POST STROKE DEMENTIA: DIAGNOSIS & INTERVENTION

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Barrow Neurological Institute Stroke Symposium
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Overview

• Stroke & Cognitive Impairment
  • The VCI continuum & terminology
• The presentation & diagnosis of PSD
  • Where & how much?
  • Complications of diagnosis
• Neuropsychological evaluation of PSD
  • Cognition, Mood, & Functional ability
• Intervention
  • Before & after stroke
  • Future directions: DMTs
Stroke is a leading cause of disability

• Among adults age 45–69 years, heart disease and stroke are the leading causes of death and lost disability-adjusted life years (DALYs) worldwide (Strong et al., Lancet Neurol, 2007)
Types of Stroke

Ischemic strokes:
- Clot causing embolic stroke
- Plaque causing thrombotic stroke

Hemorrhagic strokes:
- Burst aneurysm causing subarachnoid hemorrhage
- Torn artery causing intracerebral hemorrhage

Image from HealthCentral.com
Why cognitive impairment after stroke matters

• Research has historically focused on physical disability following stroke, but cognitive impairment affects daily functioning, quality of life, and return to work to an equal degree
• Stroke survivors are at risk for cognitive impairment due to overlapping factors
  • Acute tissue damage
  • Cognitive decline associated with age
  • Comorbid vascular risk factors
  • Pre-existing subclinical vulnerability (e.g. amyloidopathy)
• Physical impairments often improve to some degree after stroke; however cognitive impairments often progressively worsen

Mijajlović et al. BMC Medicine (2017)
Stroke Survival

- Risk factors for stroke are increasingly prevalent
  - Hypertension
  - Atherosclerosis
  - Hyperlipidemia
  - Type II diabetes
  - Obesity

- Meanwhile, death from stroke is decreasing
  - 40.6 per 100,000 in 2008
  - You are 75% less likely to die of stroke now compared to 1950 (Towfighi et al. 2011).
USA
31% with dementia 3 months after stroke; 19.3% with dementia at 10 years follow-up

Norway
57%, 1 year after stroke

Britain
24%, 3 months after stroke; 22%, annually

Sweden
39%, 1 month after stroke

Netherlands
82%, 1 month after stroke; 69%, 6 months after stroke; 58%, 1 year after stroke.

France
47.3%, 3 months after stroke

Changsha
41.8%, 3 months after stroke

Chongqing
37.1%, 3 months after stroke

India
20%, annually

Caribbean
58.9%, 5 years after stroke

Singapore
44%, 3 months after stroke; 33%, 1 year follow-up

Australia
58%, 3 or 6 months after stroke; 50%, 1 year after stroke

From Sun et al., *Ann Transl Med* (2014)
Stroke, Vascular Cognitive Impairment, & Dementia

- PSCI/PSD is diagnosed when cognitive impairment first emerges after a stroke.
- This is often difficult to ascertain since VCI/VaD may be present but unrecognized prior to stroke.
- Stroke, especially ischemic stroke, often occurs along a continuum of VCI and includes risk factors which may be pre-existing.
The VCI continuum & stroke

The VCI continuum is a spectrum that ranges from normal function to vascular dementia. It includes the following stages:

- **Normal Function**
  - Normal Cognition
  - Functional Independence

- **Vascular Cognitive Impairment**
  - Cognitive Decline
  - Preserved Independence

- **Vascular Dementia**
  - Cognitive Decline
  - Loss of Independence

**Factors** that contribute to the progression of VCI include:

- **Vascular Risk Factors**
- **Comorbid Conditions**
- **Age**

**Strokes** play a significant role in transitioning from normal function to vascular dementia.

**Cognitive Reserve** is a concept that describes the brain's ability to compensate for damage or disease, potentially delaying the onset of cognitive decline.
Complications of diagnosis

