Editorial

Thursday, September 13, 2018

System error – who will fix the Broken Window ?

Consider a building with a few broken windows. If the windows are not repaired, the tendency is for vandals to break a few more windows. Eventually, they may even break into the building, and if it's unoccupied, perhaps become squatters or light fires inside. Or consider a pavement. Some litter accumulates. Soon, more litter accumulates. Eventually, people even start leaving bags of refuse from take-out restaurants there or even break into cars.

If the concept is to be applied to the law and order situation in our society with special emphasis to the prevailing system of administration and governance, one would find the same psychological response to the prevailing situation.

This very social phenomena is termed the Broken Window Theory - introduced by James Q. Wilson and George L. Kelling in an article titled Broken Windows, in the March 1982 The Atlantic Monthly following an experiment by Philip Zimbardo, a Stanford psychologist who tested the theory in 1969. Unsurprisingly for many, the test concluded that vandalism, or for that matter, most forms of social disturbances occurs much more quickly as the community generally seems apathetic. Similar events can occur in any civilized community when communal barriers – the sense of mutual regard and obligations of civility – are lowered by actions that suggest apathy. In other words, the theory posits that the prevalence of disorder creates fear in the minds of citizens who are convinced that the area is unsafe. This withdrawal from the community weakens social controls that previously kept criminals in check. Once this process begins, it feeds itself.

Disorder causes crime, and crime causes further disorder and crime. A lot of social discrepancies- between the accepted social norms and the ground reality can be explained based on this theory. The snowballing effect of corruption, favoritism, unrest and elitism being increasingly experienced by the general public in the state can be understood more clearly and objectively when one understands the psychology behind the cause of such undesirable social occurrences. But understanding the cause is not the panacea to the festering problem, it is rather the beginning of a long and tedious process of reforms and redressals which should be pursued relentlessly. But the task at hand is easier said than done.

The present system of administration and governance which has been consciously shaped and engineered to comply and conform to the interests of a precious few having access to power and connections, with the added bonus of having in place various mechanisms to protect and cover the nefarious activities and conniving characteristics of those fortunate few, needs to be pulled down and a radical system to administration and governance has to be drawn up be implemented without further ado. In short, an overhauling of the deep rooted social evils and malpractices that has been inextricably intertwined with the present system is the need of the hour. If the present government does not have the gumption to own up and make the much delayed changes, the general public will be forced to act on their behalf. Time to fix the broken window is running out for the government.

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State of the science: use of biomarkers and imaging in diagnosis and management of Alzheimer disease.

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In 2011, the NIA and the Alzheimer's Association issued a new set of diagnostic guidelines for AD that allow use of some biomarker and imaging techniques in addition to clinical criteria (McKhann et al., 2011). The new guidelines allow clinicians to utilize cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning to improve certainty of diagnosis. The new guidelines do not require use of biomarkers and imaging for routine diagnosis in clinical practice but allow clinicians to use their judgment in deciding if use of these techniques is appropriate. It is important to note that these biomarkers and imaging techniques are still under investigation for use in diagnosing AD and are not yet recommended for routine diagnostic purposes. However, the guidelines allow that these techniques may be used as optional tools in clinical practice if they are available and the clinician feels they are appropriate to use (McKhann et al., 2011). Currently, these techniques are primarily being used in research and in a small number of neurological practices specializing in memory disorders. However, as research supporting these techniques becomes stronger and they become more widely available, their use in clinical practice is likely to increase. It is vital for nurses and nurse practitioners who treat patients with dementia to understand these new diagnostic techniques to make decisions about whether to utilize them, to be able to utilize them effectively, and to be prepared to discuss them with patients and families.

AD

AD is a neurodegenerative process in which amyloid protein forms plaques and misprocessed tau protein forms neurofibrillary tangles in the brain, disrupting neural function. The resulting clinical presentation involves progressive memory loss, loss of executive functioning, language difficulties, psychiatric and behavioral disturbances, and impairment in ability to carry out activities of daily living (Burns & Iliffe, 2009). Death typically occurs 3-9 years after diagnosis (Querforth & LaFerla, 2010).

The most significant risk factor for AD is age. At the age of 65 years, 10%-15% of people have AD, and the risk for AD doubles every 5 years thereafter. By the age of 85 years, one in three people has AD (Savica & Petersen, 2011). Family history of AD is also an important risk factor. Having a first-degree relative with AD increases risk by 10% to 40%, and concordance is higher in monozygotic twins (Bums & Iliffe, 2009). Genetic markers associated with autosomal dominant early-onset (typically occurs before the age of 65 years) familial AD include mutations in the amyloid precursor protein (APP) gene and in the genes for presenilin 1 and 2 (PSEN1 and PSEN2), proteins that make up part of the secretase protein complex. In addition, the APOE e4 genotype is associated with increased risk for sporadic, late-onset AD (Bekris, Yu, Bird, & Tsuang, 2010). Modifiable factors associated with increased risk for AD include head injury, hypertension, depression, diabetes, hyperlipidemia, and low activity level (Bums & Iliffe, 2009).

