Review Article

Neuropathology staging and treatment strategies of Alzheimer's disease: An update

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ABSTRACT

Alzheimer's disease (AD) is a devastating neurodegenerative disorder manifested by deterioration in memory and cognition, impairment in performing activities of daily living. The pathological hallmark of AD is widespread neuritic plaques which are accumulation of amyloid beta protein and neurofibrillary tangles. This review has been done on various causes due to neurofibrillary tangles, senile plaque, gene, and different factors involved in aging and injury. Treatment of AD targeting toward cholinergic deficiency, oxidative stress, protein oxidation, protein nitration, tau and tangles formation, mitochondrial dysfunction, and inflammation. Pharmaceutical therapies include cholinesterase inhibitors, memantine, antihypertensive drugs, anti-inflammatory drugs, secretase inhibitors, brain-derived neurotrophic factor, and immunization. Nutrition and natural therapies, various vitamins and minerals also play a role in treatment. Approaches that target several dysfunctions simultaneously and that emphasize nutritional, natural, and stimulatory therapies may offer the most benefit at this time.

Key words: AD, nutrition and natural therapies, pharmaceutical therapies, stimulatory therapies

INTRODUCTION

Alzheimer's disease

Alzheimer's disease (AD) is a devastating neurodegenerative disorder manifested by deterioration in memory and cognition, impairment in performing activities of daily living, and many behavioral and neuropsychiatric illnesses.[1] AD is the most common form of dementia in the old age. The percentage of persons with Alzheimer disease increases by a factor of 2 with every 5 years of age, so 1% of 60 year old and 30% of 85-year-old have the disease. By 2050, the number of cases in US is predicted to rise to 13.2 million.[2] An Indo-US study assessed prevalence of AD in a setting of rural India. They found that the prevalence of AD was low, increased with age, and was not associated with gender and literacy.[3] In 2000, India had 3.5 million patients with AD as against US, which had 4.5 million patients with AD. But with an increase in the geriatric population in India, number of AD patients is growing at a phenomenal rate. In 2005, the geriatric population was 10% of the whole population. By the year 2021, every seventh Indian will be a senior citizen.

Access this article online

Quick Response Code:

Website: www.ijnpnd.com

DOI: 10.4103/2231-0738.124612

Symptoms of AD

AD affects people in different ways, but the most common symptom pattern begins with gradually worsening ability to remember new information. This occurs because disruption of brain cell function usually begins in brain regions involved in forming new memories. As damage spreads, individuals experience other difficulties. The following are warning signs of AD:[4]

- Memory loss that disrupts daily life
- Challenges in planning or solving problems
- Difficulty completing familiar tasks at home, at work, or at leisure
- Confusion with time or place
- Trouble understanding visual images and spatial relationships
- New problems with words in speaking or writing
- Misplacing things and losing the ability to retrace steps
- Decreased or poor judgment
- Withdrawal from work or social activities
- Changes in mood and personality.

Stages of AD

- **Stage 1-No impairment**
  Memory and cognitive abilities appear normal.
- **Stage 2-Very mild**
  Memory lapses and changes in thinking are rarely detected by friends, family, or medical personnel, especially as about half of all people over 65 begin noticing problems in concentration and word recall.
- **Stage 3-Mild cognitive impairment**
  While subtle difficulties begin to impact function, the person may consciously or subconsciously try to cover up his or her problems. Expect to experience difficulty with retrieving words, planning, organization, misplacing objects, and forgetting recent learning, which can affect life at home and work. Depression and other changes in mood can also occur. Duration: 2-7 years.
- **Stage 4-Moderate**
  Problems handling finances result from mathematical challenges. Recent events and conversations are increasingly forgotten, although most people in this stage still know themselves and their family. Experience problems carrying out sequential tasks, including cooking, driving, ordering food at restaurants, and shopping. Often withdraw from social situations, become defensive, and deny problems. Accurate diagnosis of AD is possible at this stage, lasts roughly 2 years.
- **Stage 5-Early dementia/moderate severe AD**
  Decline is more severe and requires assistance. No longer able to manage independently or unable to recall personal history details and contact information. Frequently disoriented regarding place and/or time. People in this stage experience a severe decline in numerical abilities and judgment skills, which can leave them vulnerable to scams and at risk from safety issues. Basic daily living tasks like feeding and dressing require increased supervision. Duration: An average of 1.5 years.
- **Stage 6-Middle dementia/severe AD**
  Total lack of awareness of present events and inability to accurately remember the past. People in this stage progressively lose the ability to take care of daily living activities like dressing, toileting, and eating but are still able to respond to nonverbal stimuli, and communicate pleasure and pain via behavior. Agitation and hallucinations often show up in the late afternoon or evening. Dramatic personality changes such as wandering or suspicion of family members are common. Many can not remember close family members, but know they are familiar. Lasts approximately 2.5 years.
- **Stage 7-Late or severe dementia and failure to thrive**
  In this final stage, speech becomes severely limited, as well as the ability to walk or sit. Total support around the clock is needed for all functions of daily living and care. Duration is impacted by quality of care and average length is 1-2.5 years [Figure 1].

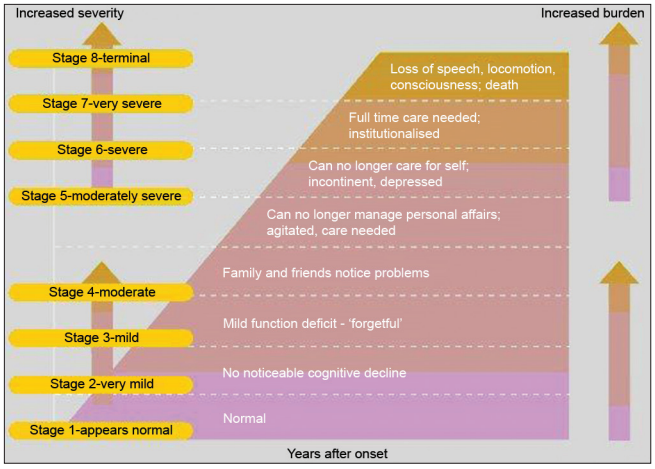

Figure 1: Stages of Alzeimer's disease

Causes of AD

The cause or causes of AD are not yet known. However, most experts agree that AD, like other common chronic diseases, develops as a result of multiple factors rather than a single cause. These factors include a variety of brain changes that begin as many as 20 years before symptoms appear. Increasingly, the period between the initial brain changes of AD and the symptoms of advanced AD is considered by scientists to represent the "continuum" of AD. At the start of the continuum, the individual is able to function normally, despite these brain changes. Further along the continuum, the brain can no longer compensate for the increased neuronal damage caused by brain changes, and the individual shows subtle decline in cognitive function.[4]

