Cognition deteriorating after stroke - a major disability

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## RoI

<table>
<thead>
<tr>
<th>Consultancy and speakers honoraria</th>
<th>Grants to University and Royalties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allergan</td>
<td>• European Commission Public Health</td>
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<tr>
<td>• Boehringer</td>
<td>• European Research Foundation FP7</td>
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<td>• Bayer</td>
<td>• Life Science Foundation Krems</td>
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<tr>
<td>• Ever Neuro Pharma</td>
<td>• Ever Neuro Pharma</td>
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<td>• Takeda</td>
<td>• Boehringer, Takeda</td>
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<td>• Pfizer, BMS</td>
<td>• Cambridge Univ Press</td>
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<tr>
<td>• AstraZeneca</td>
<td>• Wiley Blackwell</td>
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<td>• World Stroke Organisation, ESO</td>
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<td>• Europ. Federation of Neurol Societies</td>
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</tbody>
</table>
Post-stroke cognitive impairment

- Stroke
- Vascular dementia
- Alzheimer
- Poststroke cognitive impairment
- Vascular cognitive impairment
## Global burden of disabilities

**PAPF, population-attributable prevalence fractions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>YLD ($10^4$) (contribution to total chronic-disease YLDs [%])</th>
<th>Rank order (by YLD)</th>
<th>PAPF*</th>
<th>Rank order (by PAPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>8.3 (10.2%)</td>
<td>3</td>
<td>25.1%</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>3.5 (4.3%)</td>
<td>8</td>
<td>11.4%</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal diseases</td>
<td>7.2 (8.9%)</td>
<td>4</td>
<td>9.9%†</td>
<td>3</td>
</tr>
<tr>
<td>Neuropsychiatric diseases (other than dementia)</td>
<td>5.9 (7.3%)</td>
<td>6</td>
<td>8.3%</td>
<td>4</td>
</tr>
<tr>
<td>Eye diseases</td>
<td>27.5 (33.9%)</td>
<td>1</td>
<td>6.8%</td>
<td>5</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>1.6 (1.9%)</td>
<td>11</td>
<td>6.5%</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.1 (2.6%)</td>
<td>10</td>
<td>4.1%</td>
<td>7</td>
</tr>
<tr>
<td>Respiratory conditions</td>
<td>4.3 (5.3%)</td>
<td>7</td>
<td>3.3%‡</td>
<td>8</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>9.2 (11.3%)</td>
<td>2</td>
<td>2.2%</td>
<td>9</td>
</tr>
<tr>
<td>Skin conditions</td>
<td>0.5 (0.6%)</td>
<td>15</td>
<td>2.1%</td>
<td>10</td>
</tr>
<tr>
<td>Heart disease</td>
<td>6.1 (7.6%)</td>
<td>5</td>
<td>0.8%§</td>
<td>11</td>
</tr>
<tr>
<td>Oral conditions</td>
<td>2.6 (3.3%)</td>
<td>9</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>0.9 (1.1%)</td>
<td>12</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>0.8 (1.4%)</td>
<td>13</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Genitourinary diseases</td>
<td>0.6 (0.7%)</td>
<td>14</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Total chronic disease burden</td>
<td>81.1 (100%)</td>
<td>..</td>
<td>..</td>
<td>..</td>
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</tbody>
</table>

Post-stroke cognitive impairment

– What is it?
  • Definitions

– How frequent is it?
  • Prevalence rates

– Correlates in the brain
  • Neuropathology

– Indicators, markers
  • Laboratory, associated factors

– Prevention, interventions, cure?
  • Life-style, drugs
Post-stroke cognitive impairment

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Post-stroke cognitive impairment

„Vascular cognitive impairment represents the spectrum of cognitive impairment associated with frank stroke, vascular brain injury, or subclinical disease ranging from the least severe to most severe clinical manifestations“

Gorelick et al. Stroke 2011; 42: 2672-2713
Post-stroke cognitive impairment

- Definitions:
- Lack of consensus on how to operationalize established criteria
- Lack of comparability between studies
- If threshold for inclusion is chosen as 1 SD difference a large number of cases result whereas 2SD difference result in lower numbers
- Plus/minus subjective memory complaints
Post-stroke cognitive impairment

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Post-stroke cognitive impairment

- From the Framingham study a significant decline of - 3.7 points (comparable to – 1.3 SD) in the mean MMSE was found in 74 stroke patients tested within 6 months of stroke onset compared to stroke free controls (no change)

Post-stroke cognitive impairment

- Americans aged 50+ from the Health and Retirement Study 1998-2008
- N=20,567 participants
- N= 1189 strokes, survived
- N= 385 strokes, deceased
- 10 word list delayed recall
- 5-item Likert scale and 16 item version IQ code
- Results: 0.71 SD reduction in similar period than Framingham study

Wang Q et al. Stroke 2012;43:2561-66
Post-stroke cognitive impairment

Trajectory of memory score for stroke survivors (n=1189) vs stroke decedents (n=385) vs stroke-free cohort members (n=15 766) during entire follow-up.