Higher levels of education and intelligence, stimulating occupation and leisure activities, physical exercise, a healthy diet, and moderate intake of alcohol have been associated epidemiologically with reduced risk for AD (Bums & Iliffe, 2009; Buschert, Bokde, & Hampel, 2010). Studies have also found benefit from various preventative interventions such as cognitive training, vitamins, and other supplements, but evidence is of limited quantity and quality. The 2010 NIH Consensus Development Conference statement on preventing Alzheimer disease and cognitive decline states that evidence is insufficient to conclusively show that any modifiable factor prevents AD (NN, 2010).

The exact etiology of AD is unknown, but the most commonly accepted theories posit that the disease process involves deposition of improperly processed proteins in neural tissue (Ballard, 2011; Bekris et al., 2010; Castellani, Rolston, & Smith, 2010; Querforth & LaFerla, 2010; Weiner et al., 2010). These abnormal deposits of protein form plaques and neurofibrillary tangles, the histopathological lesions that allow definitive diagnosis of AD upon autopsy (Castellani et al., 2010). APP is a transmembrane protein found at neural synapses. It is cleaved by enzymes called secretases into amyloid [beta] (A[beta]) peptide, which, under normal physiological conditions, is believed to mediate excitatory transmission at synapses (Querforth & LaFerla, 2010). In AD, A[beta] forms abnormal aggregates, which are believed to impair neural function. Depending on where APP is cleaved, A[beta] can be either 40 or 42 amino acids long. For unknown reasons, A[[beta].sub.42] tends to form aggregates more readily than A[[beta].sub.40]. A[beta] forms oligomers (small aggregates of 2 12 peptides) inside neurons as well as the larger extracellular aggregates of insoluble fibrils known as plaques (Ballard, 2011). A[beta] oligomers appear to be more toxic to neurons than the fibrils in plaques (Ballard, 2011), and cognitive dysfunction is more closely correlated to levels of oligomeric A[beta] than to total A[beta] burden in the brain (Querforth & LaFerla, 2010).

Tau protein is associated with the microtubules that form part of the cytoskeleton in neurons in the brain. When tau protein becomes hyperphosphorylated, it causes microtubules to fall apart, disrupting vesicular transport in the neuron. When dissociated from microtubules, tau protein becomes insoluble and forms neurotoxic aggregates (Querforth & LaFerla, 2010). Hyperphosphorylated tau (P tau) protein forms the most abundant component of the neurofibrillary tangles found in the brains of patients with AD (Ballard, 2011). The number and distribution of phosphorylated tau (P tau) and neurofibrillary tangles is highly correlated with signs and symptoms in AD (Castellani et al., 2010).

The combination of A[beta] oligomers, A[beta] plaques, P tau, and neurofibrillary tangles is thought to interfere with normal neural function in the brain, leading to synaptic dysfunction, impaired neuronal metabolism, and neuronal death (Ballard, 2011; Bekris et al., 2010; Querforth & LaFerla, 2010; Weiner et al., 2010). However, controversy exists over whether these abnormal proteins are etiologic for AD or symptomatic of some other underlying process or processes, as well as over the order in which these protein abnormalities occur (Struble, Ala, Patrylo, Brewer, & Yan, 2010; Swerdlow, 2011). Some research even suggests that A[beta] plaques and neurofibrillary tangles may actually be protective (Castellani et al., 2009, 2010; Swerdlow, 2011). In any case, AD results in progressive degeneration in neural pathways involved in cognition, learning, and memory. As neurons die they release excessive amounts of glutamate, an excitatory neurotransmitter. Glutamate binds NMDA receptors on downstream neurons, causing an influx of calcium, which damages and eventually kills the neurons, a process referred to as excitotoxicity (Osborn & Saunders, 2010). Neuronal dysfunction and death lead to increasing cognitive impairment and the clinical syndrome of dementia (Osborn & Saunders, 2010).

New Diagnostic Guidelines for AD

The 2011 diagnostic guidelines from the NIA and the Alzheimer's Association are the first guidelines incorporating biomarker and imaging techniques in the clinical diagnosis of AD dementia. They establish core clinical criteria for the diagnosis of all-cause dementia and allow patients to be further classified as having dementia unlikely to be caused by AD, probable AD dementia, possible AD dementia, and probable or possible AD dementia with evidence of the AD pathophysiological process (McKhann et al., 2011).