Structural abnormalities

Microscopic examination reveals the critical features of the disease-A cerebral cortex peppered with neurofibrillary tangles and senile plaques. AD can, therefore, be said to be the dementia associated with these histopathologic abnormalities.[5]

Neurofibrillary tangles

Neurofibrillary tangles consist of aberrantly phosphorylated fibrillary proteins aggregated within the neuronal cytoplasm. Their presence signifies the failure of the neuron to properly maintain its cytoskeleton, which is required to support the extraordinarily complex branching shape of its numerous processes. A small number of neurofibrillary tangles are a universal consequence of aging. However, it is an increased number and the architectonic distribution of the tangles that promote the cardinal pathology and define the stages of the disease.[6] The development of tangles is a major and possibly the main mechanism of neuronal death in AD. Some groups of neurons are preferentially affected by tangles in AD. For example, neurofibrillary tangles frequently occur in areas of the hippocampus that are involved in processing experiences prior to storage as permanent memories.[7]

Senile plaques

Senile plaques are more complex; they consist of extracellular deposits of amyloid material and are associated with swollen, distorted neuronal processes called dystrophic neurites. Like amyloid elsewhere in the body, complex sugar polymer components (glycosaminoglycans) are thought to be critical in the assembly of these deposits. The specificity of cerebral amyloid is provided by its major peptide component, β-amyloid, a short 40-42 amino-acid fragment of the transmembrane protein, β-amyloid precursor protein (β-APP). The fact that the density of senile plaques does not increase with age[8] suggests that brains switch from plaque-free to plaque-bearing status in a short period of time; the mechanism responsible for this change is unknown. Plaques start as innocuous deposits of nonaggregated, putatively nonneurotoxic β-amyloid (diffuse plaques). However, in some individuals they undergo an orderly sequential transformation into the mature senile neuritic plaques that are associated with the development of AD. It is thought that the enzyme butyrycholinesterase may play an essential role in this maturation process. Although the number of senile neuritic plaques increases with age, the number remains low in most cognitively intact individuals.[9]

The role of genes

Several point mutations in the gene coding for β-APP on chromosome 21 are sufficient to cause early-onset autosomal dominant familial AD with complete penetrance; the clinical phenotype of these cases is entirely consistent with typical AD. Some mutations increase the production of β-amyloid, while others favor the formation of long (42 amino acid) forms of β-amyloid, which aggregate more readily than the short (40 amino acid) forms. In addition, mutations in two other genes coding for the novel proteins presenilin 1 and 2 are reported to account for the majority of early-onset, familial, and dominantly inherited AD.[10]

Role of environmental factors

The finding that monozygotic twins may not both develop AD suggests that environmental factors also play a role in the development of AD. One hypothesis is that AD may represent a chronic active inflammatory disease. The brains of AD patients show evidence of mild active inflammation, including microglial and complement activation, and the presence of inflammatory cytokines.[11]

Mechanisms associated with aging and AD

Aging is the major risk factor of AD in the general population. Recent research has identified potential mechanisms related to aging that may contribute to the development of the disease. One is the concept that free radicals (reactive oxygen species) produced during cellular respiration may play an important role in the process of aging and in the development of AD.[12] Another possible mechanism related to aging is messenger ribonucleic acid (RNA); mutations in messenger RNA have been reported in elderly humans and older rodents. The deletion of two consecutive bases in a protein results in an altered reading frame and; thus, a protein with an amino acid sequence unrelated to that specified in the original gene. The predicted abnormal forms of two proteins relevant to the pathogenesis of AD.

Risk factors for AD

The greatest risk factor for AD is advancing age, but AD is not a normal part of aging. Most people with AD are diagnosed at age ≥65years. These individuals are said to have late-onset AD. However, people aged <65years can also develop the disease. When AD develops in a person aged <65years, it is referred to as "younger-onset" (or "early-onset") AD.[12]

Family history

Individuals who have a parent, brother, or sister with AD are more likely to develop the disease than those who do not have a first-degree relative with AD. Those who have more than one first-degree relative with AD are at even higher risk of developing the disease. When diseases run in families, heredity (genetics), shared environmental/lifestyle factors, or both may play a role.[13]

Apolipoprotein ε4

Individuals with the ε4 form of the gene apolipoprotein E (APOE ε4) are at increased risk of developing AD. APOE ε4 is one of three common forms (ε2, ε3, and ε4) of the APOE gene, which provides the blueprint for a protein that carries cholesterol in the bloodstream. Everyone inherits one form of the APOE gene from each parent. Those who inherit one APOE ε4 gene have increased risk of developing AD and of developing it at an earlier age than those who inherit the ε2 or ε3 forms of the APOE gene. Those who inherit two APOE ε4 genes have an even higher risk.[4]

Mild cognitive impairment

(MCI) is a condition in which an individual has mild, but measurable, changes in thinking abilities that are noticeable to the person affected and to family members and friends, but that do not affect the individual's ability to carry out everyday activities. People with MCI, especially MCI involving memory problems, are more likely to develop AD and other dementias than people without MCI. In some cases, such as when MCI is caused by certain medications, MCI can be reversed. In other cases, MCI reverts to normal cognition on its own or remains stable.[14]

Cardiovascular disease risk factors

Growing evidence suggests that the health of the brain is closely linked to the overall health of the heart and blood vessels. The brain is nourished by one of the body's richest networks of blood vessels. A healthy heart helps ensure that enough blood is pumped through these blood vessels to the brain, and healthy blood vessels help ensure that the brain is supplied with the oxygen - and nutrient-rich blood it needs to function normally.

