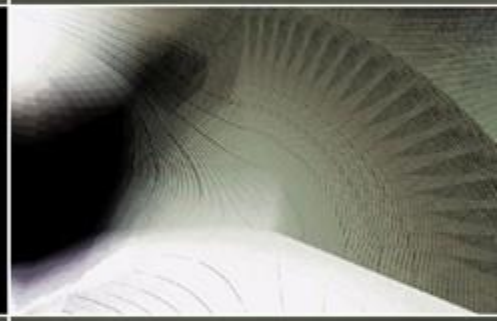
Chulalongkorn University
จุฬาลงกรณ์มหาวิทยาลัย
Pillar of the Kingdom

Chulalongkorn Comprehensive Epilepsy Centre

# Interesting case discussion



## Management in vascular-related epilepsy

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CHULALONGKORN COMPREHENSIVE EPILEPSY CENTER OF EXCELLENCE

# Case 1

- **62 yo F, RHD**
- **Epilepsy onset**: 44 yo
- **Seizure type**: 1) Dyscognitive seizure
  2) Somatosensory aura (abnormal feeling at both feet)
- Seizures disappeared since age 56 years
- **Seizure period**: 12 years (44 – 56 yrs)

# Case 1 (cont.)

- **PMHx**: Uneventful birth history

  No Hx of HS, head injury, nor CNS infection

  Dyslipidemia diagnosed since age 53 yrs
- **Current AEDs**: Phenobarbital 90 mg/day
- **Past medications**: Valproic acid (discontinued due to planned pregnancy), PHT (rash)

# Clinical course

- Noted to have dry eyes for years
- No memory or cognitive decline
- **ANA ≥ 1,280 (homogeneous speckle)**

  **Anti SS-A: strongly positive**

  **Anti SS-B: positive**

# Case 2

- **63 yo F, RHD**
- **Epilepsy onset**: 50 yo
- **Seizure type**: Generalized tonic clonic seizure ( 2 seizures in life, 10 days apart)

# Case 2 (cont.)

- **PMHx**: Uneventful birth history
  No Hx of HS, head injury, nor CNS infection
  Hypertension diagnosed since age 51 yrs
  **Chronic headache for > 20 years , blurred vision for 12 years**
  **Complained of memory decline, action tremor of both hands since age 54 yrs**
- **Current AEDs**: Lamotrigine 100 mg/day
- **Past medications**: Phenytoin 300 mg/day (discontinued due to suspicious to be cause of memory problem)

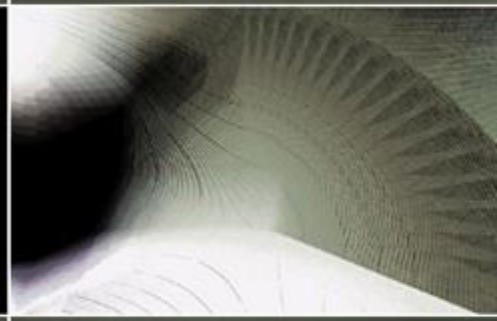
# Clinical course

- ANA ≥ 1,280 (homogeneous speckle), elevated ESR 104 mm/hr

  Anti SS-A: strongly positive

  Anti SS-B: positive

# Small vessel disease as biomarkers of epilepsy

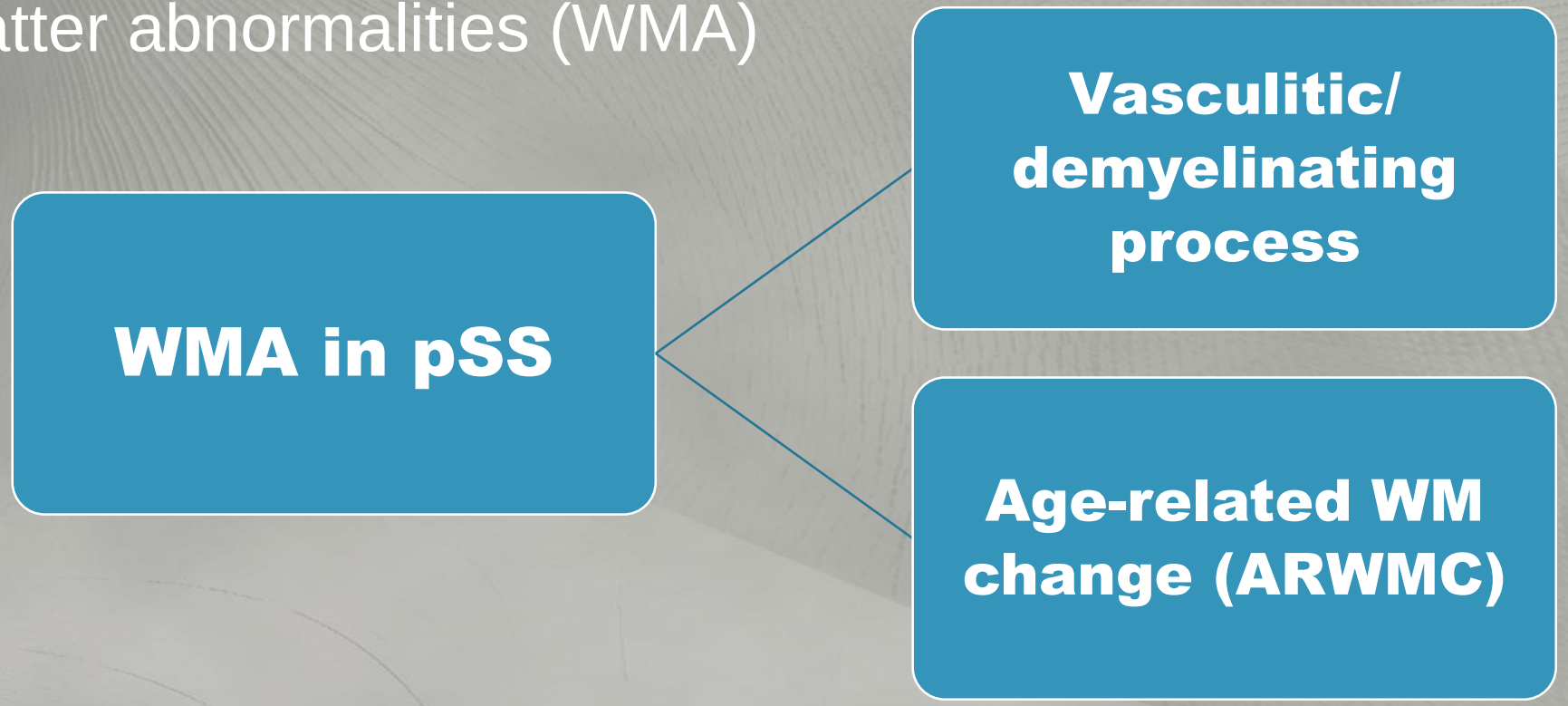


# MRI findings in primary Sjogren's syndrome (pSS)

- MRI of patients with primary Sjögren syndrome has shown multiple areas of increased signal intensity in the periventricular and subcortical white matter (WM) on FLAIR and T2-weighted images
- These findings have been observed in both patients with and those without CNS impairment

# Primary Sjogren's syndrome (pSS)

- White matter abnormalities (WMA)