• Established diagnostic criteria for dementia may not be suitable to stroke populations
• As in other forms of dementia, PSD vs. PSCI is based on limitations in ADLs; however, physical impairments following stroke may impede assessment of changes in ADLs specifically related to cognitive problems
• Definitions of dementia emphasize multi-domain cognitive impairment and memory deficits; however, in stroke, it is possible to have disabling cognitive problems but retain memory
• Stroke patients are typically older and may have (diagnosed or undiagnosed) pre-stroke cognitive decline, precluding a diagnosis of PSD
• Moreover, tissue damage continues to evolve after stroke
Post Stroke Cognitive Impairment & Dementia

Normal Function  Vascular Cognitive Impairment  Vascular Dementia

- Normal Cognition
- Functional Independence
- Cognitive Decline
- Preserved Independence
- Cognitive Decline
- Loss of Independence

Stroke

Evolution of vascular lesions

Post Stroke Cognitive Impairment  Post Stroke Dementia

Aβ plaque  Neuroinflammation  Neurotransmitter dysfunction  Brain atrophy

Vascular Risk Factors  Comorbid Conditions  Age
STROKE

- Cerebral microbleeds
- Hippocampal atrophy
- White matter lesions
- Oxidative stress
- Chronic Hypoperfusion
- Amyloidopathy
- CNS inflammation
- Mitochondrial dysfunction
- Dysfunctional neurotransmitter systems
- Disturbed lipid metabolism
Factors contributing to the presentation of PSD

- Location of the stroke → type/s of impairment
- Volume of the stroke → degree of impairment
- Degree of related neuronal or WM damage
- Presence of other cerebral pathology (e.g. Aβ or CAA)
- Presence of pre-existing cognitive impairment
MCA strokes can affect the frontal, temporal, & parietal lobes

ICA strokes can affect the frontal, temporal, parietal, or occipital lobes, as well as the basal ganglia & thalamus

ACA & ACoA strokes can affect the frontal & possibly the parietal lobes

PCA strokes can affect the parietal lobes, thalamus, brain stem, & cranial nerves associated with eye movement

Location, location, location

Adapted from BNI Stroke Education Manual, 2015
Left and Right Hemispheres

Right Brain vs Left Brain

Effects of left hemisphere strokes.
- Weakness or paralysis on the right side of your body.
- Difficulties with understanding or expressing written language or spoken language (aphasia).
- Trouble learning or remembering new verbal information such as conversations.
- Difficulty understanding where objects are in relation to your body.
- Sensory changes on the right side of your body, such as numbness or hypersensitivity.
- May have difficulty seeing or noticing objects on the right side.

Effects of right hemisphere strokes.
- Weakness or paralysis on the left side of your body.
- Sensory changes on the right side of your body, such as numbness or hypersensitivity.
- May have difficulty seeing or noticing objects on the left side.
- Difficulty understanding where objects are in relation to your body.
- Difficulty with visual memory such as pathfinding.
- Difficulty organizing visual information accurately.
- Difficulty expressing emotions effectively.
- Issues with forgetting or ignoring objects or people on your left side. This is also known as neglect.
- Can be apathetic or amotivated.
- May act impulsively.
- Poor decision making or lack of insight into your own limitations leading to safety concerns.
- Problems with short-term memory, judgment.
Location: Strategic Infarcts

- A single small infarct may cause severe deficits when located in a strategic brain region
- Most strategic locations integrate into larger networks or cortical-subcortical loops

From Ji et al. *Brain Neurorehabil.* 2014
Volume: Multi-infarct Dementia

- Larger infarct volumes &/or a higher number of smaller infarcts are associated with worse cognition & higher dementia risk (Schneider et al. *Neurology*. 2003)
White Matter Lesions: Subcortical Ischemic VaD

• Microvascular ischemic disease is associated with lacunar infarct & both are associated with risk of PSD (Pantoni L., Lancet Neurol. 2010)