Some data indicate that cardiovascular disease risk factors, such as physical inactivity, high cholesterol (especially in midlife), diabetes, smoking, and obesity, are associated with a higher risk of developing AD and other dementias.[15]

Head injury and traumatic brain injury

Head injury, head trauma, and traumatic brain injury are associated with an increased risk of AD and other dementias. Moderate head injuries are associated with twice the risk of developing AD compared with no head injuries, and severe head injuries are associated with 4.5 times the risk. Moderate head injury is defined as a head injury resulting in loss of consciousness or posttraumatic amnesia lasting >30 min; if either of these lasts >24 h, the injury is considered severe.[16]

Neuropathology of AD

Amyloid β-peptide

AD d brains are predominantly characterized by the presence of two features - Senile plaques and neurofibrillary tangles. These plaques, which are thought to play a central role in the inflammatory cascade, are composed primarily of deposits of β-amyloid (Aβ) peptide. β-amyloid is a small piece of APP. β-amyloid initially accumulates and forms the plaques between the synapses in the brain and disrupts cell to cell communication. The 39- to 43-residue Aβ peptide is produced from the cleavage of APP by β - and γ-secretase. APP is a ubiquitously expressed large type 1 transmembrane protein, the degradation of which enters either the amyloidogenic or the nonamyloidogenic pathway, possibly depending on whether processing occurs with in α lipid rafts or phospholipid domains, respectively. The more common fate of APP is cleavage by α-secretase, to generate a secreted ectodomain of APP, which acts as a neurotrophic protein, and a C-terminal fragment that is degraded internally.[17]

It is thought by some that APP processing can be directed to either pathway by modulating the cholesterol content of the membranes. Data also suggest a role for transforming growth factor-β1 (TGF-β1) in elevating the expression of β APP by transcriptional and posttranscriptional events, thereby promoting Ab production in astrocytes and possibly enhancing plaque formation.[18] Studies have shown that TGF-β1 induces the overexpression of APP in astrocytes but not in neurons, leading to TGF-β1-induced Aβ generation in both murine and human astrocytes.

Interleukin-1 (IL-1) has also been implicated as a driving force for amyloid plaque deposition through increasing APP synthesis in astrocytes. It has been demonstrated in rats that injection of IL-1 into the cerebral cortex results in an increase in APP protein synthesis by astrocytes.[19]

Deposited Aβ peptide accumulates to form diffuse, nonneuritic plaques. As Aβ continues to accumulate and APP-overexpressing, dystrophic neurites become associated, the plaques evolve into diffuse, neuritic plaques. Plaques continue to condense, forming dense-core neuritic plaques. As plaques reach their final burnt-out stage, the neurites are no longer associated and plaques consist entirely of dense compacted Aβ.[20]

Tau and formation of neurofibrillary tangles

The second major characterizing factor for AD is the presence of neurofibrillary tangles. Tangles are comprised primarily (95%) of bundles of paired helical filaments composed of the microtubule-associated protein tau, along with the related straight filaments (5%). In healthy neurons, the chief function of tau is to assist in the assembly and stabilization of microtubules, the fibrous structures largely responsible for communication and transportation within the cell. Tau proteins found in neurofibrillary tangles, however, are abnormally hyperphosphorylated, making them unable to bind to microtubules.

Stress-activated proteins 3 and 4, and tau protein kinase I/glycogen synthase kinase 3b (GSK-3) have been implicated in abnormal tau phosphorylation. Destabilization of microtubules leads to inappropriate protein metabolism, disruption in signaling and synaptic failure. This ultimately results in communication breakdown within the cell and microtubule collapse, factors that significantly contribute to neurodegeneration. Tangle development is closely aligned with cognitive impairment, with the hippocampus region, the area associated with learning and short term memory, affected early during disease progression. Final stages of the disease show profuse neuronal loss and neurofibrillary tangle formation in the neocortical and cerebral cortex, primarily in pyramidal neurons and their synapses.[21]

Oxidative stress

Oxidative stress is observed in the AD brain. This increase has been well-documented with markers for protein, deoxyribonucleic acid (DNA), and RNA oxidation as well as lipid peroxidation.[22]

Protein oxidation

Protein oxidation is indexed in the AD brain by an increase in carbonylated and HNE (4-hydroxyl-2-trans-noneal) and 3-NT (3-nitrotyrosine) modified proteins. Studies have shown an increase in protein carbonyls in the hippocampus and parietal cortex, but not in the cerebellum, where there is less significant AD pathology.[23]

Protein nitration

Another common marker of protein oxidation is the addition of a nitro group to tyrosine residues forming 3-NT. Increased protein nitration in the AD brain supports the notion that nitrosative stress also contributes to neurodegeneration in AD. The overexpression of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) could be responsible for increased levels of reactive nitrogen species (RNS).

Tyrosine is particularly susceptible to nitration, but tryptophan and phenylalanine can also be nitrated, albeit at lower rates. Tyrosine residues are important to redox cell signaling and are often the site of phosphorylation, a prominent regulation function. The nitration of tyrosine at the 3-position sterically hinders the phosphorylation and also may change the structure of proteins, thereby rendering a protein dysfunctional, and could lead to cell death. Increased levels of nitrated proteins have been reported to be present in AD brain and cerebrospinal fluid (CSF), implying a role for RNS in AD pathology.[24]

Lipid peroxidation

Amplified lipid peroxidation has been described in several neurodegenerative diseases, including AD. Analysis of AD brains demonstrates an increase in free HNE in amygdala, hippocampus, and parahippocampal gyrus of the AD brain compared with age-matched controls. A significant elevation of free HNE in ventricular CSF and serum provides a potential biomarker for AD. Protein-bound HNE alters conformation and function of proteins. Thus, processes related to excitotoxicity may be facilitated, whereas processes related to the removal of HNE from neurons (via glutathione S-tranferase GST and multidrug resistant protein MRP-1) may be compromised.[25]