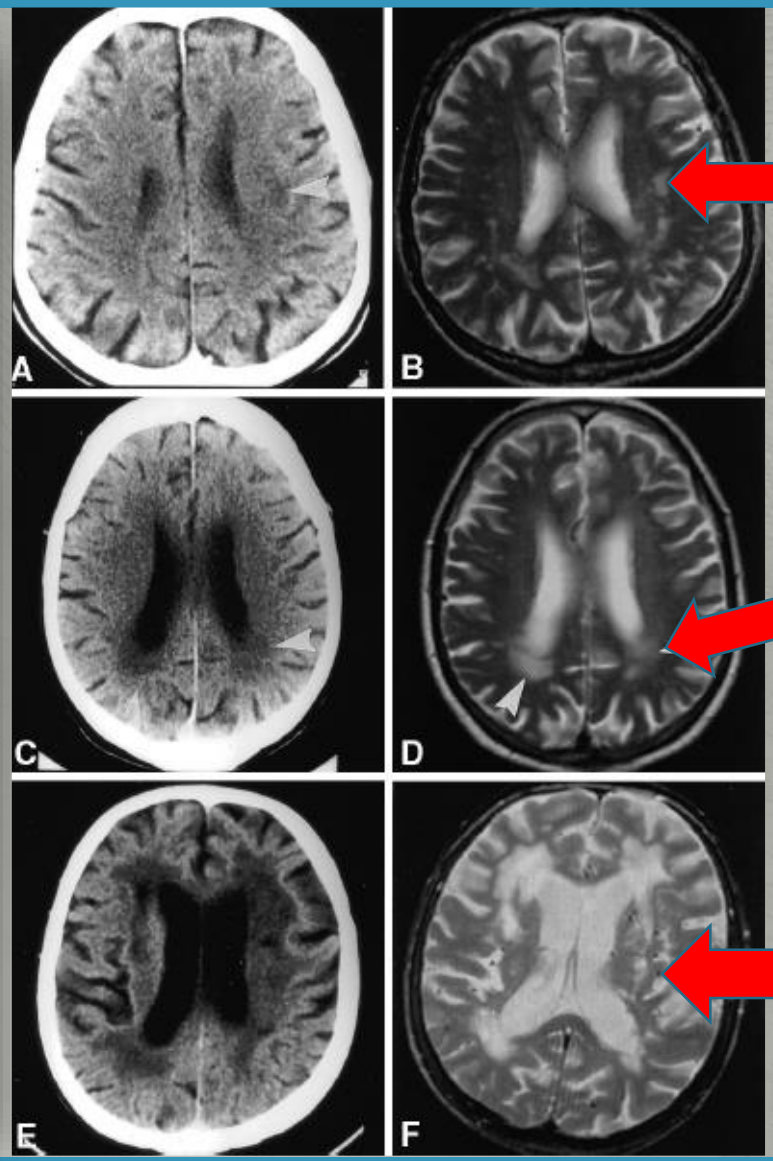
# The European Task Force on Age-related white matter changes (ARWMC)

**TABLE 1. The ARWMC Rating Scale for MRI and CT**

| | |
|---|---|
| White matter lesions | |
| 0 | No lesions (including symmetrical, well-defined caps or bands) |
| 1 | Focal lesions |
| 2 | Beginning confluence of lesions |
| 3 | Diffuse involvement of the entire region, with or without involvement of U fibers |
| Basal ganglia lesions | |
| 0 | No lesions |
| 1 | 1 focal lesion (≥5 mm) |
| 2 | >1 focal lesion |
| 3 | Confluent lesions |

White matter changes on MRI were defined as bright lesions ≥5 mm on T2, PD, or FLAIR images. Lesions on CT were defined as hypodense areas of ≥5 mm; left and right hemispheres were rated separately.

The following brain areas were used for rating: frontal, parieto-occipital, temporal, infratentorial/cerebellum, and basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule, and insula).




**Score 1: Focal lesions**

**Score 2: Beginning confluence**

**Score 3: Diffuse involvement**

*Wahlund LO et.al; Stroke 2001*

# Definition of RIS according to Okuda et.al. 2009

**Table 1** Proposed diagnostic criteria for the radiologically isolated syndrome

A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:

1. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum
2. T2 hyperintensities measuring >3 mm and fulfilling Barkhof[7] criteria (at least 3 out of 4) for dissemination in space
3. CNS white matter anomalies not consistent with a vascular pattern

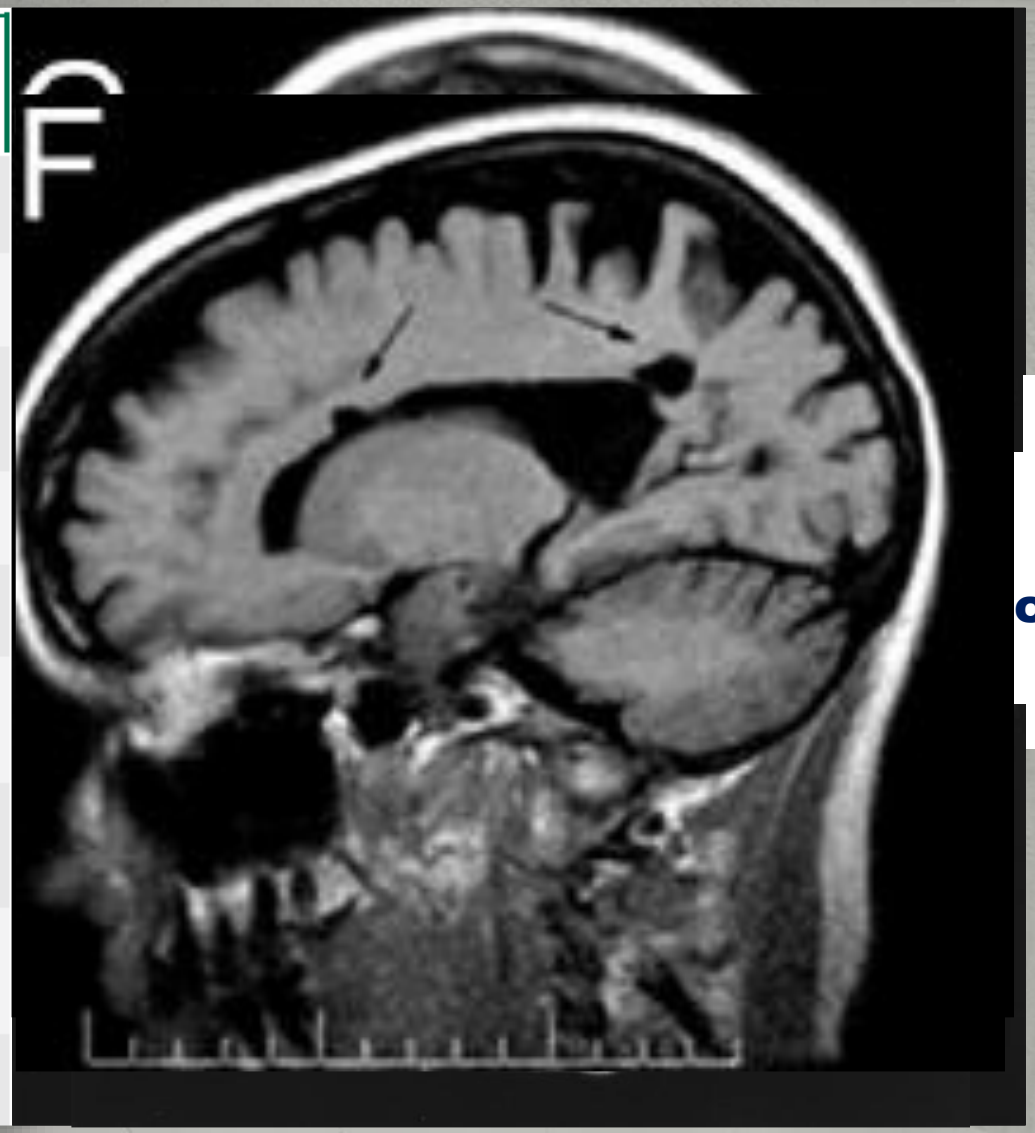
B. No historical accounts of remitting clinical symptoms consistent with neurologic dysfunction