The core clinical criteria for dementia require cognitive impairment detected with a combination of history taking and objective cognitive assessment affecting a minimum of two of the following domains: ability to learn and remember new information; reasoning, judgment, and handling of complex tasks; visuospatial abilities such as recognition of faces or common objects; language skills such as reading, writing, and speaking; and personality and behavior. Impairment must not be explainable by delirium or a psychiatric disorder; must show a decline from earlier level of function, and must interfere with the ability to work or perform usual activities (McKhann et al., 2011).

Probable AD classification requires the presence of core criteria for dementia plus the following characteristics: gradual onset over months to years; clear history of cognitive decline; and initial and most prominent deficits in learning and remembering new information, word finding, recognition of faces or objects, and reasoning, judgment, and problem solving. Probable AD with an increased level of certainty is indicated by the core criteria of probable AD plus either evidence of cognitive decline on repeated evaluation or evidence of a genetic mutation in APE PSEN1, or PSEN2 genes. Probable AD with evidence of the AD pathophysiological process requires core criteria for probable AD plus biomarker or imaging evidence of A[beta] deposition or neuronal injury (McKhann et al., 2011).

Possible AD is indicated in patients with core criteria for probable AD but with sudden onset or insufficient history of progressive decline and/or evidence of another neurodegenerative process such as cerebrovascular disease, another form of dementia, or another neurological disease or medical comorbidity affecting cognition. Possible AD with evidence of the AD pathophysiological process requires evidence of non-AD dementia plus biomarker or imaging evidence of both A[beta] deposition and neuronal injury. Dementia is unlikely to be caused by AD if the patient does not meet clinical criteria for AD dementia, if the patient meets clinical criteria but has significant evidence of another neuropathological process, or if the patient meets clinical criteria but both A[beta] and neuronal injury biomarkers are negative (McKhann et al., 2011).

Biomarkers and Imaging in Alzheimer Diagnosis and Treatment

According to a model of AD proposed by ADNI researchers, the physiological changes of AD tend to happen with a pattern of chronicity. A[beta] accumulation occurs early in the disease process, followed by synaptic dysfunction. Neurodegeneration and atrophy in specific areas of the brain begin to occur next, as tau protein accumulation occurs. Because of this pattern of chronicity, imaging techniques and biomarkers reflecting these changes might be used to identify the pathophysiological process of AD in the living brain and track its progression. Although evidence is currently insufficient to recommend use of these techniques to definitively diagnose AD before the development of dementia, this is an area under intense investigation. In the near future, research may become strong enough to make it possible for clinicians to use biomarkers to diagnose AD in its preclinical stages (Weiner et al., 2011).

All pharmaceutical therapies currently FDA-approved for use in AD provide symptomatic relief only, without modifying the disease process (Osborn & Saunders, 2010). However, there are currently 75-100 therapies intended to slow or stop the progression of AD in clinical trials (Alzheimer's Association et al., 2011). Use of biomarkers to identify patients with preclinical AD could allow use of therapies before the development of the extensive neuronal damage that results in clinical symptoms, enabling preservation of neural and cognitive function (Fagan & Holtzman, 2010). Biomarker and imaging techniques could also potentially be used to monitor effects of new disease-modifying treatments in clinical trials and may soon enable clinicians to monitor the effects of these new treatments in patients (Weiner et al., 2011).

Biomarkers indicating A[beta] deposition included in the guidelines are positive PET amyloid scanning and low CSF A[[beta].sub.42]. Biomarkers indicating neuronal injury include decreased [sup.18]flourodeoxyglucose (FDG) uptake on PET in the temporo-parietal cortex, atrophy in the temporal lobe and parietal cortex on structural MRI, and elevated CSF tau. The guidelines state that, for biomarker and imaging techniques to be considered to provide evidence of the AD pathophysiological process, measures of A[beta] deposition and neuronal injury must be both positive. For biomarkers to provide evidence that dementia is unlikely to be caused by AD, measures of A[3 deposition and neuronal injury must be both negative (McKhann et al., 2011).

PET amyloid scanning methods use radioactive tracers that bind directly to A[beta] in brain tissue. For example, Pittsburgh Compound B ([sup.11]C-PIB) is a fluorescent dye labeled with radioactive carbon that binds to amyloid plaques. On PET scans, these tracers reveal the presence of amyloid plaques in living patients. PET amyloid scanning has been shown to be 75%-90% accurate in identifying patients with AD (Rowe & Villemagne, 2011). Because amyloid plaques form early in the disease process before the development of symptoms, this technique has potential for diagnosing preclinical AD and for assessing treatment effects in therapies designed to modify amyloid plaque formation (Hampel et al., 2008; Weiner et al., 2011). It could also be useful in differentiating AD dementia from other forms of dementia if the clinical presentation is unclear (Hazewinkel & Barkhof, 2011; Zetterberg, Blennow, & Hanse, 2010).

(To be contd.)