CBZ (Epilepsia, 2007)
Conclusions

- The optimal timing and type of antiepileptic treatment for post-stroke seizure and epilepsy: uncertain
- Difficult to determine whether the occurrence of a second seizure hamper the overall outcome
- The decision to initiate AED treatment after a first or a second post-stroke seizure should be individualized, primarily based on the functional impact of the first seizure episode and the patient’s preference.
Conclusions

• At present, low-dose LTG (100 -150 mg) or GBP(900-1200) represents the optimal first-line therapy for poststroke seizure and epilepsy in elderly patients or in younger patients requiring anticoagulants.

• Low dose of CBZ-CR might be a reasonable and less expensive option in patients with appropriate bone health who do not require anticoagulation.

• OXC & LEV share many of the advantages offered by LTG & GBP, but have not yet been specifically assessed in elderly or stroke patients.