DNA oxidation

DNA is the primary target of reactive oxygen species (ROS), leading to cellular aging. Due to the high oxygen consumption rate by the brain, ROS may contribute to neuronal damage in aging and neurological disorders. Oxidative damage to DNA by ROS results in strand breaks, DNA–DNA and DNA–protein cross-linking, and sister-chromatid exchange and translocation. DNA bases are also attacked by the lipid peroxidation products HNE and acrolein, which

leads to the formation of bulky exocyclic adducts. This modification can cause inappropriate base pairing that alters protein synthesis. DNA oxidation by ROS also produces oxidized base adducts, such as 8-hydroxy-2-deoxyguanine (8-OHdG). Guanine, because it has the lowest oxidation potential of the four DNA bases, is the most readily oxidized base and, therefore, the most commonly used analysis of DNA oxidation.

Previous studies have demonstrated a 2-fold increase in DNA strand breaks in AD brain that consequently results in depletion of energy stores and cell death.[26]

RNA oxidation

Studies have shown 30-70% oxidation of the mRNAs in the frontal cortex of the AD brain in comparison to only 2% oxidation in age-matched controls. Increased levels of 8-hydroxyguanine (8-OHG) have also been reported in the hippocampus and cerebral neocortex of the AD brain, whereas the 8-OHG level in the cerebellum was not significantly altered compared with controls.

An increase in 8-OHdG has been identified not only in brain tissue but also in CSF from AD patients. RNA oxidation in the AD brain could render the cell incapable of initiating protein synthesis, hindering the cell's defense against further oxidative damage, an effect observed in AD.[27]

Mitochondrial dysfunction

Mitochondrial dysfunction in AD is central to the development of oxidative stress because it is a primary source of cellular oxidants. *In vivo* positron emission tomography has provided specific evidence of brain metabolism abnormalities associated with AD, which precede neuropsychological impairment and visual atrophy.

Mitochondrial changes would limit ATP production and increase ROS production and suggest possible abnormalities in mitochondrial functions in AD. ROS production is directly related to the mitochondrial membrane potential ($\Delta\Psi$) such that hyperpolarization (high $\Delta\Psi$) promotes ROS production. Several *in vitro* studies of Aβ and mitochondrial function have reported that Aβ affects mitochondrial DNA and proteins, leading to impairment of the electron transport chain and ultimately mitochondrial dysfunction. Dysfunction of mitochondria is reported to alter APP metabolism, enhancing intraneuronal accumulation of amyloid β-peptide and enhancing neuronal vulnerability.

The accumulation of Aβ in the mitochondria may be associated with diminished enzymatic activity of mitochondria, where the peptide is proposed to disrupt energy production while promoting mitochondrially derived apoptotic processes via the intrinsic pathway. This claim of mitochondrial Aβ needs replication.[28]

Microglia and their association

Microglia, considered the macrophages of the central nervous system (CNS), are found to cluster around Aβ deposits and may even be a driving force in the evolution of diffuse nonneuritic plaques into condensed neuritic plaques. When microglia become activated, they undergo morphological changes including enlargement and show increased expression of major histocompatibility complex type II, cytokines, chemokines, and complement. Activated microglia surrounding senile plaques in AD have also been shown to upregulate their expression of the macrophage scavenger receptor (MSR) and receptor for advanced glycation end products RAGE. Both MSR and RAGE have been associated with stimulation by Ab and AGEs, leading to activation of microglia and subsequent expression of proinflammatory agents.[29]

ROS

ROS, such as superoxide, hydroxyl radicals and hydrogen peroxide, and RNS such as nitric oxide and nitrogen dioxide, are generated normally during oxygen intake, oxidative metabolism of some substances and in the event of infection. Cells maintain the balance between production of ROS and reactive nitrogen species (RNS) and their detoxification via effective antioxidation systems including enzymatic and nonenzymatic antioxidants. The glutathione system, which consists of glutathione, glutathione peroxidase, and glutathione reductase, and the thioredoxin system, consisting of thioredoxin and thioredoxin reductase, are two important enzyme systems involved in maintaining homeostasis. Catalase and superoxide dismutase are two other significant antioxidant enzymes naturally produced by the body.[30,31]

Oxidative stress occurs when the balance between prooxidants and antioxidants is disrupted in favor of the prooxidant, possibly as a result of endogenous or exogenous triggers. This leads to undue oxidation of biomolecules generating an overproduction of free radicals that can damage cells in a variety of ways. Examples of oxidative damage are altered protein and enzyme function, due to tertiary structure modification, destruction of structural proteins,

mutations in DNA, and oxidation of membrane lipids leading to membrane dysfunction and cell lysis.[32]

Inflammation involves ROS activation of signaling pathway

AD is also characterized by a chronic inflammatory process around amyloid plaques, activation of microglia, and astrocytes and increased levels of radicals and proinflammatory cytokines. For example, iNOS, IL-1β, IL-6, and tumor necrosis factor (TNF) have been detected in amyloid plaques and plaque surrounding microglia and astrocytes.