Pre-existing Pathology: AD

- Vascular risk factors may lead to hippocampal atrophy & raise risk of stroke
- Brain infarcts are associated with smaller hippocampi; both are independently associated with memory decline (Blum et al., Neurology 2012)
Cerebral Pathology: Cerebral Angiopathy

• Accumulation of cerebral amyloid-β (Aβ) in cortical vessels of the brain
• Along with AD it is a common cerebral amyloid deposition disease
## Summary: Diagnosis of PSD

<table>
<thead>
<tr>
<th>Imaging</th>
<th>CT scan</th>
<th>Identifies strokes &amp; hemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT angiography</td>
<td></td>
<td>Identifies aneurysms, AVMs, &amp; other vessel abnormalities</td>
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<tr>
<td>MRI angiography</td>
<td></td>
<td></td>
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<tr>
<td>Angiogram</td>
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<tr>
<td>Echocardiogram</td>
<td></td>
<td>Identifies blood clots &amp; assesses blood flow through the heart</td>
</tr>
<tr>
<td>Lab work</td>
<td>Blood tests</td>
<td>Identifies vascular risk factors (e.g., HLD, DM2, clotting disorder)</td>
</tr>
<tr>
<td>Neuropsychological evaluation</td>
<td>Cognitive Tests</td>
<td>Identifies cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Functional Tests</td>
<td>Identifies functional impairment</td>
</tr>
</tbody>
</table>
Summary: Complications of PSD Diagnosis

- Failure to exclude individuals with undiagnosed cognitive decline prior to stroke
- Overlap of PSD/VaD and other dementias (e.g. AD)
- Overlap of PSD & post stroke mood disorder
- Heterogeneity of test batteries
  - Beside testing (e.g. MMSE; MoCA) vs Comprehensive NP testing
- Heterogeneity of samples
  - National differences
  - Ethnic differences
  - Genetic differences
  - Age/education differences
  - Duration since stroke
Neuropsychological evaluation after stroke
Mini-Mental State Examination (MMSE)

**Instructions:** Ask the questions in the order listed. Score one point for each correct response within each question or activity.

### Maximum Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Patient's Score</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td></td>
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</tbody>
</table>

1. **What is the year? Season? Date? Day of the week? Month?**
2. **Where are we now? State? County? Township? Hospital? Floor?**
3. **I would like you to count backward from 100 by sevens.** (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: “Spell WORLD backwards.” (D-L-R-O-W)
4. **Earlier I told you the names of three things. Can you tell me what those were?**
5. **Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.**
6. **Repeat the phrase: “No ifs, ands, or buts.”**
7. **Take the paper in your right hand, fold it in half, and put it on the floor.** (The examiner gives the patient a piece of blank paper.)
8. **“Please read this and do what it says.” (Written instruction is “Close your eyes.”)**
9. **“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)**
10. **“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)**
“Set the time to 2:45”

Alzheimer’s disease
Spatial distortions & errors of impaired semantic knowledge

Vascular dementia
Planning errors, perseverations, & stimulus-bound responses

Frontotemporal lobar dementia
Planning errors, perseverations, & stimulus-bound responses

Lewy body dementia
Gross spatial distortions and perseverations

Luigi & Guido, J of Alz Dis, 2016
### Memory
Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th></th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
<th>No points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trial</td>
<td></td>
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<tr>
<td>2nd trial</td>
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### Attention
Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order.

- 21854

Subject has to repeat them in the backward order.

- 742

Read list of letters. The subject must tap with his hand at each letter. No points if ≥ 2 errors.

