# Prestroke Dementia: Characteristics, Clinical Features and Primary Outcomes of in Consecutive Series of Patients

*Salvatore Caratozzolo, Maddalena Riva, Giulia Mombelli, Marina Zanetti, Federica Gottardi, Luca Rozzini, Alessandro Padovani.*

# …brief history

- ✓ *The world's population is ageing.*
- ✓ *Improvements in health care have contributed to people living longer and healthier.*
- ✓ *Ageing populations face an increase in disease burden from chronic neurodegenerative conditions.*
- ✓ *Dementia will be a major contributor to this increased burden*

*International statistical classification of diseases and related health problems, 10th Revision. Geneva, World Health Organization, 1992.*
*World Alzheimer's Report 2009. London, Alzheimer's Disease International, 2009. Neurological disorders: public health challenges. Geneva, World Health Organization, 2006.*
*World Population Ageing 2009. New York, NY, United Nations, 2009 (http://www.*
*un.org/esa/population/publications/WPA2009/WPA2009_WorkingPaper.pdf accessed 4 February 2012).*

- ✓ *Cerebrovascular disease is thought to be the second most common cause of dementia*
- ✓ *A spectrum of cognitive disorders related to cerebrovascular disease is now recognised*

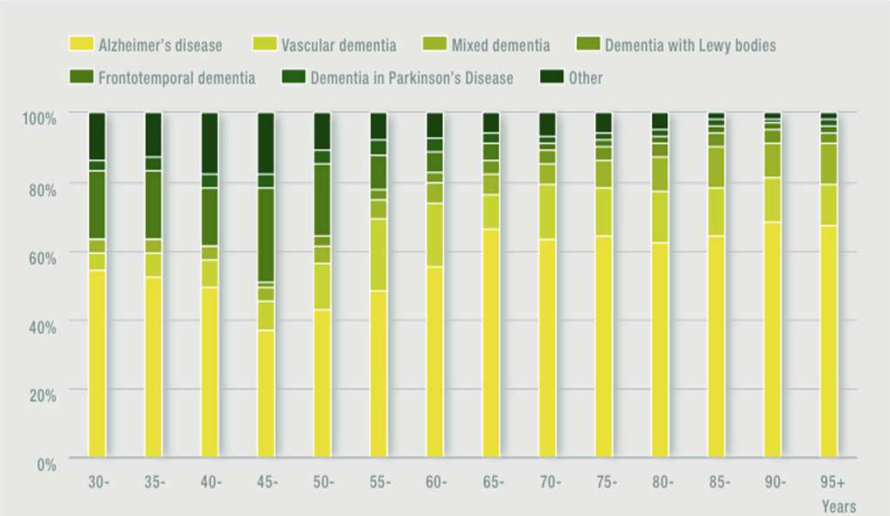


FIG 2.4A *Dementia UK* report: consensus estimates of the proportion of all dementia cases accounted for by different dementia subtypes, by age and gender. **Women**

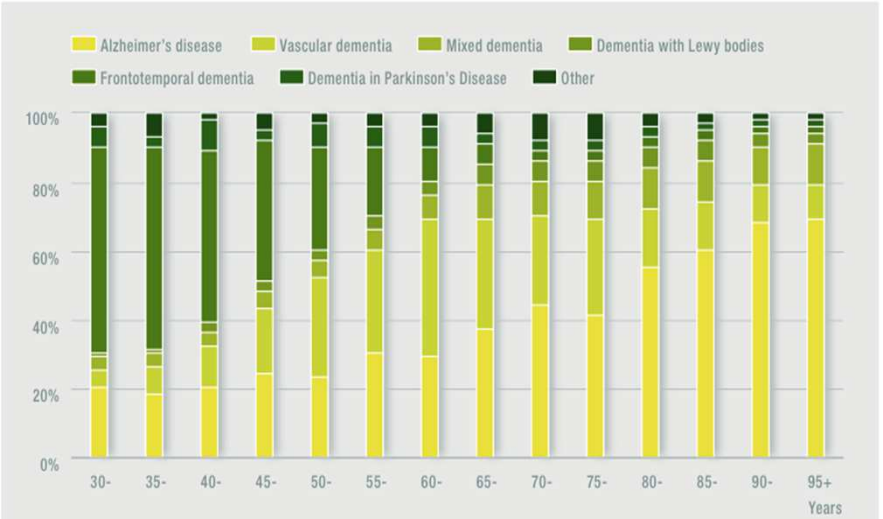


FIG 2.4B *Dementia UK* report: consensus estimates of the proportion of all dementia cases accounted for by different dementia subtypes, by age and gender. **Men**