C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized areas of functioning

D. The MRI anomalies are not due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure) or a medical condition

E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of the corpus callosum

F. The CNS MRI anomalies are not better accounted for by another disease process

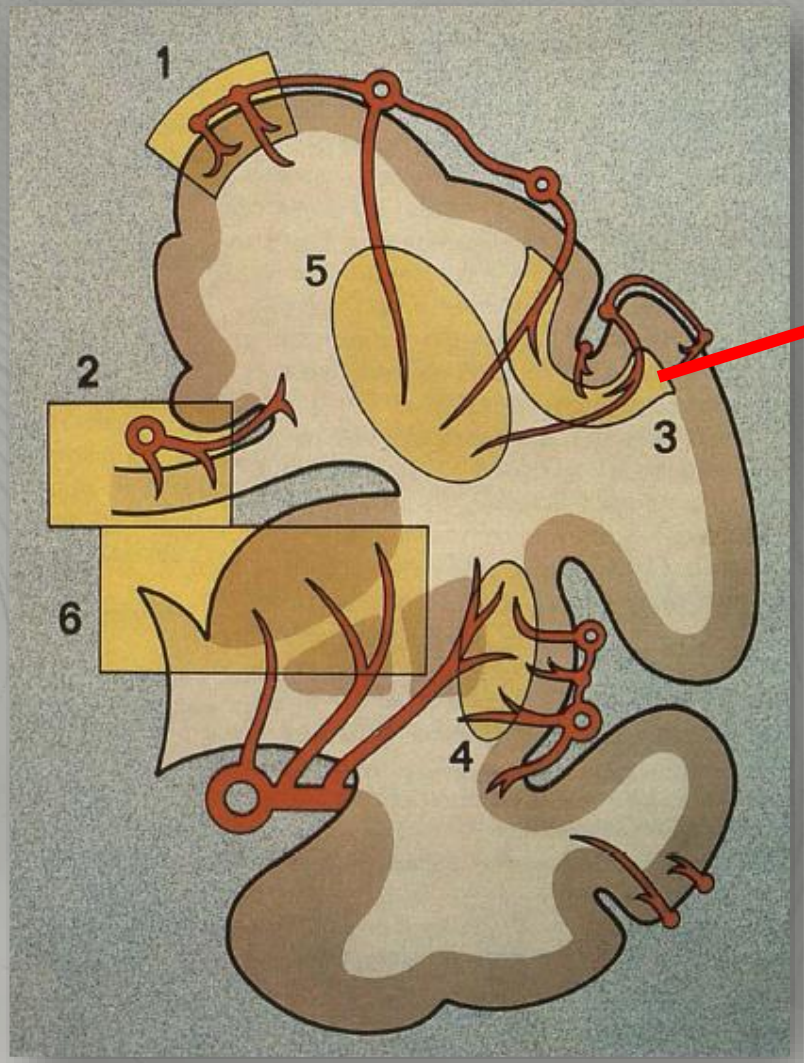



**Periventricular lesions (peri-venule)**

**callosal/subcallosal locations**

**on T2WI**

*Okuda DT et.al; Neurology 2009*




**Subcortical**
**U fiber**
**“dual supply”**

*Moody DM et.al; AJNR 1990*

**321 pSS pts**

**51 (16%) had ≥ 1 imaging study**

**25/51 (49%) had WMA**

**21/25 (84%) ARWMC**

**4/25 (16%) MS-like**

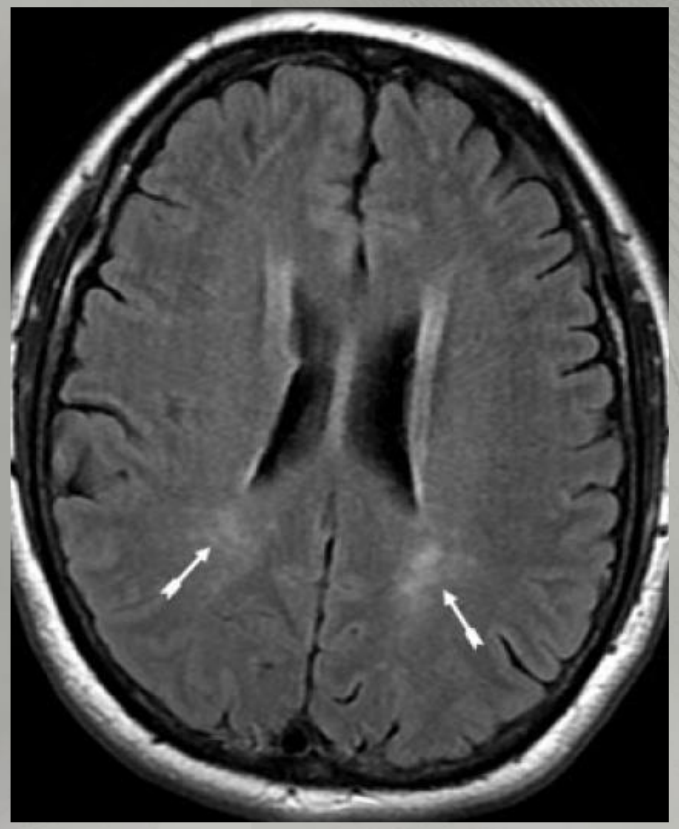
| | Absence of WMA, $n=26$ (%) | Presence of WMA, $n=25$ (%) | Bilateral, $P$-value |
|---|---|---|---|
| Hypertension | 6 (23) | 19 (76) | **<0.001*** |
| Diabetes mellitus | 8 (31) | 17 (68) | **0.012** |
| Hypercholesterolemia | 12 (46) | 11 (44) | 1.000 |
| Hypertriglyceridemia | 8 (31) | 10 (40) | 0.565 |
| Smoking | 5 (19) | 5 (20) | 1.000 |
| Obesity | 3 (14) | 7 (44) | 0.260 |
| Metabolic syndrome | 2 (8) | 10 (40) | **0.009** |
| Altered MDRD (<60) | 9/24 (37) | 14/23 (61) | 0.148 |
| Mean HDLc levels (mg/dl) | 64.29 ± 6.85 | 42.00 ± 3.95 | **0.009*** |
| Mean LDLc levels (mg/ dl) | 139.35 ± 9.44 | 134.94 ± 16.64 | 0.816 |
| Mean apoA1 levels (mg/ dl) | 147.80 ± 6.91 | 130.38 ± 8.41 | 0.119 |
| Mean apoB levels (mg/ dl) | 108.40 ± 5.72 | 100.69 ± 9.90 | 0.492 |