- FbAcmnaajKlbafakdeAAajAMoFaAb

Serial 7 subtraction starting at 100

- 93 86 79 72 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

- 3/3
**Fluency / Name maximum number of words in one minute that begin with the letter F**

<table>
<thead>
<tr>
<th>ABSTRACTION</th>
<th>Similarity between e.g. banana - orange = fruit</th>
<th>train - bicycle</th>
<th>watch - ruler</th>
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</table>

**DELAYED RECALL**

Has to recall words **WITH NO CUE**

<table>
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<tr>
<th>FACE</th>
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</tbody>
</table>

Optional

- Category cue
- Multiple choice cue

**ORIENTATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Month</th>
<th>Year</th>
<th>Day</th>
<th>Place</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
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www.mocatest.org  Normal ≥26 / 30  TOTAL

Administered by: ____________________________

Add 1 point if ≤ 12 yr edu
<table>
<thead>
<tr>
<th>A Typical Neuropsychological Test Battery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intellectual Ability</strong></td>
</tr>
<tr>
<td>• Estimated premorbid FSIQ (demographics + word reading)</td>
</tr>
<tr>
<td>• Verbal abilities vs spatial abilities (lateralization)</td>
</tr>
<tr>
<td>• Abstract vs concrete response style</td>
</tr>
<tr>
<td><strong>Attention &amp; Working Memory</strong></td>
</tr>
<tr>
<td>• Attention span (digits forward)</td>
</tr>
<tr>
<td>• Divided &amp; Complex attention (working memory)</td>
</tr>
<tr>
<td>• Sustained attention</td>
</tr>
<tr>
<td><strong>Processing Speed</strong></td>
</tr>
<tr>
<td>• Target cancellation, Visual scanning &amp; sequencing</td>
</tr>
<tr>
<td>• Motor speed</td>
</tr>
<tr>
<td>• Oral vs manual speed</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
</tr>
<tr>
<td>• Verbal fluency: semantic vs phonemic retrieval</td>
</tr>
<tr>
<td>• Verbal vs Design fluency (lateralization)</td>
</tr>
<tr>
<td>• Card sorting: deductive reasoning</td>
</tr>
<tr>
<td><strong>Language &amp; Visuospatial Skills</strong></td>
</tr>
<tr>
<td>• Naming: word finding ability</td>
</tr>
<tr>
<td>• Visuoconstruction: visual defects, organizational strategies</td>
</tr>
<tr>
<td><strong>Learning &amp; Memory</strong></td>
</tr>
<tr>
<td>• Verbal vs nonverbal</td>
</tr>
<tr>
<td>• Encoding vs retrieval vs recognition</td>
</tr>
<tr>
<td><strong>Mood &amp; Functional Ability</strong></td>
</tr>
<tr>
<td>• Mood disorder</td>
</tr>
<tr>
<td>• Functional independence</td>
</tr>
</tbody>
</table>
Mood Disorder

• In a recent meta-analysis of post-stroke MDD, the point prevalence of depression was 17.7% (95% CI = 15.6% to 20.0%) (Mitchell et al., *Gen Hosp Psychiatry* 2017)
  • 15.8% in outpatient settings and 20.0% in rehabilitation settings
  • An additional 3.1% had dysthymia and 6.9% had adjustment disorder

• The relative risk of MDD was 50% higher and the relative risk of any depressive disorder was 26% higher following left (dominant) hemisphere stroke.
  • The relative risk of any depressive disorder was 50% higher following aphasia

• Family history of mood disorder and personal history of prior mood disorder also increased risk of PSD
Measures of Functional Independence

- Texas Functional Living Scale (TFLS): Requires that the patient demonstrate practical skills necessary for IADLs
- IADLs questionnaire: Best used as a caregiver report; provides a valuable second opinion regarding functional independence
- Test of Practical Judgment (TOP-J): Measures subjective decision-making in a variety of circumstances
Intervention

Prevention

Cure
Before Stroke: Management of Vascular Risk Factors

• Prevent the development of vascular risk factors
  • Patient education
  • Diet & exercise
  • Consultation with nutritionists
  • Eliminate tobacco use
  • Minimize alcohol use

• Adequately manage risk factors that emerge
  • Same as above, with the addition of medication
    • Anti-hypertensives
    • Anti-platelet therapy
    • Statins
    • Metformin/insulin
# After stroke: Rehab therapies

