PTSD and Dementia: is there a connection?

Prof Y Barak, MD, MHA.
Abarbanel MHC and the Sackler School of Medicine, Tel-Aviv university, Israel.
More than twenty years ago in a relatively obscure Polish journal, Doctor Ryn of the Department of Social Pathology, Medical Academy, Krakow, Poland published his intensive observations on former prisoners of the Nazi concentration camps.

He reported being able to distinguish characteristic phases during the life-cycle in the evolution of their sufferings emphasizing in late life premature aging, and an organic phase.

He concluded this moving clinical testimonial by writing: "...the camp stress has left in human nature traces so painful that they cannot disappear when the generation of former prisoners is gone" (Ryn, 1990).

History
However, the "premature aging" and "organic phase" late in the course of PTSD were not noted or extensively researched.

It was only recently new research showing that PTSD significantly increases the risk for dementia in later life has come to light.
• Yaffe and colleagues working at UCSF, San Francisco, in the first study to show this association, found that older veterans with PTSD had nearly a 2-fold increased risk for dementia compared with their counterparts without PTSD.

• Their findings show that veterans with PTSD developed new cases of dementia at a rate of 10.6% over 7 years of follow-up, versus 6.6% of those without PTSD.

• In addition, PTSD did not appear to be associated with a particular dementia type but rather had an “across-the-board effect” for all dementias, including vascular dementia and Alzheimer's disease.
To examine the question of whether PTSD might carry an increased risk for dementia, these researchers used data from the Department of Veterans Affairs National Patient Care Database. The retrospective cohort study included 181,093 veterans aged 55 years and older without dementia at baseline and compared rates of newly diagnosed dementia or cognitive impairment in 53,155 subjects with a diagnosis of PTSD and 127,938 subjects without PTSD. Subjects' mean age at baseline was 68.8 years, and the great majority were male. After adjustment for demographics and medical and psychiatric comorbidities, PTSD patients were still nearly twice as likely to develop incident dementia (HR, 1.77; 95% CI, 1.7 – 1.9).

The results were similar when investigators excluded subjects with a history of traumatic brain injury, substance abuse, or depression.

**Yaffe et al, Arch Gen Psychiatry. 2010**
• It is established that persons who have a history of severe and prolonged trauma, such as exposure to war genocide or combat, captivity and torture, may continue to experience physical and mental health problems as they age.

• Given the neurochemical, neurological, and neuropsychological impairments that appear to accompany PTSD, several investigators have suggested that severe and prolonged trauma or a history of PTSD may place aging individuals at increased risk of cognitive decline and inception of dementia (Sapolsky, 2000).

• It has been observed that former prisoners of war and survivors of Nazi concentration camps may demonstrate concomitant neuropsychological disorders decades after the traumatic experience, with a possible increase in rate of cognitive decline and risk of dementia (Vasterling et al, 1998; Vasterling et al, 2002; Golier et al, 2002).

• Many investigators have documented deficits in memory performance in trauma survivors with PTSD although a great variability across studies and questions regarding the associations between memory impairments and trauma exposure remain unanswered.
The Traumatic Stress Studies Program, Mount Sinai School of Medicine, New York, research group has reported memory changes in PTSD in late life not previously observed in young trauma survivors.

Both Holocaust survivors and elderly combat veterans show reductions in performance on performance and total learning in contrast to younger participants with PTSD.

The similarity in deficits between combat veterans and Holocaust survivors taken together with a more pronounced negative correlation between age and learning deficits in Holocaust survivors with PTSD may be viewed as supporting evidence for an accelerated age-related decline in aging trauma survivors with PTSD (Golier et al, 2006; Yehuda et al, 2006).
There are a number of plausible explanations for the association besides the obvious one of **head trauma** causing both PTSD and vulnerability to subsequent cognitive impairment.

Many of the protective factors we acquire during development are not available to victims of mass violence, prolonged war or Holocaust survivors while they accumulate risk factors.

- Lack of education
- Severe hunger
- Exposure to CNS infections
- Elevated homocysteine levels
- Chronic activation of glucocorticoids secretion

All are involved in the excessive risk.

As these victims of massive trauma become adults and then age many "acquire" so-called "secondary" risk factors for dementia such as diabetes, cardiovascular disease, nicotine and alcohol abuse, depression and reduced social networks (Barak, 2007; Shasha et al, 2009).
There are several major studies that form the scientific infrastructure to the claim put forward that PTSD – especially exposure to massive prolonged trauma – constitutes a risk factor to the development of dementia.