# *…what is Vascular Dementia (VaD)*

- ✓ *First described in the late 19° century by Binswanger and Alzheimer who described variety of underlying pathologic mechanisms including the role of multiple infarction and chronic ischemia.*
- ✓ *Pathologic studies demonstrated the amyloid plaques and neurofibrillary tangles (AD).*
- ✓ *There are no pathological criteria for the diagnosis of VaD, as there are for AD.*
  *A number of clinical diagnostic criteria exist.*

# ….NINDS-AIREN criteria for diagnosis of VaD

I. The criteria for the clinical diagnosis of *probable* vascular dementia include *all* of the following:

1. *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
   *Exclusion criteria*: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
2. *Cerebrovascular disease*, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of nof relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes*, or *extensive periventricular white matter lesions*, or combinations thereof.
3. *A relationship between the above two disorders*, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of *probable* vascular dementia include the following:

> *(a) Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.*

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include (a) early onset of of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging; (b) absence of focal neurological signs, other than cognitive disturbance; and (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of *possible* vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of *definite* vascular dementia are (a) clinical criteria for *probable* vascular dementia; (b) histopathologic evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

The term "AD *with* CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term "mixed dementia," used hitherto, should be avoided.

## Reference

Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop.
Neurology 1993 Feb;43(2):250-60.

# …DSM IV criteria of VaD

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:
   (a) aphasia (language disturbance)

   (b) apraxia (impaired ability to carry out motor activities depite intact motor function)

   (c) agnosia (failure to recognize or identify objects despite intact sensory function)

   (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exggeration of deep tendon reflexes, extensor plantar response, psuedobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlyig white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not ocurr exclusively during the course of a delirium.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

# …DSM V

*Major and Mild Neuro cognitive disordes due to:*

- ✓*Alzheimer's disease*
- ✓*Vascular disease*
- ✓*Traumatic Brain Injury*
- ✓*Lewy body disease*
- ✓*(several others)*
- ✓*Other NCDs*

# ...Post Stroke Dementia (PSD)

- ✓ *PSD includes all types of dementias that happen after stroke, irrespective of their cause.*

- ✓ *VaD is a direct consequence of cerebral infarcts, haemorrhages, and white-matter changes. But not all patients who have had a stroke, have VaD.*

- ✓ *Patients, followed up after stroke, can be diagnosed as affected by vascular dementia (VaD), degenerative dementia (especially Alzheimer's disease), or mixed dementia (dementia as a result of the coexistence of vascular lesions of the brain and neurodegenerative lesions).*

# …Epidemiology

- ✓ *In community-based studies with adjustment for age, the prevalence of dementia in people with a history of stroke is about 30%.*

- ✓ Prencipe M, Ferretti C, Casini AR, Santini M, Giubilei F, Culasso F. Stroke, disability, and dementia: results of a population survey. Stroke 1997; 28: 531–36.

- ✓ *In hospital-based studies, the prevalence of PSD ranges from 5-9 to 32%.*

Rasquin SM, Verhey FR, van Oostenbrugge RJ, Lousberg R, Lodder J. Demographic and CT scan features related to cognitive impairment i the first year after stroke. *J Neurol Neurosurg Psychiatry* 2004; **75:** 1562–67.

# …Epidemiology

- ✓ *Incidence of PSD changes if pre-existing dementia was included or not in PSD.*
- ✓ *Pre- existing dementia is present in 7–16% of stroke patients, and undiagnosed before stroke in many patients.*
- ✓ *In a community-based study done over 25 years, the cumulative incidence of PSD was 7% after 1 year, 10% after 3 years, 15% after 5 years, 23% after 10 years, and 48% after 25 years.46*
- ✓ *In hospital- based studies, the incidence of PSD ranged from 9%47 to 16·8% after 1 year, 24% to 28·5%17 after 3 years, 21·5%48 to 33·3%38 after 4 years, and was 32%38,49 after 5 years.*

*Henon H, Pasquier F, Durieu I, et al. Preexisting dementia in stroke patients: baseline frequency, associated factors, and outcome. Stroke 1997;* ***28:*** *2429–36.*