## Inpatient
- **Acute care**: 24-hour hospital based medical care; therapies as ordered by physician
- **Inpatient Rehab**: 24-hour care with at least 3 hours of therapy per day
- **Skilled Nursing**: daily nursing care, less demanding therapy but longer stay
- **Long-term Care**: long-term nursing care with limited rehab

## Outpatient
- **Outpatient Rehab**: 1-2 hour sessions several times a week
- **Home Health Care**: Nursing + 1-2 hour sessions several times a week
- **Adult Day Care**: Nursing, no therapies provided
- **Group Home**: Limited nursing, therapies as ordered by physician
- **Assisted Living**: Limited nursing, no therapies

Adapted from BNI Stroke Education Manual, 2015
Holistic Neuro-Rehabilitation

- Multimodal treatment approach
- PT, OT, Speech & therapies
  - Adjuvant therapies such as Botox
- Education on future stroke prevention
- Training in compensatory strategies
- Support groups for mood and adjustment disorders
BNI Center for Transitional Neuro-Rehabilitation

- Transitional Neuro-rehabilitation
  - Helps individuals transition back to work, school, or the community
  - Team helps patient set personal goals & build skills important to their unique circumstances
- Programs offered at the BNI Center for Transitional Neuro-rehabilitation (CTN)
  - Home Independence Program
  - Work Reentry Program
  - School Reentry Program
  - Transitional Program
  - Refresher Program
  - Fast-Track Program
Supplements

- Citicoline (cytidine-5’-diphosphocholine)
  - Some evidence suggests citicoline improves post-stroke cognition compared to placebo (Cotroneo et al., Clin Interv Aging 2013)

- Ginkgo biloba
  - Studies of GB have suggested improvement in cognitive function and IADLs in AD & VaD after 24+ weeks of treatment (Ihl et al., Pharmacopsychiatry 2012; and Zhang et al. Asian Pac J Trop Med 2012).
Non-pharmacological Treatments

- Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)
  - Several studies have shown that TMS might improve cognitive performance.
  - In AD, effects are likely mediated by compensatory mechanisms supporting residual abilities; similar plastic phenomena are invoked in VaD.
Disease Modifying Therapies

• A disease modifying therapy aims to change the natural course of an illness, usually a chronic disease, e.g. neurodegenerative & neuroinflammatory diseases
• Like remitting neurodegenerative diseases, PSCI and VCI:
  • Have a preclinical phase
  • Have acute episodes with a gradual evolution of functional deficits
  • In older patients, VCI or PSCI are often combined with AD-type pathology that contributes to the evolution and provides other targets for a disease-modifying strategy

Bordet et al. *BMC Medicine* 2017
Targets of DMTs

- Endothelial & BBB dysfunction
- Reduce Neuronal death & Increase cerebral plasticity
- Impaired neurotransmission

Inflammation

- Metformin
  - Anti-hypertensives
  - Anti-inflammatories

Neurotrophic factors

- Cerebrolysin
  - Actovegin
  - Ginko biloba extract

AChEIs & NMDAR antagonists

- Donepezil
  - Memantine

Bordet et al. *BMC Medicine* 2017
Potential pitfalls of DMTs

- Addressing the wrong target
- Interfering with the target pathology outside the window of opportunity
- Patients lacking the target pathology
- Choosing insensitive outcomes
In conclusion

• Vascular risk factors are increasing & survival after stroke is improving, leading to increased prevalence of PSCI and PSD
• Especially in older adults, PSCI and PSD often occur in conjunction with pre-existing vascular risk factors and/or occult neurodegenerative disease, complicating diagnosis
• Comprehensive neuropsychological assessment can help determine degree of impairment, identify other possible etiological contributors, and provide treatment recommendations
• Typical interventions include controlling risk factors to prevent future stroke & rehab therapies
• DMTs present a novel pathway for intervention
Thank you for your attention.