PTSD after Stroke

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- Stroke is a stressful, life-threatening experience. The threat remains even after the acute stroke is over.

- Stroke is a sudden and unanticipated event over which the victim has no control.

- In addition to the brain damage, the patient’s sense of wholeness and safety might be shattered, leaving a lasting sense of vulnerability.
Stroke as a traumatic event and a risk factor for posttraumatic stress reaction

- The psychological symptoms:
  - Direct consequence of focal lesions,
  - Or indirect consequence of psychological stress.

- According to DSM-IV-TR, PTSD develops “following exposure to an extreme traumatic stressor involving direct personal experience of an event that involves actual or threatened death or serious injury”.

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DSM-IV-TR criteria for PTSD

1. History of exposure to a traumatic event meeting two criteria and symptoms from each of 3 symptom clusters:
   2. Intrusive recollections
   3. Avoidant/numbing symptoms
   4. Hyper-arousal symptoms.
5. Duration of symptoms (more than one month)
6. Functioning.
Any life threatening experience accompanied by an emotional response (including intense fear, helplessness or horror) may lead to various PTSD-like symptoms, involving intrusions of traumatic memories, symptoms of avoidance, emotional numbing, and hyperarousal.

previous case record series that PTSD-like symptoms can result due to stroke and even TIA.
Cognitive Deficits

- Attention and memory deficits are seen as core to PTSD and are incorporated as part of the DSM-IV diagnostic criteria.

- When neuropsychological deficits accompany PTSD, they are likely MILD and in the areas of:
  - Attention
  - Memory impairment

- Deficits typically do not reflect basic language, visual recognition, or fine motor dysfunction.
Brain Regions

- Known to be dysregulated in individuals with PTSD:
  - Prefrontal cortex
  - Amygdala
  - Hippocampus
  - Dorsal raphe nucleus
Hippocampus

- A medial temporal lobe structure
- Involved in memory processes
- Severe stressors and high levels of stress-related hormones associated with
  - Memory impairment
  - Abnormal hippocampal functioning (decreased communication w/ amygdala).
Stress and cognitive decline

- Exposure to physical or psychological threat triggers the release of a cascade of hormones: CRF, adrenocorticotropic hormone, and glucocorticoids from the HPA axis.
- Hippocampal atrophy has been described in Depression, PTSD, AD.
Does stress damage the brain?

- Studies PTSD demonstrated significantly reduced hippocampal volumes in PTSD vs. controls.
- Stress and the GCs secreted by the adrenal steroids during stress can damage the hippocampus.
- This damage includes alteration of pyramidal cell morphology, pyramidal cell death and suppression of granule cells.
Veterans with PTSD had smaller hippocampal volumes compared to co-twins of veterans without PTSD (trauma unexposed twin study).

PTSD symptom severity inversely correlated with hippocampal volume in both the exposed and unexposed identical co-twin.

No consensus?

- The finding of smaller hippocampal volumes in PTSD was not replicated.
- No significant decline in hippocampal volumes over time (2y FU) in PTSD.
- Smaller hippocampal volumes may occur in only some subgroups, or secondary to comorbid conditions, or hippocampal pathology subtle and not readily detectable by morphometric MRI procedures.
High levels of GCs released under stress have been associated with deficits in new learning:

- Cortisone treatment of healthy humans at acute-stress levels impaired retrieval of declarative long-term memory.
- Retrieval of declarative memory may well occur under conditions of elevated GC levels.

de Quervain, Nat Neurosci 2000

Fig. 1. Effects of administering a single oral dose of cortisone (25 mg) on distinct memory phases. Cortisone administered 1 h before the delayed retention test (24 h after word presentation) significantly impaired the number of words freely recalled. Cortisone administration one h before or immediately after word presentation did not impair delayed free recall. *p < 0.005 as compared with placebo treatment. Error bars represent s.e.; n = 12 per group.
What about other serious medical conditions?

- PTSD-like manifestations have been also described after other medical conditions and treatment.
- Most studies have focused on cancer, MI or traumatic brain injury.
- Probably, stroke is not more associated with PTSD symptoms than any other serious medical condition.
So - What is stress?

- A state of threatened homeostasis provoked by a psychological, environmental or physiological stressor.

- Two neuroendocrine systems are involve with the stress hormones increase:
  1. The **sympathetic adreno-medullary (SAM)** system with the secretion of the two catecholamines: epinephrine and norepinephrine
  2. The **hypothalamic pituitary adrenocortical (HPA)** system with the secretion of cortisol.
Stress

- Release of chemical mediators: norepinephrine, serotonin, acetylcholine activate cells in the hypothalamus.
- These cells produce CRF, which enters the hypothalamus to form ACTH.
- ACTH stimulates the adrenal cortex to produce corticosteroids, the major stress hormones.
Cholinergic enzymes

The cholinergic enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), both hydrolyze and inactivate ACh.

Stress and the cholinergic system

- Acute stress elicits a transient increase of ACh and a phase of enhanced neuronal excitability.
- Modulated cholinergic gene expression acts to reduce available ACh and depress cholinergic neurotransmission following stress.

Acute stress induces changes in cholinergic genes expression

RT-PCR was performed on RNA extracts from cortex of control mice and stressed mice.