Wang Q et al. Stroke 2012;43:2561-66
Mild cognitive impairment after stroke

- Mild cognitive impairment (no dementia) at 3 months varies from 17% - 66% depending on the criteria used.
- RR 1.5 - 2.1 compared to stroke free controls
- more characterized by executive dysfunction, psychomotor speed slowing than by memory problems
- 41% had executive dysfunction at 3 months poststroke

Patterns of cognitive impairment excluding subjects with preexisting cognitive decline (79 strokes, 87 nonstrokes)

Cognitive decline

- 0.8-2 points decline on MMSE / year
- 10-32% had cognitively declined after 1 year from baseline (3 months post-stroke)
- cognitive decline increases with recurrent stroke
- detection of cognitive decline depends on the cognitive tests used

Cognitive testing in patients with first ischemic stroke with MMSE and MoCA at baseline, after 3 and 6 months

Popovic et al. 2007. J Neurol Sci 257: 185-93
Cognition - test instruments

1) Short neuropsychological test-battery including (20min)
   Can be administrated by non-neuropsychologists
   - Montreal Cognitive Assessment (MOCA)
   - Trail making test A and B
   - Digit-Span forward and backward

2) More detailed test-battery (1-1.5h) for centres with
europsychologists (substudy) to describe in detail the
neuropsychological profile of the participants
   includes: tests for alertness, reaction time, verbal fluency,
verbal memory, visual spatial perception, visual memory...
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Post-stroke cognitive impairment

- **Neuropathological changes in VaD/VCI:**
  - Lacunar infarcts
  - Microinfarcts
  - White matter changes
  - Hippocampal atrophy and sclerosis
  - Overlap with AD pathology
    - Amyloid plaques
    - Neurofibrillary tangles

Kalaria RN Stroke 2012; 43:2526-34
Ageing related Vascular disease
(hypertension, diabetes, atherosclerosis)

Cerebral Microangiopathy
Arteriolosclerosis

Amyloid associated Microangiopathy
Arteriolosclerosis

Cell-molecular events in NV unit

↑ eNOS activity
Cytokines / Growth factors

EC activation

↑ BBB leakiness

↑ Perivascular macrophages (CD68+ cells)
Perivascular oedema

↑ Astrogliosis / ↑ ECM

Progression

Parenchymal changes

GM lacunes and microinfarcts
↓ Vascular tone
↑ PVS

WM lacunes and microinfarcts
↑ Hypoxic state
(HIF1α, VEGF)
↓ Oligodendrocytes

CAA related bleeds and microinfarcts
↑ Aβ accumulation,
↓ SMC, wall rupture

Kalaria RN Stroke 2012;
43:2526-34
Post-stroke cognitive impairment

Neuronal volumes in hippocampal subregions CA1, CA2, and entorhinal cortex Layer V (ECV).

All PS: all poststroke subjects; PSND: poststroke nondemented; PSD: delayed poststroke dementia; VaD: vascular dementia; mixed: mixed Alzheimer, and vascular dementia; AD: Alzheimer disease.

Asterisks indicate significantly different to controls (black) or PSND (gray; P<0.05).
Dots indicate trend to significance (P<0.01).

Gemmell E et al. Stroke 2012;43:808-814
Post-stroke cognitive impairment

• „These findings provide evidence of a vascular basis for hippocampal neurodegeneration in delayed PSD and VaD“
Difference in MTL activation between healthy controls and stroke patients

Risk factors for post-stroke cognitive impairment – delayed onset

1. Not the infarct itself is the cause but the disturbance of cross talk between endothelium, astrocytes, and neurons

2. Tertiary (epigenetic) mechanisms play a role resulting in degeneration of brain structures remote from the infarct
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Patient-related variables associated with an increased risk of dementia after stroke

increasing age, low education level, dependency before stroke, pre-stroke cognitive decline without dementia, diabetes mellitus, atrial fibrillation, myocardial infarction, epileptic seizures, sepsis, cardiac arrhythmias, congestive heart failure, silent cerebral infarcts, global and medial temporal lobe atrophy, and white matter changes.

Stroke-related variables associated with an increased risk of dementia after stroke severity, volume, location, and recurrence of stroke. Dementia in stroke patients may be due to vascular lesions, Alzheimer pathology, or summation of these lesions.

Post-stroke cognitive impairment

- Biomarkers:
- N=368 consecutive stroke patients (mild to moderate): high level of C-reactive protein and elevated ESR was associated with worse performance in cognitive tests, particularly memory scores.
- In addition, ESR values correlated with hippocampal atrophy

Kliper et al. Stroke 2013
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Post-stroke cognitive impairment

- Pharmacological treatment:
  - Donezepil
  - Galantamine
  - Rivastigmine
  - Memantine
- Modest benefit, if any, on standard cognitive measures. Small samples of executive dysfunctions, inconsistent benefit in global and daily function, not distinguishable from Alzheimer disease

Gorelick et al. Stroke 2011; 42: 2672-2713
ASPIS - Austrian Polyintervention Study to Prevent Cognitive Decline after Ischemic Stroke

Interventions

- Dietary counselling individually & in groups: diary, feedback, motivation, recommendations & strategies for weight reduction and diet changes
- Goal: moderate or vigorous activity 3-5x/week. Individually adapted strength & balance training; aerobic exercises, diary, feedback, motivation
- Goal: 75% of measurements <140/90 mmHg. (diabetes: 130/85 mmHg) self-monitoring, diary at least 2x/week
- According to ESO guidelines motivation to increase compliance, regular calls by study doctors
- Strategies, techniques, home training material

Post-stroke cognitive impairment

- Time-delayed onset of cognitive impairment following stroke needs to be better understood in its dynamic properties and molecular development.
- Prestroke markers (epigenetic, imaging and laboratory) need to be studied.
- Most likely, multimodal interventions aiming at early restoration and recovery stand the best chance of becoming an effective preventive strategy.