# ...Epidemiology

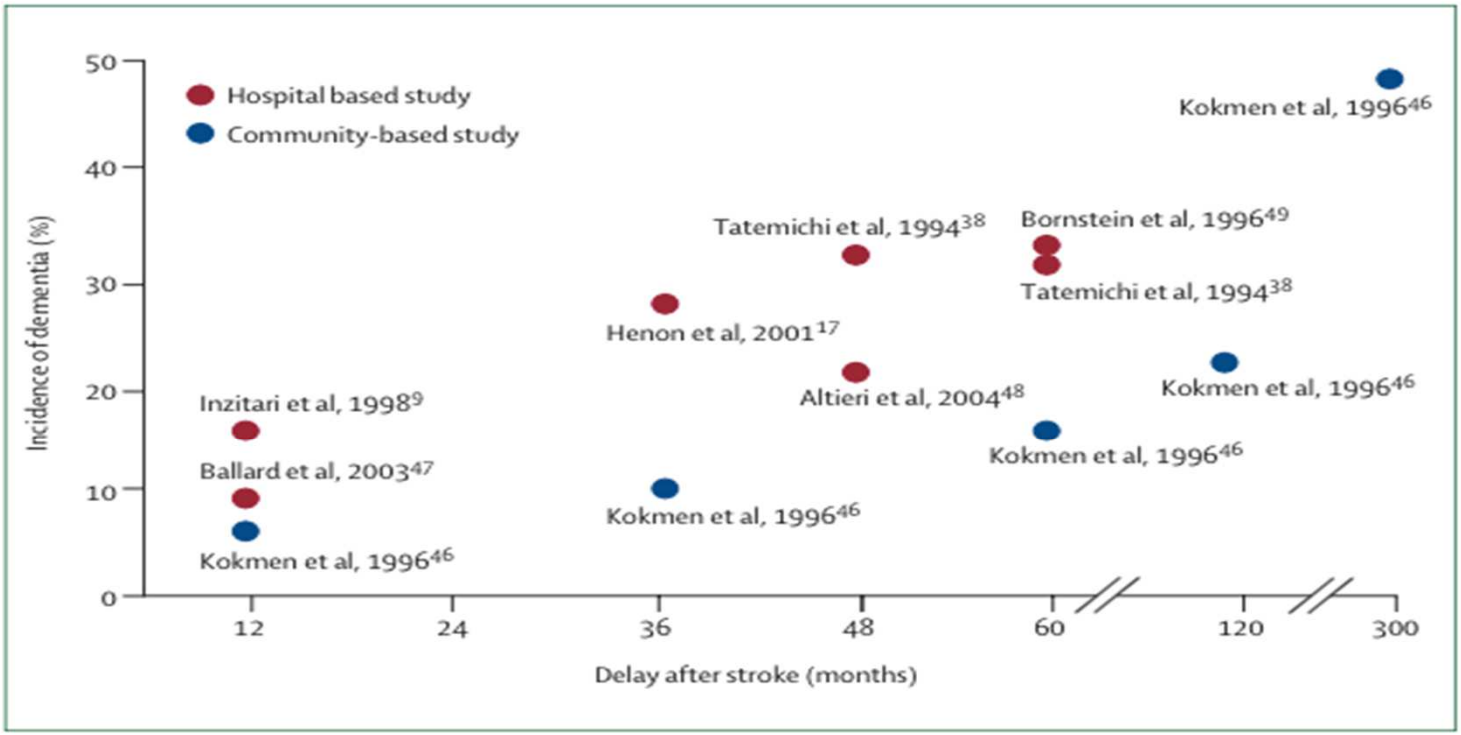


***Figure:*** **Incidence of poststroke dementia at different time intervals after stroke onset, in hospital-based studies (red) and community-based studies (blue)**

When the reference appears several times, data provided correspond to different assessments at different time intervals in the same cohort of patients.