**WMA in patients with primary SS were overwhelmingly associated with concomitant cerebrovascular risk factors**

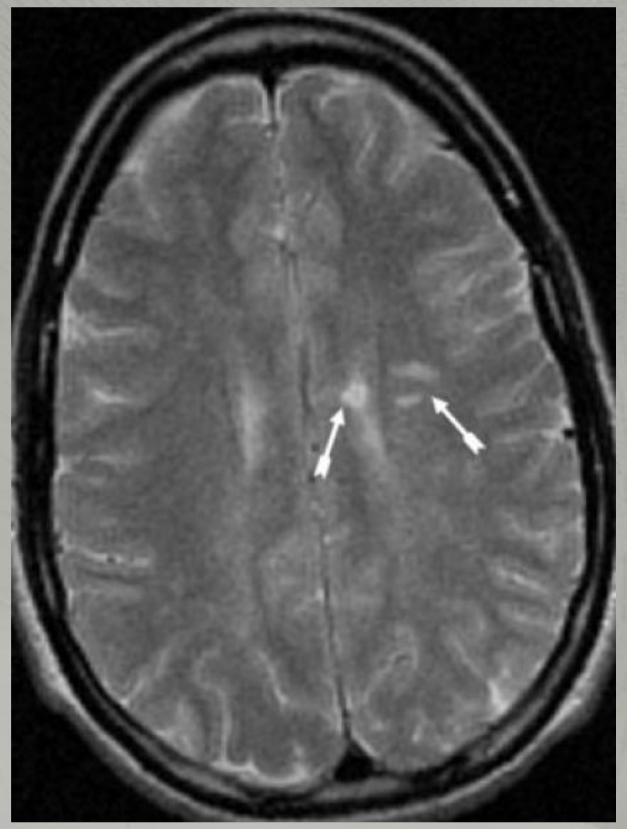
*Akasbi M et.al; QJM 2012*

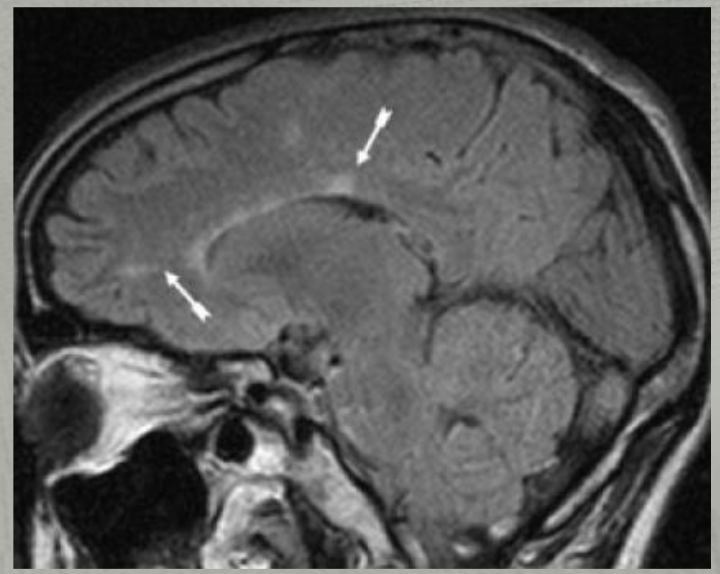
# WMA in pSS

**ARWMC rating score 2**



**Inflammatory/demyelinating (MS-like) lesions**





*Akasbi M et.al; QJM 2012*

# Prevalence of WMA in pSS

**Table 4** Prevalence of WMA in patients with primary Sjögren syndrome

| Author (reference) | Year | N | Mean age (years) | Clinical profile | WMA (*n*) | Percentage of lesions | Cardiovascular risk factors |
|---|---|---|---|---|---|---|---|
| Alexander *et al.*[25] | 1988 | 16 | NS | NRL involvement | 12 | 75 | NE |
| | | 22 | | Asymtomatic | 2 | 9 | NE |
| Pierot *et al.*[26] | 1993 | 15 | NS | Asymptomatic | 9 | 60 | NE |
| Escudero *et al.*[27] | 1995 | 48 | 58.2 | Mixed | 25 | 51 | NE |
| Tajima *et al.*[28] | 1997 | 21 | 51.7 | Suspected NRL inv | 1 | 5 | NE |
| Govoni *et al.*[29] | 1999 | 7 | 47.3 | NRL involvement | 6 | 86 | NE |
| Coates *et al.*[30] | 1999 | 30 | 63.0 | Unselected | 24 | 80 | HTA 23%, DM 0% |
| Belin *et al.*[31] | 1999 | 14 | 50.3 | Mixed | 7 | 50 | NE |
| Lafitte *et al.*[32] | 2001 | 9 | NS | NRL involvement | 5 | 56 | NE |
| Mataro *et al.*[33] | 2003 | 15 | 55.7 | NRL involvement | 8 | 61 | NE |
| Delalande *et al.*[5] | 2004 | 58 | NS | NRL involvement | 41 | 70 | NE |
| Le Guern *et al.*[34] | 2009 | 10 | 40.2 | Unselected | 2 | 20 | HTA 10% |
| Alhomoud *et al.*[35] | 2009 | 12 | 40.0 | NRL involvement | 7 | 58 | NE |
| Gono *et al.*[36] | 2010 | 10 | NS | NRL involvement | 5 | 50 | NE |
| Massara *et al.*[7] | 2010 | 23 | 55.8 | NRL involvement | 20 | 87 | Analysed but not detailed |
| Present study | 2010 | 51 | 64.2 | Suspected NRL involvement | 25 | 49 | HTA 49%, DM 49%, Hcol 45%, HTG 35% |
| **Total** | – | **361** | – | – | **199** | **55** | – |

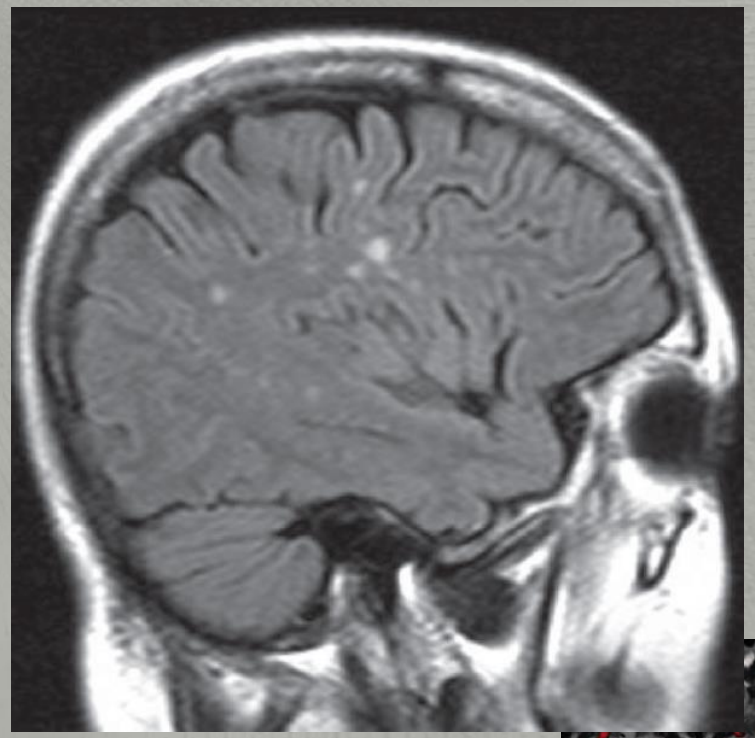
NRL: neurological, WMA: demyelinating lesions, NS: not specified, NE: not evaluated, HTA: hypertension, DM: diabetes mellitus, Hcol: hypercholesterolemia, HTG: hypertriglyceridemia

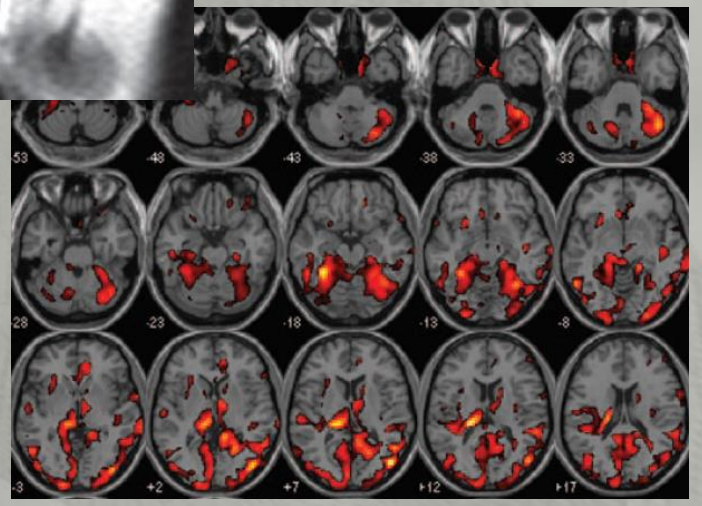
*Akasbi M et.al; QJM 2012*

# CNS Involvement in Primary Sjögren Syndrome: Assessment of Gray and White Matter Changes With MRI and Voxel-Based Morphometry

**51 pSS pts, compared with 18 age- and disease duration–matched patients with systemic sclerosis, and 35 age-matched control subjects**

**Compared with controls, Patients with pSS have WMHIs and gray and white matter atrophy, probably related to cerebral vasculitis (small vss)**





