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Teaching Course 8

Medical management issues of dementia – Role of the neurologist (Level 2)

Treatment of dementia in Epilepsy

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Management of epilepsy in dementia

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Disclosures

- I have no disclosures

Lecture outline

- The clinical management issue
- Background – epidemiology and pathophysiology
- Available evidence
- Clinical guidelines and good practice statement

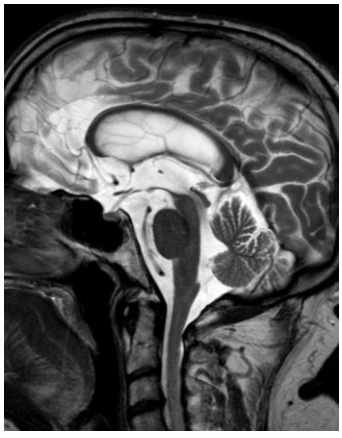
Case presentation

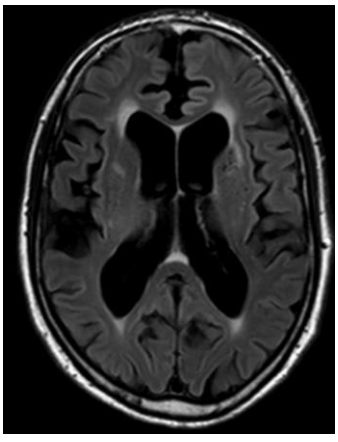
- 68-year old male. Married. University educated. Non-smoker, moderate alcohol consumption.
- Localized prostate cancer. Op for lumbar spinal stenosis same year.
- Four year history of progressive problems with gait, general psychomotor slowing and dysexecutive problems.
- Admitted to hospital for new-onset delirium and urinary voiding where EEG shows bilateral focal epileptiform activity in frontal lobes. Diagnosed with epilepsy, treatment with valproate initiated. Cognitive worsening and lethargy - treatment is changed to carbamazepine.

Case presentation (contd.)

- Cognitive improvement after medication change to carbamazepine. Discharged to home with assistance. Referral to Memory clinic.
- MRI: Mild atrophy of frontal lobes and mesencephalon
- CSF analysis: NFL 3740 (<1850), Alb-ratio raised, AD-markers normal
- Exam: Prominent psychomotor slowing, horizontal and vertical gaze palsy, bilateral but assymetric rigidity and bradykinesia. Can only stand and walk a few steps with support by two persons

MRI





Case presentation (contd.)

Diagnosis

1. Neurodegenerative disorder - probable Progressive supranuclear palsy (PSP)
2. Adverse effect of AED: Encephalopathy caused by carbamazepine (700 mg per day), with worsening of pre-existing gait/cognitive sx

Management

1. Repeated EEG shows slight increase in bifrontal epileptic activity. Fluctuating condition – due to epilepsy?
2. Change of AED-treatment to Levetiracetam 1000 mg daily

Case presentation (contd.)

Follow-up visit 1 month after treament change

- The patient is much better, walks independently, talks and jokes spontaneously, MMSE 23/30, but cannot do cube or clock test
- Broad-based gait and decreased postural reflexes. No bradykinesia, rigidity or gaze palsy.
- He does not want to spend time in rest home and home assistance is stopped.
- Long term follow-up over six years: Progression. 6 years later same state as in the first visit. Dies in pneumonia 7 years after first visit.
- Diagnosis?

Summary of problems (from case)

- Epilepsy is a common occurrence in older adults and in dementia
- Diagnosis can be difficult due to:
  - Varying presentation (eg fluctations)
  - Underreporting (by patient and carer)
  - Paroxysmal activity on EEG without clinical significance
- Treatment of epilepsy in dementia is complicated by:
  - Ageing brain
  - Co-morbidity
  - Polypharmacy (multiple medications with risk of interactions)
  - Decreased renal capacity and drug metabolism
- Lack of clinical guidelines

New onset epilepsy in older adults

- Incidence: $28/10^5$ at 50 yrs, $40/10^5$ at 60 yrs, $139/10^5$ at 70 yrs (USA 1940 - 80). Incidence increased over time by 5x in Finland (1973 - 2013)
- Causes: Stroke (16-38%), Alzheimer and other dementias (10-20%)
- Seizure type: focal seizures (+/- secondary generalization)
- Prognosis: Seizure freedom 84-92%, but high initial hospitalization rate and mortality, higher risk of recurrence with AED withdrawal
- Problems: Reduced drug metabolism and clearance, sensitivity to adverse effects, polypharmacy common
- Compliance: ? Could be lower when adverse events occur

Epilepsy in dementia

- Pathophysiology: Mixed, mainly cerebrovascular or neurodegenerative. Role of amyloid?
- Prevalence: 2-6 times higher in Alzheimer dementia (AD) than in age-matched controls; 10-22% of patients with AD have at least one unprovoked seizure
- Guidelines: Only two national clinical guidelines published for management of epilepsy in dementia (2018)