In addition to damaging various cell components through oxidation, ROS and RNS can activate redox sensitive transcription factors such as NF-κβ, heat-shock transcription factor 1, and p53. Each of these transcription factors, along with the PI (3) K/Akt and MAP-kinase pathways that regulate additional transcription factors through phosphorylation, trigger the generation of proinflammatory molecules, resulting in chronic inflammation.[32] Chronic inflammation, in turn, leads to further ROS and RNS generation, consequently amplifying the damaging effects of oxidative stress and chronic inflammation. The NF-jB pathway is thought to be a primary inflammatory pathway in AD due to its ability to induce expression of a variety of proinflammatory molecules. NF- κβ is activated by cytokines IL-1, IL-17, and TNF, oxidative stress in the form of hydrogen peroxide and super oxide molecules, as well as a range of pathogens and other substances including Aβ and AGE stimulation of RAGE.[33] Activation of NF-κβ requires the phosphorylation of inhibitor κβ (Iκβ) which exposes the translocation sequence of NF-κβ, enabling it to be transported into the nucleus. NF- κβ signaling induces the expression of IL-1, IL-6, TNF, macrophage colony-stimulating factor and iNOS, which have a range of actions including proinflammatory functions, feedback loops leading to self-reinforcement and transcription regulation. The inflammatory process, which occurs mainly around the amyloid plaques in AD brains, induces the production of superoxide via nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase in activated macrophages and microglia. Described as an ''oxidative burst,'' this process is involved in destroying bacteria or virus-infected cells and in normal circumstances these radicals are scavenged by antioxidant enzymes, such as catalase. In AD patients, however, oxidative burst is an important source of oxidative stress in inflammatory situations.[34]

Treatment

AD is regarded as a brain amyloidosis. Prevention/deletion of amyloid beta protein deposition is one of the most promising targets of the treatment. A cascade of pathophysiological events is triggered in AD. This process is asynchronous, meaning that viable neurons remain as targets for therapy even in the advanced diseased state and each stage of cascade affords the possibility for therapeutic intervention.

There is a prominent loss of cholinergic, noradrenergic, dopaminergic, and GABAergic neurons transmission in AD. Neurotransmitter-based treatments with cholinesterase inhibitors (ChEls) and N-methyl- D-aspartate (NMDA) receptor antagonists are now in current use. Therapeutic options for treatment of AD have so far focused on modifying neurotransmitter systems, in particular the cholinergic system, to maximize the remaining activity in affected neuronal circuits.[35]

Anticholinesterase inhibitors

Symptomatic treatment of AD is based on cholinergic neurotransmission enhancement obtained by pharmacological means. This approach is supported by three sets of facts: Brain biopsies and autopsy studies have shown that patients with AD have reduced cortical activity of choline acetyltransferase ChAT, the enzyme that synthesizes ACh from choline. Additional post mortem studies have shown a pattern of cholinergic denervation with a reduction in presynaptic muscarinic type 1 and nicotinic receptors, with relative preservation of postsynaptic muscarinic type 2 receptors. The loss of cholinergic neurons in the nucleus basalis of Meynert and other subcortical nuclei from which originate diffuse cortical projections support this hypothesis. These large neurons are mainly responsible of cerebrocortical cholinergic supply and play an important role in mediating attention and learning of new information. Among the different compounds that can modify cholinergic neurotransmission, the only class of drugs that have been obtained from regulatory authorities the indication for the symptomatic treatment of AD are the ChEIs. These drugs act by slowing the biochemical breakdown of acetylcholine and thereby, at least theoretically, prolonging cholinergic neurotransmission. Three ChEIs are commonly used to treat patients with mild to moderate AD: Donepezil, rivastigmin, e and galantamine. Donepezil and galantamine are selective AChE inhibitors. Rivastigmine inhibits both AChE and butyryl cholinesterase from degrading

ACh. ChEIs are indicated in patients with mild to moderate AD.[36]

NMDA receptor antagonist (memantine)

Overstimulation of the NMDA receptor by glutamate is implicated in neurodegenerative disorders. Glutamate is the principal excitatory neurotransmitter in the brain. Glutamatergic overstimulation may result in neuronal damage, a phenomenon that has been termed excitotoxicity. Such excitotoxicity ultimately leads to neuronal calcium overload and has been implicated in neurodegenerative disorders. Glutamate stimulates a number of postsynaptic receptors, including the NMDA receptor, which has been particularly implicated in memory processes, dementia, and the pathogenesis of AD.

Memantine is a relatively new drug specially developed for use in moderate to severe dementia. It is a noncompetitive NMDA receptor antagonist and reduces glutamatergic excitotoxicity Memantine's mechanism of action is a voltage-dependent, low-moderate affinity, uncompetitive NMDA receptor antagonism with fastblocking/unblocking kinetics. The low-moderate affinity is important because other NMDA receptor antagonists, such as ketamine and amantadine, are high-affinity compounds with neuropsychiatric side effects. The fast on/off kinetics are also important because this means that memantine sits on the receptor just long enough to prevent pathologic activation of the glutamate receptors and then quickly goes away when physiologic activation of the glutamate receptors needed. Memantine blocks the effects of abnormal glutamate activity that may lead to neuronal cell death and cognitive dysfunction. The fast on/off kinetics and low-moderate affinity are the key to memantine action because it blocks the effects of excessive glutamate while preserving physiologic activation of NMDA receptors required for learning and memory. Like other NMDA receptor antagonists, memantine at high concentrations can inhibit mechanisms of synaptic plasticity that are believed to underlie learning and memory. However, at lower, clinically relevant concentrations memantine can promote synaptic plasticity and preserve or enhance memory in animal models of AD.[37] Moreover, memantine can protect against the excitotoxic destruction of cholinergic neurons. NMDA-receptor-dependent excitotoxicity plays a major role in progressive neuronal loss seen in dementia and the weak NMDA-receptor blocking property of memantine may confer on it a disease-modifying activity. Moreover, recent *in vitro* studies suggest that memantine abrogates Ab toxicity and possibly inhibits its production.

Antihypertensive drugs

Angiotensin-converting enzyme (ACE) inhibitors reduced inflammation and mental decline in AD patients by 50%. Mild to moderate AD subjects with high blood pressure had less cognitive decline when given an ACE inhibitor that crossed the blood-brain barrier (perindopril or captopril) than when given an ACE inhibitor that did not (enalapril or imidapril) or a calcium channel blocker (nifedipine or nilvadipine). A recent study confirmed that ACE inhibitor slow the progression of AD. A potential downside of ACE inhibitors is that they may block ACE form converting βA_{1-42} to less damaging βA_{1-40}, thereby reducing its protective function.