*Tzarouchi LC et.al; AJR 2011*

# Association between lacunar infarcts and epilepsy

# Epileptic seizures in subcortical vascular encephalopathy

A. Schreiner, B. Pohlmann-Eden, A. Schwartz, M. Hennerici *

*Department of Neurology, Mannheim Medical School, University of Heidelberg, Mannheim, Germany*

Received 25 August 1994; revised 19 December 1994; accepted 26 December 1994

**The association of SVE, multiple subcortical lacunas are suggestive for an increased risk for epileptic seizures**

Table 4
Localization of lacunar infarctions and white matter lesions

| Localization | Group A ($n$) | Group B ($n$) | $p$ |
|---|---|---|---|
| (A) Localization of lacunar infarctions (due to multilocular localization the total number exceeds $n = 18$) | | | |
| Brain stem | 3 | 11 | |
| Subcortical white matter | 15 | 4 | < 0.001 |
| Basal ganglia | 7 | 15 | |
| Thalamus | 0 | 2 | |
| (B) Localization of white matter lesion (WML) (Group A: $n = 10/18$, Group B: $n = 11/18$) | | | |
| Subcortical WML | 3 | 1 | |
| Periventricular WML | 7 | 10 | n.s. |
| Temporal WML | 3 | 1 | |

*Schreiner A et.al; J Neurol Sci 1995*

# Seizures and epilepsy in patients with lacunar strokes

J. De Reuck [a,*], E. Nagy [a,c], G. Van Maele [b]

Table 2
Comparison of the location and the number of lacunes, and of the severity of the white matter changes on CT and/or MRI of the brain in the patients with and without seizures

| Items | Seizure ($n$=37) | Non-seizure ($n$=205) | $P$ value |
|---|---|---|---|
| Putamino-capsular | 25 | 108 | 0.140 |
| Internal capsule | 15 | 71 | 0.509 |
| Thalamus | 8 | 43 | 0.845 |
| Brainstem | 8 | 52 | 0.482 |
| Number of lacunes | 56 | 274 | 0.167 |
| Degree of white matter changes | 0.59 | 0.64 | 0.524 |

Table 1
Percentage comparison of the vascular risk factors in lacunar stroke patients with and without subsequent seizures

| Items | Seizure ($n$=37) | Non-seizure ($n$=205) | $P$ value |
|---|---|---|---|
| Arterial hypertension | 78.4 | 75.6 | 0.836 |
| Coronary artery disease | 16.2 | 22.9 | 0.517 |
| Atrial fibrillation | 16.2 | 14.1 | 0.799 |
| Peripheral artery disease | 10.8 | 8.8 | 0.755 |
| Heart valve disease | 2.7 | 5.9 | 0.698 |
| Hypercholesterolemia | 32.4 | 31.7 | 1.0 |
| Diabetes mellitus | 21.6 | 30.7 | 0.328 |
| Smoking | 5.4 | 15.1 | 0.189 |

**No evidence that seizures are directly induced by lacunar infarcts**

*De Reuck J et.al; J Neurol Sci 2007*

# Cognitive Impairment and Seizures in Patients with Lacunar Strokes

J. De Reuck[a] G. Van Maele[b]

Departments of [a]Neurology and [b]Medical Statistics, University Hospital, Ghent, Belgium

**Seizure occurrence in patients with a lacunar infarct is not related to the severity of the stroke but rather to the degree of cognitive impairment**

**Table 1.** Comparison of the demographic features, NIHSS and mR scores in the stroke patients with and without seizures

| | Seizure group (n = 44) | Nonseizure group (n = 248) | p value |
|---|---|---|---|
| Age, years (mean ± SD) | 72.2 ± 11.2 | 69.9 ± 11.3 | 0.287 |
| Gender, % | | | |
| Female | 45.5 | 39.5 | |
| Male | 54.5 | 60.5 | 0.506 |
| NIHSS score (mean ± SD) | 3.7 ± 2.9 | 5.5 ± 3.6 | 0.00133 |
| mR | | | |
| Dependent, % | 45.5 | 27.0 | |
| Independent, % | 54.5 | 73.0 | 0.019 |

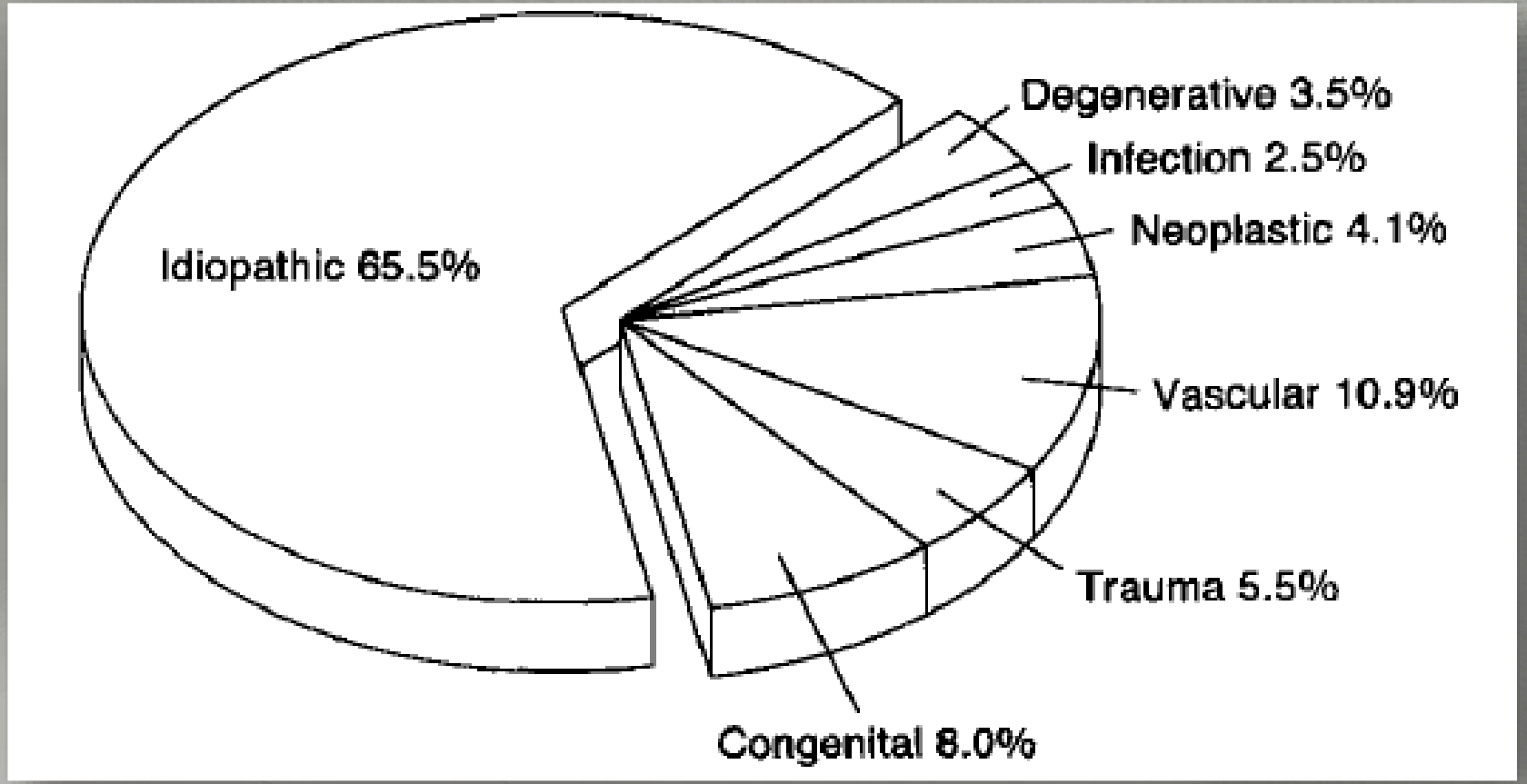
The p value for age was determined by the Mann-Whitney U test; all other p values were determined using Fisher's exact test.