Stress induces AChE expression

Reduced ACh availability

It was previously shown that transient increases and delayed reduction in ACh levels accompany stress (Imperato et al 1991).
Low AChE activities predicted post stroke survival

- Lower AChE activities in stroke patients than controls (p=0.004)

- 12 months non-survivors presented lower AChE and during the acute phase of stroke compared to 12 month survivors (p =0.036).

Ben Assayag, Shenhar-Tsarfaty et al. Molecular Medicine 2010
The BChE K variant associates with higher risk for stroke

Carriers of the unstable BChE-K variant were more abundant among patients than controls ($\chi^2 = 8.8$, $p=0.012$). Carriers of the unstable K variant showed reduced activity ($p<0.001$).

Ben Assayag, Shenhar-Tsarfaty et al. Molecular Medicine 2010
Hypothesis

- Chronic brain exposure to physical/psychological threats → HPA axis over-activation → neuronal damage, hippocampal atrophy → cognitive impairment.
- The “stressogenic vulnerable patient” is prone to develop anxiety symptoms and cognitive impairment.
- Measure stress response via biochemical and psychological methods to create an individual stress coping profile.
- Profiles might serve as predictors for subsequent cognitive function in stroke victims.
The TABASCO study is an ongoing, prospective study designed to evaluate the association between markers measured during the acute phase of ischemic stroke and its long-term outcome:

- Cognitive deterioration
- Affective changes
- Vascular events
- Falls
- Functional outcome
- Mortality

**Variables and Measures:**

- Demographic variables
- Inflammatory profile
- Biochemical markers
- Neuropsychological measures
- Genetic markers
- Neuro-imaging

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Preliminary results from the TABASCO (Tel Aviv Brain Acute Stroke Cohort) study
Among 246 first ever mild ischemic stroke/TIA patients 54 (22%) patients developed significant PTSD symptoms on the PTSD inventory (>30) 6M after the acute stroke. PTSD-like syndrome was independent of neurologic deficit.

PTSD symptoms inversely correlated with the cognitive scores: MoCA, global computerized score and executive function scores (p<0.001, p=0.001, p=0.011, respectively).
Cortisol levels and hippocampal volume

- Bedtime saliva cortisol inversely correlated with hippocampal volume (p=0.023 and p=0.006 for Lt. and Rt. Hippocampi).
- PTSD symptoms 6 months after the event inversely correlated with amygdala and Rt. hippocampal volume (p=0.006, p=0.003 for Lt. and Rt. amygdala, p=0.036 for Rt. hippocampus).
Hippocampal volume by tertiles of bedtime cortisol

In some of the patients the smaller hippocampi might reflect prolonged exposure to neurotoxic levels of cortisol during chronic stress or past stressogenic events.
Cortisol levels and cognition

We observed inverse correlation between bedtime saliva cortisol levels during the event and the patients' 6 months executive function scores ($r=-0.31$, $p=0.002$).
Longitudinal changes in cognitive scores

- At baseline, no difference in cognitive or neurological scores.
- As expected, 6 months post-stroke both groups showed significant improvements in their MoCA scores. Patients with larger hippocampi demonstrated significantly larger improvement.
- 12 months thereafter, patients with larger hippocampi significantly improved compared to the 6 month evaluation (p<0.001). The smaller hippocampal group demonstrated no change.

The results suggest that stroke patients presenting with smaller hippocampi may be at higher risk for cognitive decline.
Patients with higher cortisol presented similar psychological stress during the acute event to patients with lower cortisol. Yet, 12 months later their PSS was significantly higher than those who had lower cortisol, suggesting a "stressogenic pattern"
Individuals in the severe PTSD-like group presented lower cognitive scores 6 months after the event compared to those in the non-PTSD-like group.
Stress and the cholinergic system: The butyrylcholinesterase (BChE K) variant and 6 months PTSD symptomatology

- The observed genotype distribution of the BChE-K is 61.9% UU, 34.7% UK and 3.4% KK variants.

- Carriers of the BChE-K variant showed higher PTSD scores 6 months after the event (p=0.002).
Conclusions

- A potential mechanism by which stress can alter the hippocampus and the long-term outcome post stroke.
- The smaller hippocampi might be the result of prolonged exposure to neurotoxic levels of cortisol secreted during chronic stress, and/or genetic vulnerability to the neurotoxicity of stress.
- The early identification of stroke patients who are at high risk for post-traumatic stress symptoms is important.
- Studies of trauma survivors suggest that immediate intervention may be effective in averting the chronicization of the stress disorder.
How about some good news?

If excessive stress-induced cortisol is bad for the aging brain, what should be done?

• Regular physical exercise reduces the cortisol response to stress.

• Lean body mass is associated with reduced cortisol response to stress.

• Keep a daily routine that is predictable but interesting (easier said than done).
• The “stress-vulnerable” patients would benefit from early interventions (such as psychotherapy, psychopharmacological medications, changes in environment or teaching stress-coping strategies).

• We need to develop a novel and urgently necessary paradigm in rehabilitation approach for stroke patients.
2. Prophylaxe-Seminar des KNS

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Thank you!

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