Possible mechanism by which ACE inhibitor work induce reducing angiotensin II (a substance that interferes with memory formation by reducing Ach), increasing an enzyme that breaks down βA, and increasing acetylcholine. Another possibility is that angiotensin II is converted to angiotensin III and then to angiotensin IV. Angiotensin IV binds at AT_4 receptor sites, which are most prevalent in the neocortex, hippocampus, and other areas important in cognition and memory. This counteracts a dysfunctional cholinergic system, resulting in more Ach and improved learning and memory.[38]

Calcium channel blocker are another category of antihypertensive drugs. It may be that βA, mutations in presenilin proteins, or other factors open channels that permit Ca^{2+} to enter and damage cells. If so, calcium channel blockers might be expected to benefit AD patients.[39]

Anti-inflammatory drugs

Most research on nonsteroidal anti-inflammatory drugs has focused on prevention rather than treatment of AD.

Animal models have demonstrated that anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors (rofecoxib) reduced oxidative stress but nonspecific COX inhibitors (flurbiprofen and ibuprofen) did not.[14] An animal model revealed that naproxen, and a COX-2 (MF-tricyclic) inhibitors each restored memory, but only MF-tricyclic blocked the suppressive effect of βA on synaptic plasticity.[40]

Secretase inhibitors

Secretases are enzyme that breaks APP, found in cell membranes, in βA fragment that forms plaques.

Consequently, secretase inhibitors should slow the production of βA.

Beta-secretase inhibitors have been shown to reduce βA in animal models and may have fewer adverse effects. Memoquin is beta-secretase inhibitors that also inhibits AChE, reduce βA production, limits tau hyperphosphorylation, and fights oxidation, but it early in the developmental stage.[41]

Insulin

Insulin has many roles in normal cell functioning. Nasal administration of insulin improved several cognitive measures in subjects with early AD or MCI. Nasal administration allows insulin to reach the brain quickly without affecting insulin levels elsewhere in the body. Nasal administration has also improved verbal memory but only for persons with a specific genetic makeup (the apolipoprotein E4 [APOE [epsilon] 4]allele). Insulin resistance can affect the brain as well as other organs, making it difficult for the brain cells to acquire energy for cell maintenance and synaptic connections; thus, cell death can occur. Also, hyperinsulinemia has been found to increase inflammation and βA_{1-42} in healthy adults. A possible mechanism underlying insulin resistance in the CNS is the formation of toxic protein fragments called beta-amyloid derived diffusible ligands (ADDLs). According to this view, ADDLs bind to synaptic receptor sites, where they prevent insulin from working, causing synaptic dysfunction and eventual dementia. Other possible mechanisms of action are described elsewhere.[42]

Etanercept (Enbrel[R]) (TNF-α modulator)

Etanercept has recently generated interest, because it produced dramatic cognitive improvement. AD brains have elevated levels of the cytokine TNF-α. Since TNF-α regulates neural transmission, lowering it by spinal injections of etanercept might restore the brain to more normal functioning. A dramatic cognitive improvement was evidenced in one moderate to severe AD subject within minute.[43]

Brain-derived neurotrophic factor

A major problem is that the BDNF molecule is too large to penetrate the blood-brain barrier. Human trials, mostly investigating Parkinson's disease, have used a micropump to directly infuse BDNF into the brain through a cannula inserted into the skull. This risky procedure accounts for the lack of human trials. In addition, too large a close can produce serious side effects. Although *in vitro* and animal data are promising, it is unlikely that BDNF therapy will be in use anytime soon. However, physical exercise and diets rich in omega-3 fatty acids have been found to normalize BDNF without the difficulties associated with brain infusions.[44]

Immunization

βA has been reduced by injecting AD patients with a synthetic form of βA called AN1792. Although this

Table 1: The advantages and disadvantages of pharmaceutical therapies

Pharmaceutical	Advantages	Disadvantages
Acetylcholinestarase inhibitors	Prolong ACh; some evidence for neuroprotection; FDA approved	Often short-term efficacy; severe side effect; high costs; modest benefits
Memantine	Decrease glutamate excitotoxicity; possible other neuroprotective effects; well-tolerated; FDA approved for moderate to severe AD, but also helps mild to moderate AD	Possible neurotoxicity; some severe adverse effects; primarily recommended for moderate to severe AD; high cost
Antihypertensive drugs	Reduce inflammation; may block $Ca2^{+}$; may reduce βA and increase Ach	Most human research on hypertensive individuals and animals
Anti-inflammatory drugs	May reduce neural inflammation	Most research focused on risk of acquiring AD and not on treatment; human research correlation in nature, making causation impossible to determine; effect on intestinal tract, liver, and kidneys; therapeutic benefit questionable
Secretase inhibitor	May reduce βA and inhibit AchE	Little human research; severe adverse effect; insufficient data
Insulin drugs	Improve energy production and cellular functions; may resuce ADDLs and oxidative stress; reduce cell death	Must be administered nasally to prevent insulin changes in nonbrain areas; little human data
Entercept	Produce dramatic improvement within minutes	Little research; risky spinal injection requried
BDNF	Stimulates neurogensis; reverses synaptic damage; improves signaling; reduces oxidative stress and cell death	Molecule too large to penetrate blood-brain barrier; risky administration via a cannula in skull; can produce serious side effect; little human research
Immunization	Reduce βA	Often ineffective; clearing of βA not always accompanied by symptom reduction; early in the development stage

AD: Alzheimer's disease; ADDLS: Amyloid derived diffusible ligands; FDA: Food and drug administration; BDNF: Brain-derived neurotrophic factor

reduces βA, the effect on AD is unclear. Some people respond to immunization with a slowing of disease progression even after 4.6 years, but other studies have found a clearing of without any cognitive benefit. It may be that βA accumulation starts a chain of events that cannot be stopped by merely clearing βA deposits.[45]

Antipsychotics and sedatives warning

Antipsychotics and sedatives have accelerated the progression of AD, defined as an increase of one or more points in the Global Deterioration Scale, and produced a 50% decrease in cortical plasticity in cats. Thus, care should be exercised in using such drugs for AD patients.