First, Hasegawa proposed the following hypothesis: the physiological functions of amyloid beta and amyloid precursor protein (APP) have been greatly clarified in the last decade. In particular, one of its functions is of importance for synaptic plasticity. Extracellular amyloid beta may suppress synaptic plasticity or inhibit long-term potentiation (LTP) from outside the cell. LTP is considered one of the major the molecular bases of memory. Amyloid beta may induce the inhibition or loss of memory. If indeed amyloid beta has a truly physiological function such as to suppress LTP, then how does this physiological function of amyloid beta induce Alzheimer’s disease?

Recent observations document that homocysteic acid is part of the cascade leading to accumulation of amyloid beta into neurons, suggesting that its physiological function is inhibited by homocysteic acid through this very accumulation of amyloid beta into neurons. In addition, these researchers observed that homocysteic acid induced hypermethylation of the alpha-synuclein protein in the presence of excess methionine and this hypermethylation is overexpressed with aging process.

Thus, Hasegawa hypothesized that prolonged stress induces typical Alzheimer’s disease pathological changes in the elderly (Hasegawa, 2007).
Although put forward only as a theory, soon in that same year Levine and colleagues demonstrated the presence of elevated serum homocysteine levels in male patients with PTSD. The group tested total serum homocysteine levels in 28 male patients with PTSD were compared to those of 223 healthy controls. The effect of PTSD on the serum homocysteine level was significant as well as the duration of PTSD (Levine et al, 2007).

Second, Sutker and colleagues (1990) evaluated former prisoners of war from both the Korean Conflict and World War II with special focus on confinement weight losses. High weight-loss subjects performed more poorly than combat veterans on a wide battery of cognitive tests including worse performance IQ.

The authors conclude that their findings support the hypothesis that severity of stress reflected by trauma-induced weight loss is predictive of long-term compromise in cognitive performance.

Finally smaller hippocampal volume has been observed in young and middle-aged adults with chronic PTSD. These alterations may put trauma survivors with PTSD at greater risk for cognitive decline in later life.
One postmortem and one MRI study support this contention. Bracha and colleagues (2005) investigated whether war-related PTSD is associated with a postmortem change in neuronal counts in the locus coeruleus relying on the demonstrations that enhanced central nervous system noradrenergic postsynaptic responsiveness has been shown to contribute to PTSD.

Three veterans with PTSD were found to have substantially lower locus coeruleus neuronal counts compared to four comparison subjects. The very small sample size warrants larger neuromorphometric studies in veterans and other victims of mass trauma.

Nevertheless, an MRI study undertaken by Yehuda and colleagues (2007) examined whether there are PTSD related differences in hippocampal volume in middle-aged and elderly veterans. Seventeen veterans with chronic PTSD and 16 veterans without chronic PTSD agreed to an MRI scan. Veterans with PTSD did not differ from those without PTSD in hippocampal volume, but smaller left hippocampal volumes were observed in veterans who developed PTSD in response to their first reported traumatic exposure.

The authors concluded that although hippocampal volume was not found to differ between subjects with and without PTSD, smaller hippocampal volumes in PTSD may be associated with specific risk and resilience factors.
Does late onset depression predispose to dementia?
A retrospective, case-controlled study.

Irit Ohanna, Hava Golander, Yoram Barak
Recent research suggests that there are clinical and biologic characteristics typical of late onset depression (LOD).

Furthermore, evidence has been put forward that LOD may be a prodrome of dementia.

This study aimed to assess the association between LOD and the development of dementia.

A retrospective, case-controlled study design was used.

Fifty-one patients with LOD who developed dementia at least 1 year after diagnosis of LOD were defined as the index group: 18 males and 33 females, with a mean age of 75.4 ± 9.2 years.

These were compared with 51 patients with LOD who did not develop dementia during a 10-year follow-up period.

Dementia types were as follows: 73% Alzheimer disease, 24% vascular and mixed dementia, and 3% Parkinson dementia.

Patients with LOD who developed dementia were significantly characterized by having longer hospitalization for their first depressive episode (P = .048), having a family history of dementia (P = .022), and having been exposed to the Holocaust as young adults (P = .013).

Conclusions: Patients with a history of significant traumatic experience in early life and a prolonged onset of depression may be at particular risk of developing dementia. This issue requires further long-term prospective studies.
Little empirical work has been performed evaluating the epidemiology, clinical presentation, assessment, diagnosis, treatment and management of PTSD in the late life. With an aging population that will continue to live longer, greater clinical knowledge and more research into all aspects of PTSD in the aging population is urgently needed and overdue. There are research and clinical centers that produce important and significant contributions to our understanding of the complexities of PTSD in late life. There is however a need to create a comprehensive network of mental health professionals that will cooperate and share experience and data. An elderly patient of mine who passes away taught me of the Holocaust experience more than many nights spent in the laboratory or the library. She said:"...I am not a Holocaust survivor – I was there – you are the survivors by being spared the horror..." This legacy should guide us all.