**Table 3.** Comparison of the MMSE scores in the stroke patients with and without seizures and of the percentage distribution of the subgroups according to their degree of cognitive impairment

| Items | Seizure group (n = 44) | Nonseizure group (n = 173) | p value |
|---|---|---|---|
| MMSE (mean ± SD) | 20.9 ± 6.6 | 25.1 ± 5.0 | <0.001 |
| Cognitive status | | | |
| Normal, % | 18.2 | 29.8 | |
| Mild decline, % | 18.2 | 16.9 | |
| Moderate decline, % | 31.8 | 16.9 | |
| Severe decline, % | 31.8 | 6.0 | <0.001 |

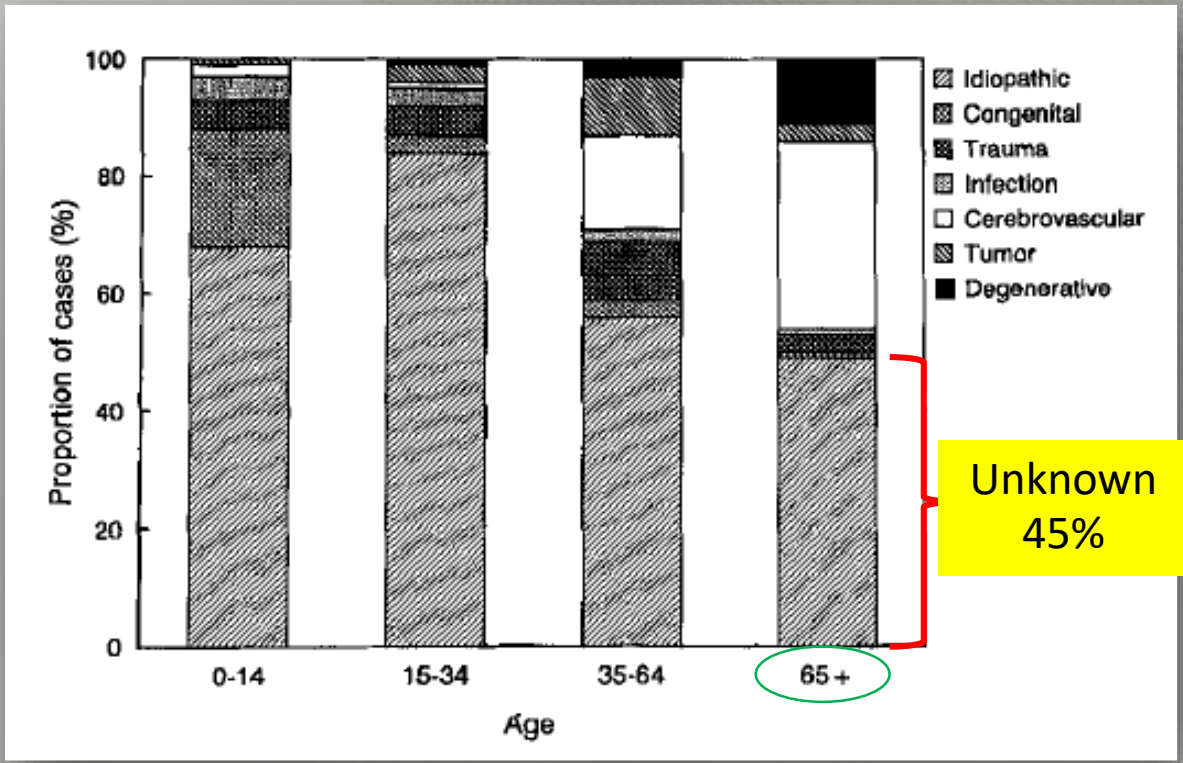
*De Reuck J et.al; Eur Neurol 2009*

# Cause of epilepsy in general population

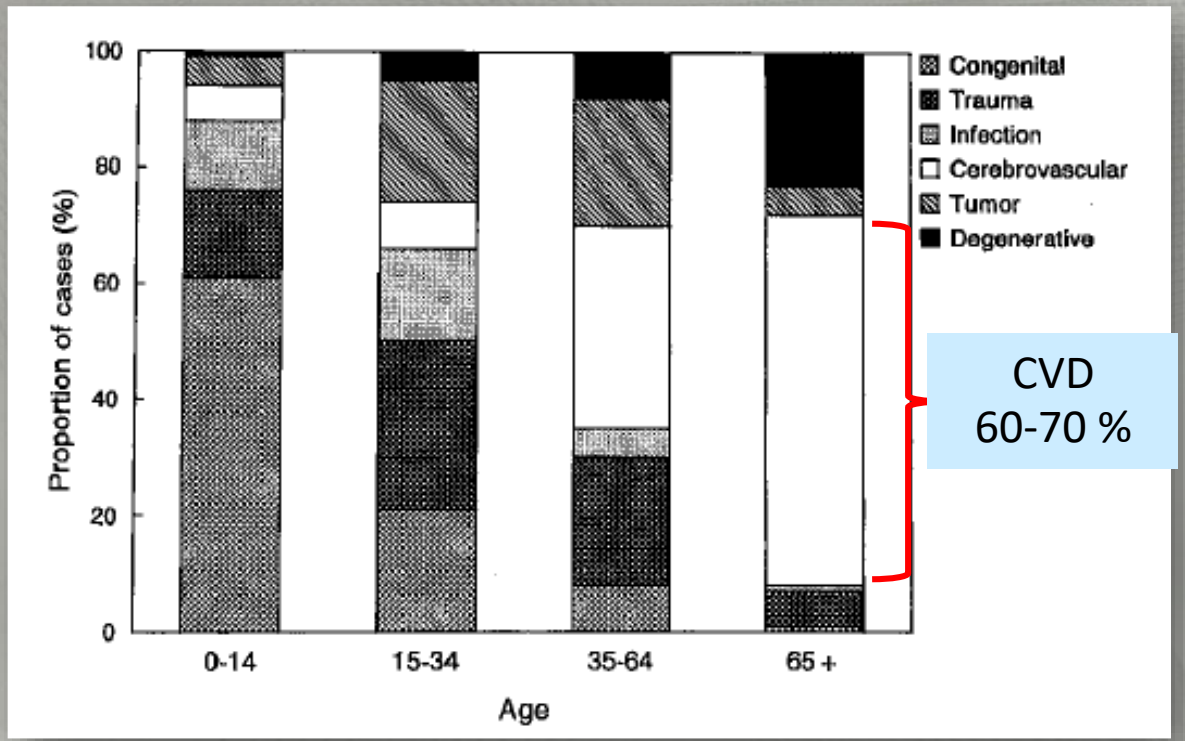



*Hauser WA et.al; Epilepsia: 1993*

# Cause of epilepsy in the elderly




Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories within age groups




Among cases with known etiology; **CVD** was the leading cause of epilepsy in the elderly

*Hauser WA et.al; Epilepsia: 1993*

# Cause of epilepsy in the elderly

- **Cerebrovascular disease (CVD)**: most common (60-70%)
- **Neurodegenerative disease**: Alzheimer's disease and other dementias (20%)
- Trauma
- Brain tumor