# *…what about pre morbid conditions?*

- ✓ *The risk of PSD is higher in patients who were dependent before stroke.*

- ✓ *Pre-Stroke cognitive decline (no dementia), assessed by standardized questionnaires, is also associated with a higher risk of PSD after 3 months and 3 years.*

*Henon H, Pasquier F, Durieu I, et al. Preexisting dementia in stroke patients: baseline frequency, associated factors, and outcome. Stroke 1997;* ***28:*** *2429–36.*

# …Pre Stroke Dementia

- ✓ *To have the ability to accurately interpret the impact of stroke on the risk of PSD, prestroke level of cognitive function must be taken into account.*

- ✓ *It requires assessment of prestroke cognitive status using an adequate neuropsychological test battery, a long enough follow-up time between prestroke cognitive assessment and occurrence of stroke, and subsequently a long enough follow-up time between the incident stroke.*

- ✓ *Ideally, the impact of prestroke cognitive status should be assessed using the slope of prestroke cognitive performance over time because the effect of stroke on risk of cognitive impairment may depend on the rate of decline in cognitive function before stroke.*

# *…Evaluation of pre-existing cognitive decline and dementia*

- ✓ *The systematic assessment of pre-existing dementia uses the short version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). (Jorm, 1994)*

- ✓ *This questionnaire consists of 16 questions regarding the changes experienced by the patient over the last 10 years in aspects of daily behaviour requiring memory and other intellectual abilities.*

- ✓ *A close relative needs to be interviewed and therefore the IQCODE does not require the participation of the patient when neuropsychological functions and consciousness may be influenced by intracerebral haemorrhage.*

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**Table 1.** Baseline sociodemographic and clinical characteristics of patients (n = 158) with an acute cerebrovascular event grouped by IQCODE score

| | PSD group (IQCODE ≥3.3; n = 37) | | | PSND group (IQCODE ≤3.3; n = 121) | | | p |
|---|---|---|---|---|---|---|---|
| | mean | SD | n | mean | SD | n | |
| Age, years | 77.4 | 10.5 | | 68.4 | 14.3 | | 0.000 |
| Female | | | 23 (62) | | | 46 (38) | 0.008 |
| Education, years | 5.7 | 2.6 | | 7.5 | 3.4 | | 0.003 |
| Living at home with relatives | | | 28 (76) | | | 97 (80) | NS |
| Comorbidity: number of diseases | 6.3 | 3.5 | | 4.9 | 2.9 | | 0.013 |
| IADL: functions lost | 2.1 | 2.8 | | 0.4 | 1.2 | | 0.000 |
| Barthel Index (prestroke) | 87.1 | 23.3 | | 97.3 | 11.2 | | 0.000 |
| Family history of dementia | | | 13 (19) | | | 7 (11) | NS |

All variables refer to the prestroke condition. Figures in parentheses represent percentages. IADL = Instrumental Activities of Daily Living; NS = not significant.

Table 2. Baseline vascular risk factors of patients (N=158) with acute cerebrovascular event grouped by IQCODE scc

| | Pre Stroke dementia IQCODE ≥3.3 n=37 | Pre Stroke Non Demented IQCODE ≤3.3 n=121 | |
|---|---|---|---|
| | *N(%)* | *N(%)* | *p.* |
| Smoking | | | |
| Smokers | 3(8) | 21(17) | NS |
| Previous smokers | 12(32) | 27(23) | NS |
| Alcoholism | | | NS |
| Adequate consume of alcohol | 14(38) | 50(41) | NS |
| Inadequate consume of alcohol | 7(19) | 21(18) | NS |
| Heart diseases | | | NS |
| Angina pectoris | 5(13) | 5(4) | NS |
| Myocardial infarction | 2(6) | 20(16) | NS |
| Atrial fibrillation | 8(22) | 18(15) | NS |
| Hypertension | 22(59) | 69(57) | NS |
| Diabetes | 9(23) | 23(19) | NS |
| COPD | 3(8) | 12(10) | NS |
| Hypertriglyceridemia | 2(5) | 12(10) | NS |
| Hypercholesterolemia | 8(22) | 31(26) | NS |
| Carotid atherosclerosis | | | NS |
| Carotid stenosis <50% | 14(38) | 50(41) | NS |
| Carotid stenosis >50%<75% | 8(22) | 12(10) | NS |
| Carotid stenosis >75% | 12(32) | 9(7) | NS |
| Previous cerebrovascular events | 11(30) | 24 (20) | NS |

Table 3. Characteristic of ischemic stroke of patients (N=158) with acute cerebrovascular event grouped by IQCODE score.