The advantages and disadvantages of pharmaceutical therapies are summarized in Table 1.

Herbal treatment

HuperzineA

HuperzineA (HupA) is an extract from the Chinese moss Huperzia serrata that has been used for centuries in Chinese folk medicine to treat a wide range of diseases. A review of in vitro and animal studies found HupA preserves ACh longer than tacrine, galantamine, or donepezil. HupA reduces βA-induced neuronal degeneration in the hippocampus and cortex, decreases oxidative damage from free-radical induced βA plaques, protects neurons from cytotoxins and apoptosis induced by βA and free radicals, and inhibits glutamate toxicity. The research and potential mechanisms of action underlying these effects have been reviewed in detail.

Acetylcholinesterase exists in different molecular forms referred to as G1, G2, G3, and G4. Human brains have mostly the G4 form with a smaller amount of G1. Hence, inhibition of G4 is more germane in terms of prolonging ACh and facilitating synaptic transmission in humans. In the striatum and hippocampus (areas important in learning and memory), HupA primarily inhibits G4, whereas donepezil primarily inhibits G1. HupA penetrates the blood-brain barrier better than donepezil, rivastigmine, or tacrine.[46,47]

Polyphenols

Polyphenols are a group of plant-derived chemical substances with more than one phenol unit. They protect plants from stress induced by ultraviolet radiation, disease, pests, and physical damage. Polyphenols also protect animals by activating a number of intracellular processes that preserve neurons.

Curcumin

Curcumin is extracted from the plant Curcuma longa (turmeric). Reviewers suggest curcumin may be a promising therapy for AD because it has at least 10 neuroprotective properties, including anti-inflammatory, antioxidant, inhibition of βA formation, clearance of existing βA, and copper and iron chelation. Turmeric is a widely used spice in India, which may explain why India has a much lower incidence of AD than the United States. Bioavailability may not be a problem for Indians because it is combines with oil in cooking.[48]

Resveratrol

Resveratrol, a polyphenol found in red wine, peanuts, and other plants, reduces oxidative stress, decreases inflammation, reduces βA, protects DNA, decreases cell death, and modulates various other systems that protect cells. Animal models suggest that resveratrol mimics the effects of caloric restriction on longevity and negates the harmful effects of a high-fat diet, doubles resistance to muscle fatigue, reduces neurotoxicity, decreases cell death, reduces degeneration of the hippocampus, and prevents learning impairment. Several studies have shown that moderate consumption of red wine reduces the risk of developing AD.

Resveratrol is similar to curcumin in that oral bioavailability is low, because it is quickly metabolized and excreted. Attempts have been made to increase bioavailability by the use of quercetin, catechin, apigenin, fisetin, myricetin, and kaempferol. Whether resveratrol will slow the progression of AD awaits the outcome of trials currently underway.[49]

Herbal supplements

Ginkgobiloba

Ginkgo biloba contains compounds that have antioxidant and anti-inflammatory properties that protect neuron membranes, regulate neurotransmitters, and retard cell degeneration. It is sold as a supplement in the United States, dispensed as a pharmaceutical in Europe, and has been used for centuries in traditional Chinese medicine. *In vitro* data show that Ginkgo biloba extract EGb 761 reduces βA and neuron death.[47,50]

Panax ginseng

The active components in ginseng are thought to be steroid-like compounds called ginsenosides. Ginsenoside Rg3 reduced βA_{1-42} by 84% *in vitro* and by 31% *in vivo*[51]

Withania somnifera

Withania somnifera, a small evergreen shrub commonly called ashwagandha or Indian ginseng,

has been used in India for thousands of years to treat many different diseases. A recent review enumerated many neuroprotective properties of ashwagandha, including anti-inflammatory, antioxidant, inhibition of βA, inhibition of calcium, inhibition of ACHE, and reduction of cell death. *In vitro* research has demonstrated that ashwagandha regenerates damaged axons, dendrites, and synapses. Oral administration of ashwagandha to mice reversed damage to the hippocampus and cortex by decreasing neurite atrophy, restoring synapses, and improving memory. At least 18 withanolides, the active components in ashwagandha, have been identified. Withanolides have different neuroprotective properties; for example, withanolide-A preserves axons, whereas withanolides IV and VI preserve dendrites.[52]

Nutrients

Phosphatidylserine

Phosphatidylserine is important in neurotransmission, mitochondria function, and cell metabolism. It has also been implicated in the enhancement of nerve growth factor. *In vitro* research demonstrates PS increases Ach and provides neuroprotection by inhibiting βA and inflammation.[53]

Alpha-lipoic acid

Alpha-lipoic acid (ALA), a fatty acid found in all cells and in some foods, is manufactured in the body. It is a powerful antioxidant that readily penetrates the blood-brain barrier, chelates metals, reduces inflammation, and increases ACh. The potential mechanisms underlying these and other neuroprotective effects are reviewed elsewhere.[54]

Omega-3fatty acids

Omega-3 fatty acids have many beneficial effects that make them investigative prospects for AD.[55]

Acetyl L-Carnitine

Acetyl L-Carnitine (ALCAR), derived from the amino acid L-carnitine, works synergistically with ALA to transport acetyl groups and fatty acids into the mitochondria for energy production. ALCAR is a small molecule that readily penetrates the blood-brain barrier and promotes biosynthesis of ACh while clearing mitochondria of toxic fatty-acid metabolites. Its effect on APP helps prevent the buildup of amyloid plaque and preserves synaptic function. ALCAR also increases nerve growth factor.[56]

Coenzyme Q10 (CoQ10; ubiquinone)/idebenone

Coenzyme Q10 is essential for mitochondrial energy production. Mitochondrial dysfunction can result in generation of reactive oxygen species and oxidative stress. Many mitochondrial dysfunctions occur in AD brains, including disruption of energy production, apoptosis deregulation, altered calcium homeostasis, and others (reviewed elsewhere). For these reasons, mitochondria are viewed as promising therapeutic targets. CoQ10 reduced oxidative stress and tau pathology in mice, and metabolized βA and inhibited its formation *in vitro*. The reduction of βA found in a mouse model was attributed to the antioxidant properties of CoQ10.[57]