*Hauser WA et.al; Epilepsia: 1993*
*Stefan H et.al; Acta Neurol Scand: 2014*

# Association between late-onset seizures/epilepsy and subsequent stroke

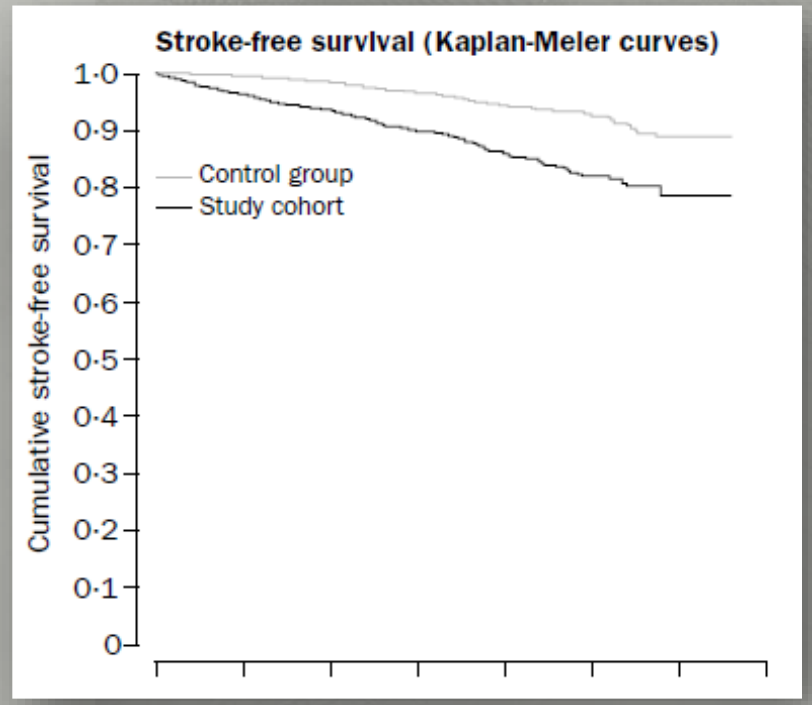
- Epileptic seizures/epilepsy and cerebrovascular disease show a **"bidirectional relation"**
- The hypothesis of **"Vascular heralding epilepsy"** emerged in 1978 and has been supported by subsequent studies

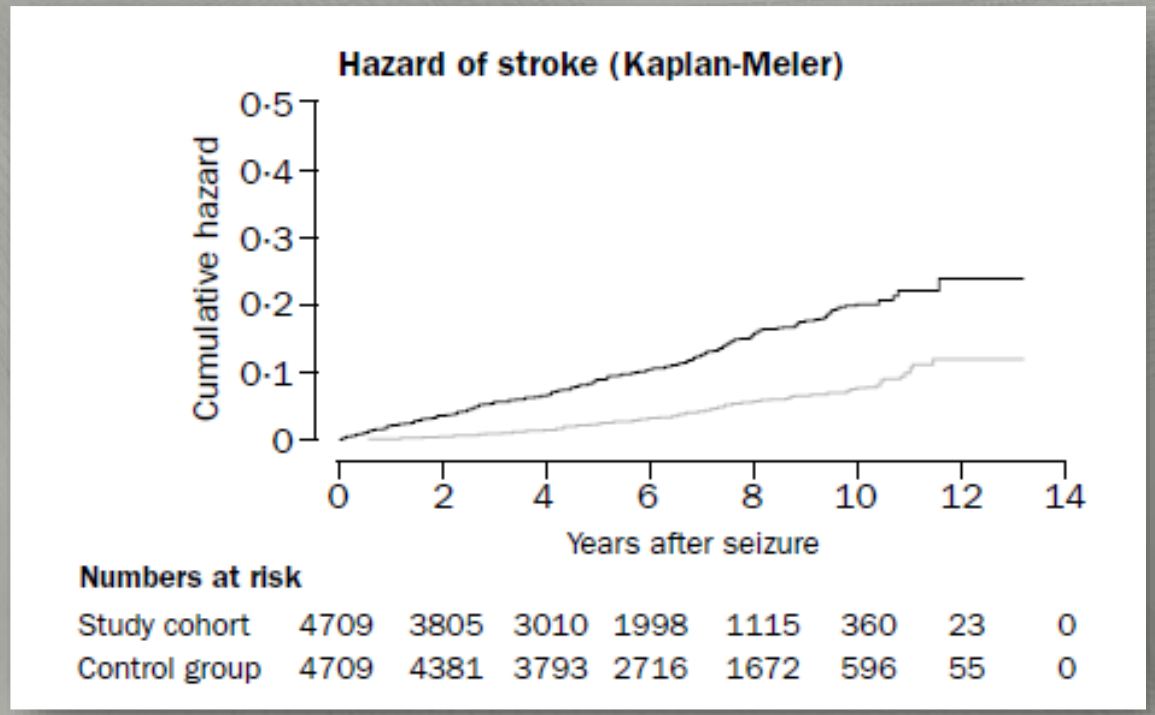
  -**The onset of seizures in late life is associated with a striking increase in the risk of stroke**

  - Many patients who present with otherwise unexplained seizures are found to have occult cerebrovascular disease
- **"Epileptic seizures might be a harbinger of future stroke"**

*Shinton RA et.al; Lancet: 1987*
*Cleary P et.al; Lancet: 2004*
*Brigo F et.al; Epilepsy & behavior: 2014*