| | Pre Stroke dementia IQCODE ≥3.3 n=37 | Pre Stroke Non Demented IQCODE ≤3.3 n=121 | |
|---|---|---|---|
| | *N(%)* | *N(%)* | *p.* |
| Stroke Type | | | |
| Large artery arteriosclerosis | 7(19) | 25(20) | NS |
| Cardioembolism | 5(14) | 14(12) | NS |
| Small-vessel occlusion | 2(5) | 11(11) | NS |
| Stroke of undetermined etiology | 23(62) | 71(59) | NS |
| Stroke localization | | | NS |
| Right hemisphere | 15(40) | 63(52) | NS |
| Left hemisphere | 21(57) | 54(45) | NS |
| Bilateral | 0(0) | 4(3) | NS |
| Anterior circulation | 28(76) | 89(74) | NS |
| Posterior circulation | 9(24) | 29(24) | NS |
| Antero-posterior circulation | 0(0) | 2(1) | NS |
| Clinical OCSP | | | NS |
| TACI | 16(43) | 70(59) | NS |
| PACI | 5(14) | 10(8) | NS |
| LACI | 12(32) | 14(12) | NS |
| POCI | 4(11) | 27(22) | NS |

OCPS indicates the Oxfordshire Community Stroke Project;
TACI indicates total anterior circulation infarcts
PACI indicates partial anterior circulation infarcts
LACI indicates lacunar infarcts
POCI indicates posterior circulation infarcts
NIH indicates National Institutes of Health.
NS: Not Significant

# ...Neuroradiological evaluation

- ✓ **Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomograpy.**
- ✓ **KA Jobst et al. The Lancet, 1992**
- ✓ **Medial temporal lobe atrophy in stroke patients: relation to pre-existing dementia.**
- ✓ **HHF Pasquier et al. J Neurol Neurosurg Psychiatry,**
- ✓ **1998**
- ✓ **Poststroke Dementia: Influence of Hippocampal Atrophy.**
- ✓ **MA Cordoliani-Mackowiak et al. Arch Neurol, 2003**

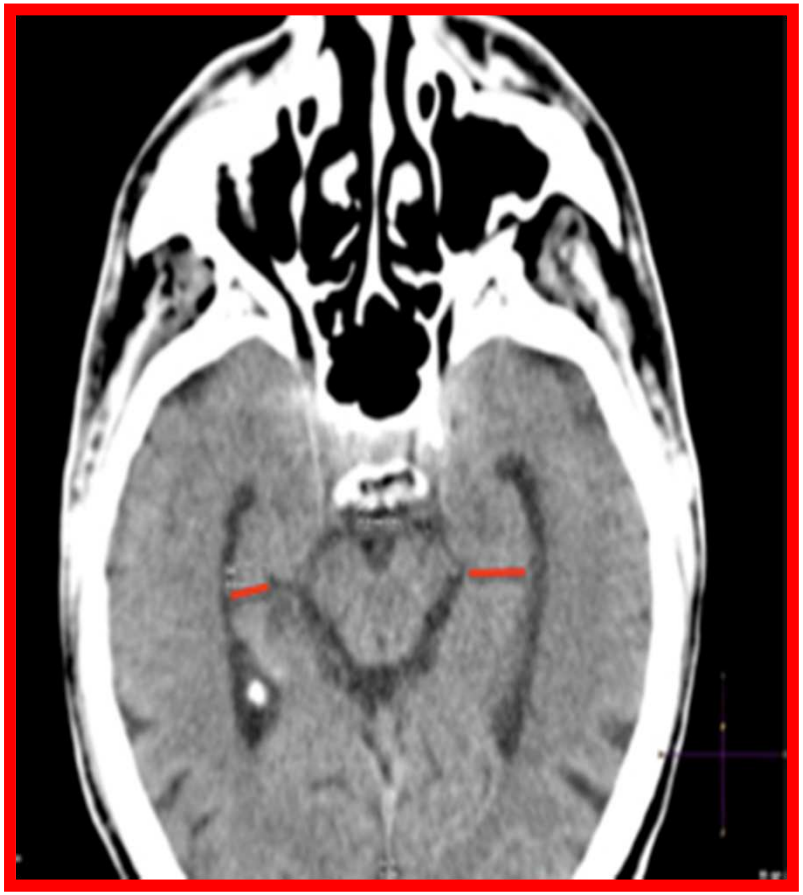

**Table 3.** Neuroradiological characteristics evaluated by CT scan of patients (n = 158) with an acute cerebrovascular event grouped by IQCODE score

| | PSD group (IQCODE ≥3.3; n = 37) | | | PSND group (IQCODE ≤3.3; n = 121) | | | p |
|---|---|---|---|---|---|---|---|
| | mean | SD | n | mean | SD | n | |
| MTL width, mm | 9.2 | 3.2 | | 10.5 | 3.1 | | 0.024 |
| Leukaraiosis | | | 11 (29) | | | 28 (23) | NS |

MTL width was measured as the thickness found on 2-mm contiguous slices on CT scan. Values in parentheses represent percentages. NS = Not significant.