Commonly used anti-epileptic drugs

Generic name	Mechanisms	Metabolism, excretion	Interactions
Carbamazepine	Sodium channel blocker	Hepatic metab., mixed excr. Enzyme inducer	+++
Phenytoin	Sodium channel blocker	Hepatic metab. and excretion Enzyme inducer	+++
Valproate	GABA-ergic (+)	Hepatic, renal excretion Enzyme blocker	+++
Levetiracetam	Calcium (-) GABA, glycine	Minor metabolism Renal excretion	+
Lamotrigine	Sodium channel blocker	Hepatic metabolism Renal excretion	++
Gabapentin	Calcium(?)	No metabolism Renal excretion	+

EAN Guideline on Medical management issues in dementia:

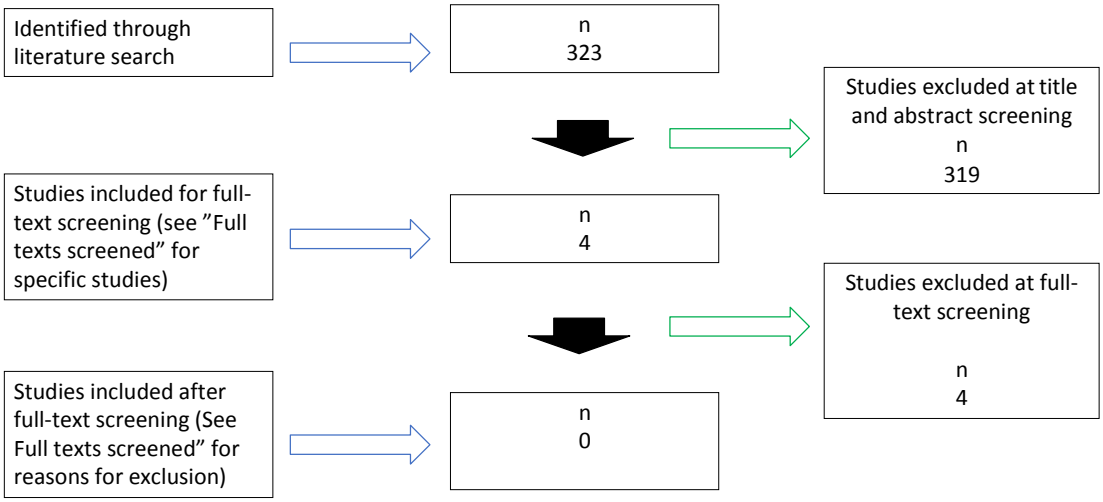
Treatment of epilepsy in dementia

- Large number of AEDs now available with different modes of action and adverse effects
- Some of these adverse effects may be more pronounced in patients with dementia
- The effect of AEDs might not be as effective in patients with dementia
- Clinical experience and some data suggest that newer AEDs are better tolerated than older AEDs such as carbamazepine, valproate and phenytoin

Research question 1: Should patients with dementia and 1 or more seizures after diagnosis be treated with either levetiracetam/lamotrigine or carbamazepine/phenytoin/valproate?

PICO Epilepsy		
Population	Patients with dementia and 1 or more seizures of undertermined origin after the diagnosis of dementia	
Intervention	Treatment with either levetiracetam or lamotrigin	
Comparator	Treatment with either carbamazepine, phenytoin, valproate	
Outcome	1. Serious adverse events	Important
	2. Global cognitive function	Critical
	3. ADL	Important
	4. Number of seizures	Critical

Epilepsy



Other studies - RCTs

- 4 studies on new-onset epilepsy in older adults (> 60 years)
- 1 study comparing Levetiracetam with Lamotrigine and Phenobarbital in patients with AD
- Cochrane review on treatment of epilepsy in Alzheimer's disease (2016) found only the above study

Other RCTs on epilepsy in older adults

Study	No of participants and type of epilepsy	Intervention	Main findings
Wernbahn et al (2015)	N=359 (age > 60) New-onset focal epilepsy	CBZ 380 mg/day LEV 950 mg/day LTG 95 mg/day	Discontinuation due to AE: LEV (17%) < LTG (26%) < CBZ (32%)
		Follow up 58 weeks	Seizure freedom CBZ (33%) < LTG (38%) < LEV (43%) p=0.33
Saetre et al (2007)	N=184 New-onset idiopathic or symptomatic epilepsy	LTG 100-500 mg/day CBZ 400-2000 mg/day	Discontinuation due to AE: LTG (14%) < CBZ (25%)
		Follow up 40 weeks	Seizure freedom CBZ (33%), LTG (38%) Non-significant