# Association between late-onset seizures/epilepsy and subsequent stroke



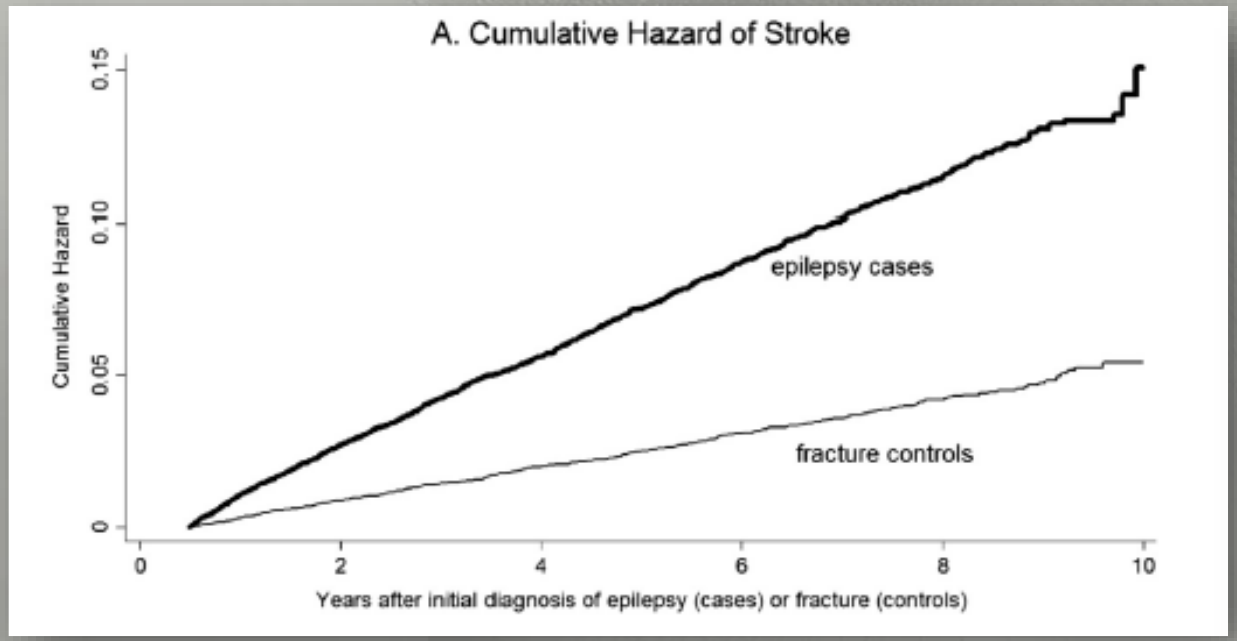



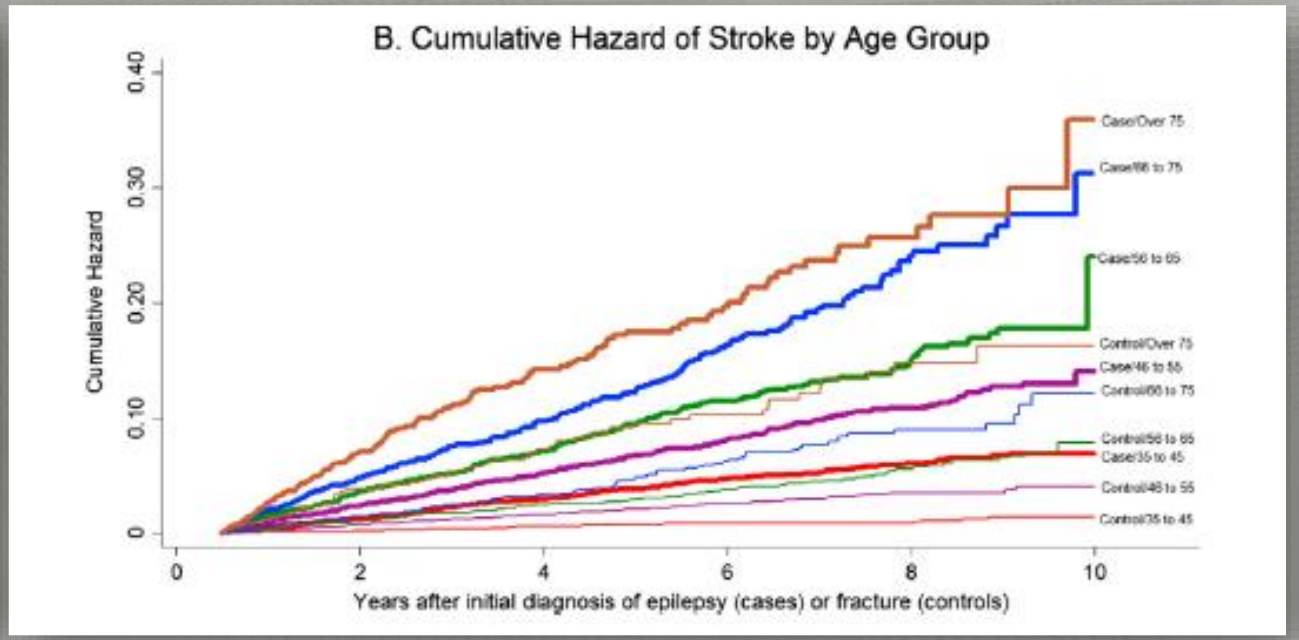

**The relative hazard of stroke at any point for people with seizures compared with the control group was 2.89 (95% CI 2,45-3.41)**

**The hazard of stroke over time in studied patients and control group**

*Cleary P et.al; Lancet: 2004*

# Stroke after adult-onset epilepsy (aged ≥ 35 years)




**Cases with epilepsy showed a *60% higher risk of stroke* (HR 1.6; 95% CI 1.42-1.80)**

**The risk of stroke in cases with epilepsy increased faster and was similar to that in controls who were ≥ 10 yrs older**

**Adult-onset epilepsy (age ≥ 35 yrs) warrants consideration for occult CVD as an etiology of epilepsy**

*Wannamaker BB et.al; Epilepsy & behavior: 2015*

# Vascular determinants of epilepsy

- There may be a relationship between vascular factors and the risk of late-onset epilepsy

  - presence of any of these indicators **(myocardial infarction, peripheral vascular disease, hypertension, serum total cholesterol, and left ventricular hypertrophy)** was **twice** as common among subjects with late-onset epilepsy as compared with subjects without epilepsy (**OR = 2.0**, 95% CI 0.9-4.2)

*Li X et.al; Epilepsia: 1997*

# Adult and late-onset epilepsy and risk of stroke

- **A patient who presents with seizures for the first time in adults/ late life, when there is no apparent predisposing cause (even without clear infarction of brain tissue), should be deemed to be at increased risk of stroke** (in the similar manner as low HDL-cholesterol (relative risk of 1.4), smoking (2.0), and lack of exercise (2.0-3.0))

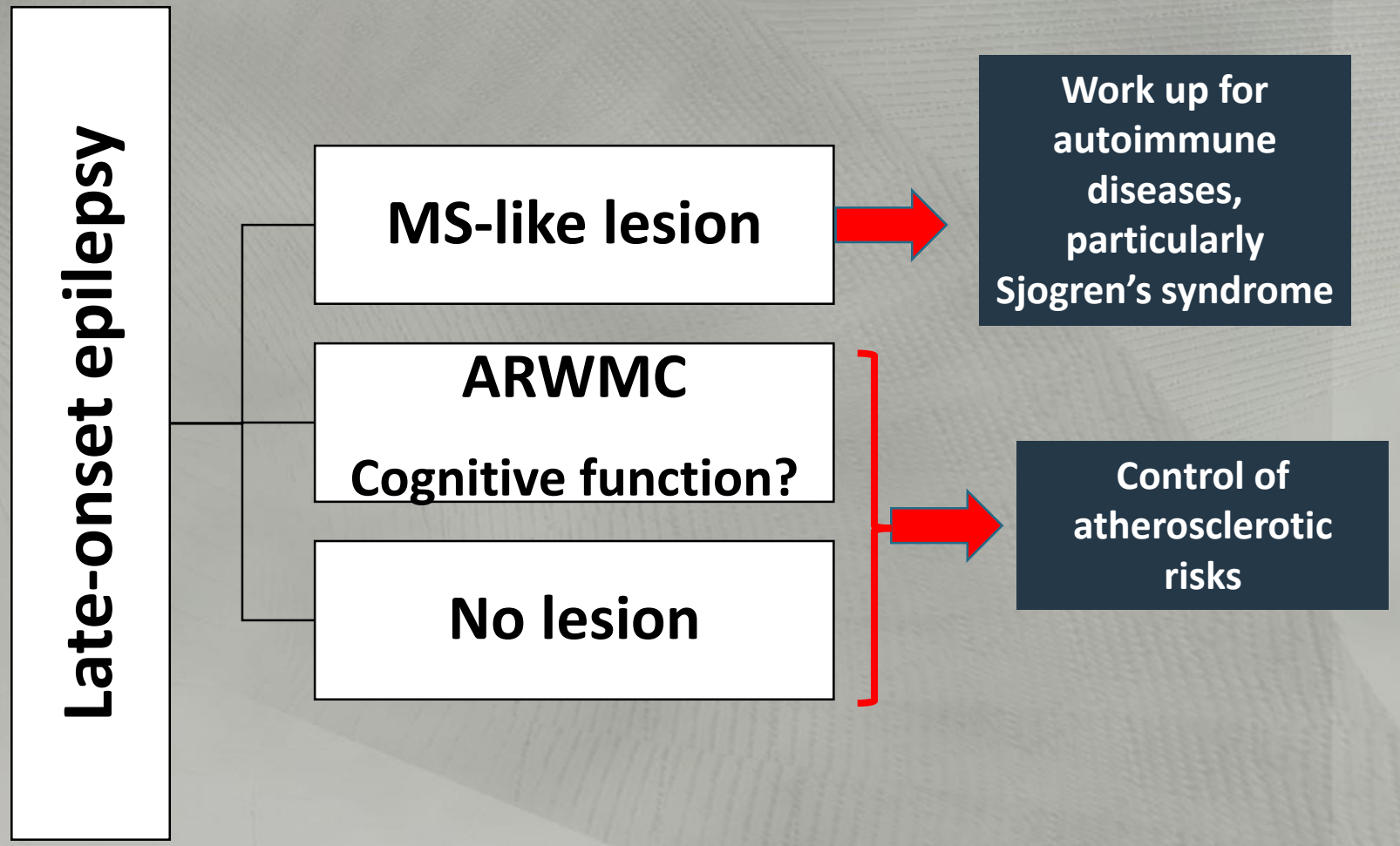
- **Possible pathophysiology**: subcortical small vessel disease might lead to

  - **disruption of cortico-subcortical circuits** altering the balance between excitability and inhibitory pathways with subsequent epileptogenicity

  - **neurovascular unit dysfunction** with altered integrity of blood-brain barrier and subsequent disruption of cerebral metabolism and/or purfusion

# In summary

- When encounter patients with late-onset epilepsy (> 35 years), evidence of small vessel disease may be of clinical significance



# Thank you for your attention