**Table 4.** Logistic regression analysis with PSD as dependent variable

| | OR | 95% CI | p |
|---|---|---|---|
| Age (years) | 1.05 | 1.0–1.1 | 0.05 |
| Female gender | 2.3 | 0.9–5.5 | 0.05 |
| Education (years) | 1.1 | 0.9–1.3 | NS |
| NPI total score | 1.1 | 1.0–1.2 | 0.001 |
| MTLA | 1.1 | 0.9–1.3 | 0.05 |
| Comorbidity (number of diseases) | 1.0 | 0.8–1.2 | NS |
| Previous cerebrovascular events | 1.0 | 0.3–2.9 | NS |

NS = Not significant.

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8. Logistic regression analysis with Barthel Index as dependent variable of patients (N=145) with acute cerebrovascular event grouped by IQCODE score.

| | OR | 95% CI | p |
|---|---|---|---|
| Age, years | 1,0 | 0,9-1,0 | NS |
| Gender, female | 0,9 | 0,4-2,2 | NS |
| Education | 0,1 | 0,7-1,0 | NS |
| IQcode, pre stroke | 0,7 | 0,2-2,3 | NS |
| MTLA | 1,0 | 0,3-2,8 | NS |
| Comorbidity (number of disease) | 1,0 | 0,4-2,6 | NS |

NS= Not significant
MTLA = Medial Temporal Lobe Atrophy considered as thickness not over 11.5 found in 2mm contiguous slice of CT scan.

9. Logistic regression analysis with NIHSS as dependent variable of patients (N=145) with acute cerebrovascular event grouped by IQCODE score.

| | OR | 95% CI | p |
|---|---|---|---|
| Age, years | 0,9 | 0,9-1,0 | NS |
| Gender, female | 0,8 | 0,2-1,4 | NS |
| Education | 0,9 | 0,7-1,0 | NS |
| IQcode, pre stroke | 0,3 | 0,1-0,9 | .040 |
| MTLA | 2,1 | 0,9-5,1 | NS |
| Comorbidity (number of disease) | 0,6 | 0,2-1,5 | NS |

NS= Not significant
MTLA = Medial Temporal Lobe Atrophy considered as thickness not over 11.5 found in 2mm contiguous slice of CT scan.

10. Logistic regression analysis with IADL as dependent variable of patients (N=145) with acute cerebrovascular event grouped by IQCODE score.

| | OR | 95% CI | p |
|---|---|---|---|
| Age, years | 0,9 | 0,9-1,0 | .003 |
| Gender, female | 0,5 | 0,2-1,3 | NS |
| Education | 0,9 | 0,8-1,1 | NS |
| IQcode, pre stroke | 1,4 | 0,5-3,9 | .040 |
| MTLA | 0,9 | 0,4-2,2 | NS |
| Comorbidity (number of disease) | 0,3 | 0,1-0,9 | .046 |

NS= Not significant

MTLA = Medial Temporal Lobe Atrophy considered as thickness not over 11.5 found in 2mm contiguous slice of CT scan.

11. Logistic regression analysis with outcome (death) as dependent variable of patients (N=145) with acute cerebrovascular event grouped by IQCODE score.

| | OR | 95% CI | p |
|---|---|---|---|
| Age, years | 1,6 | 0,9-1,1 | NS |
| Gender, female | 0,6 | 0,1-2,3 | NS |
| Education | 1,0 | 0,8-1,3 | NS |
| IQcode, pre stroke | 5,3 | 1,3-20,7 | .014 |
| MTLA | 1,3 | 0,3-5,9 | NS |
| Comorbidity (number of disease) | 1,8 | 0,3-9,4 | NS |

NS= Not significant
MTLA = Medial Temporal Lobe Atrophy considered as thickness not over 11.5 found in 2mm contiguous slice of CT scan.

***These findings support the hypothesis that cognitive impairment in patients with stroke may not only be a direct consequence of acute cerebrovascular event but also a consequence of underlying neurodegenerative pathology.***

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