Other RCTs on epilepsy in older adults

Study	No of participants and type of epilepsy	Intervention	Main findings
Rowan et al (2005)	N=593 (> 65 years) Any type of epilepsy	LTG GBP CBZ	Discontinuation due to AE: LTG (12%) < GBP (22%) < CBZ (31%)
		Follow up 12 months	Seizure freedom LTG (61%) = GBP (61%) < CBZ (71%)
Brodie et al (1999)	N=150 (mean age 77 years) Type of epilepsy – not reported	LTG 75-100 mg CBZ 300-600 mg	Discontinuation due to AE: LTG (18%) < CBZ (42%)
		Follow up 24 weeks	Seizure freedom CBZ (21%) < LTG (39%)

Conclusions: AEDs in older adults

- Similar efficacy of newer and older AEDs
- Newer AEDs (Levetiracetam, Lamotrigin and Gabapentin) are better tolerated than older AEDs (Carbamazepine, (and probably Phenytoin, Phenobarbital, Valproate))
- Safety profile (interactions, metabolism, adverse events) better for newer AEDs

Other RCTs on epilepsy in dementia (1)

- **Cumbo E, Ligori LD**. Epilepsy and Behaviour (2010) 17:461-6
- Type of study: RCT
- Study group: Patients with Alzheimer's disease (n=95)
- Treatment groups: Levetiracetam (LEV; n=38), Lamotrigine (LTG; n=29), Phenobarbital (PB; n=28). Compared with untreated AD control group (n=68) for cognitive measures.
- Follow up time: 12 months

Other RCTs on epilepsy in dementia (2)

Results – efficacy and safety

- LEV: 71% responders, 17% adverse events, withdrawal rate0%
- LTG: 59% responders, 28% adverse events, withdrawal rate0%
- PB: 64% responders, 43% adverse events, withdrawal rate 17%
- No significant differences in response or adverse events

Results – cognition (difference in MMSE score after 12 months)

- Controls +1.07 > LEV +0.23 > LTG -0.64 > PB -1.57
- All group differences in cognition were statistically significant

Good practice statement: Treatment of epilepsy in dementia

Research question 1:

- Should patients with dementia and 1 or more seizures after diagnosis be treated with either levetiracetam/lamotrigine or carbamazepine/phenytoin/valproate?

Level of evidence:

- No evidence was identified for this PICO

Good practice statement: Treatment of epilepsy in dementia

Recommendation:

- The newer anticonvulsants (including levetiracetam and lamotrigine) should be considered first line treatment of epilepsy in patients with dementia due to their lower potential for drug interactions, lower incidence of adverse effects and linear pharmacokinetics.

Supplemental considerations:

- Always ask patient/carers about symptoms of epilepsy and consider other diagnoses
- Indication for treatment should be individualized (as in persons without dementia)
- Consider comorbidities and concomitant medication
- Use monotherapy, low start-dose, gradual dose titration
- Rapid follow-up after initiation
- Awareness of risk for sedative and cognitive adverse effects, as well as increased risk for osteoporosis

Valproate encephalopathy – The Gulli case

- 1995-96: 64 yrs, female, prev healthy – new-onset epilepsy
- Allergic reactions to CBZ and phenytoin. Valproate initiated with 2 years of seizure freedom
- 1998: Relapse of attacks – addition of LTG. Sign decrease in seizure frequency but onset of cognitive and gait problems
- LTG- and VAL-concentrations within therapeutic intervals
- 1998-2002: Progressive cognitive impairment, diagnosed with dementia
- 2005: Cannot communicate
- 2007: Stops taking food and drink. Medication stopped
- Gradually wakes up, after 1 month patient can communicate normally and asks what has happened. Condition normalizes after 1,5 years

Valproate encephalopathy

- Idiosyncratic reaction, unknown mechanism
- Case reports in older adults, but also younger adults
- Causes progressive parkinsonism and cognitive impairment which can lead to dementia
- Delayed onset common (years!)
- Valproate concentrations within therapeutic interval
- Reversible condition!
- Greater rate of atrophy in AD-patients with valproate than AD-controls (Fleischer et al, Neurology 2011)

Conclusions and take-home message

- Epilepsy is common in dementia
- Diagnosis can be difficult
- Epilepsy in dementia should be treated as in elderly without dementia
- Newer AEDs are as effective and better tolerated than older AEDs
- Start with low dose, titrate slowly, aim for minimum effective dose
- Always perform a follow-up within 2-4 weeks
- Always take a thorough drug history, including when each drug was started
- Clinical head-to-head trials of AEDs in dementia are urgently needed

Recommended literature

- **Vu LC, et al.** New-onset epilepsy in the elderly. Br J Pharmacol (2018) 84:2208-17
- **Liu J, et al.** Treatment of epilepsy for people with Alzheimer's disease. Cochrane Database of Systematic Reviews (2018) Issue 12

Thank you for your attention!