Vitamins and minerals

Vitamin B

Low levels of vitamin B_{12} and folate appear to be associated with an increased rate of cognitive decline. Since AD patients typically have high levels of homocysteine, researchers have examined the possibility that lowering homocysteine would be therapeutic. A combination of vitamins B_{12} and B_6 and folate lowered homocysteine both in normal seniors and in those with mild to moderate AD, but had no effect on cognition. Homocysteine levels appear to correlate with aging but not with cognition.[58]

Vitamin A

Vitamin A has received attention because it is essential for learning, memory, and cognition, and because vitamin A levels in the brain decline with age and are lower still in individuals with AD. A metabolic product of vitamin A, retinoic acid, is known to slow cell death and offer protection from βA.[59]

Multiple nutrients

Since AD patients often have multiple deficiencies, it makes sense to use multiple supplements. A mixture of aALA, acetyl-L-carnitine, DHA, phosphatidylserine, and glycerophosphocholine prevented cognitive decline in aged mice.[60]

Minerals lithium

Lithium is a naturally occurring mineral found in small amounts in many foods. The lithium salts, orotate and aspartate, are sometimes recommended for neurogenerative disorders.

Lithium increases the level of a neuroprotective protein called bcl-2 in the rat hippocampus and frontal cortex and inhibits GSK-3, which is implicated in increasing levels of phosphorylated tau and is thought to be a factor leading to βA plaques and cell death. There is also human evidence that lithium increases N-acetyl-aspartate which protects cells

from dysfunction and death. An *in vitro* study found lithium's neuroprotection resulted from inhibiting [Ca. sup. $^{2+}$] influx mediated by NMDA receptors.[61]

Hormones

Melatonin

Melatonin is a naturally occurring hormone that is produce in decreasing amounts with age. Melatonin is a powerful antioxidant, provides mitochondrial support, protects against tau tangles, and reduces βA toxicity. Melatonin readily crosses the blood-brain barrier and enters all cell structures. Despite numerous studies, few have examined its effect on AD and the ones that did were small and of poor quality. Since melatonin improves sleep, it might help memory by facilitating memory consolidation.[62]

Diet

The Mediterranean diet was recently demonstrated to be associated with lower AD risk. A subsequent study has now shown that the Mediterranean diet is also associated with lower mortality in AD with a possible dose-response effect. This diet is characterize by high intake of fish; a low-to-moderate intake of saturated fatty acids, moderately high intake of fish, low-to-moderate intake of dairy products, low intake of meat and poultry, and a moderate amount of ethanol.[63]

Selegiline

Selegiline, a monoamine oxidase inhibitor, similarly to alpha-tocopherol may have beneficial effects in patients with AD. Selegiline also increases levels of catecholamines, and adrenergic stimulation may improve cognitive deficits associated with AD. A number of studies have examined evidence for the use of selegiline, a selective monoamine oxidase inhibitor, in the treatment of AD.[64]

Hormone-replacement therapy

Descriptive studies have shown that postmenopausal women who take estrogen have a lower incidence of AD. In addition, a recent review of estrogen and neuroimaging studies demonstrated improved cerebral metabolism in women taking estrogen. Although estrogen may have a neuroprotective effect, it does not appear to improve cognition or function in patients with AD, and the combination of estrogen and progestin actually may increase the risk for dementia and stroke.[65]

Lipid-lowering drugs

The links or connections between cholesterol and AD have been known and have been strengthened by the discovery of a risk factor, ApoE, a gene and protein participating in the transport of cholesterol. Concomitantly, it has been demonstrated that statins, cholesterol-lowering compounds, decrease the risk of developing AD via a mechanism which may be independent of cholesterol (induction of nitric oxide synthase; decrease of endothelin-1). These compounds may inhibit the formation of Aβ by giving priority to α-secretase activity and by decreasing the activities of β- and γ-secretases, with the latter enzymes co-localized in cholesterol-rich membrane rafts (the α-secretases including ADAM are in a sphingomyelin environment). Furthermore, it has been demonstrated that inhibitors of acyl-coenzyme A β- or γ-secretase activity could be therapeutic in the early clinical phases of the disease, particularly in patients with the subtle syndrome of minimal cognitive impairment (MCI). G-secretase inhibitors could be designed to decrease β-amyloid protein production by 30%–40%, without interfering in a quantitatively important way with notch signaling. Whether such a beneficial therapeutic index for a g-secretase inhibitor can be achieved by cholesterol acetyltransferase, and inhibitors of cholesterol esterification, inhibit the secretion (release) of Aβ.[66]

AD immunotherapy

An alternative approach to secretase inhibition would be to use small molecules to bind Aβ protein monomers and prevent their aggregation into potentially neurotoxic oligomers. The utility of vaccine strategies to treat neurodegenerative diseases, such as AD may still hold promise. Both active and passive immunization strategies reduced AD-like pathology and restored cognitive deficits in transgenic mice. Three general mechanisms for the beneficial effects of active and passive immunization have been proposed: (1) anti-Aβ protein antibodies may cross the blood-brain barrier in small amounts and bind to Aβ protein, followed by gradual clearing of the resultant Aβ protein antibody complexes by local microglia; (2) high titers of anti-Aβ protein antibodies in the peripheral circulation may bind and sequester Aβ protein in adjuvant to humans with mild to moderate AD resulted in a 6% of patients developing an inflammatory reaction in the CNS that resembled a postvaccinal meningoencephalitis.[67]

Antiamyloid immunotherapy for AD has received considerable attention following reports that amyloid pathology was reduced in an APP transgenic mouse model on vaccination with aggregated Aβ42. A postmortem study of a patient admitted to the clinical

Table 2: Stimulatory therapies for Alzheimer's disease

Activity	Advantages	Disadvantages
Physical exercise	Increases blood to brain; improves vascular function; aids sleep; reduces inammation; elevates mood; increases brain volume; increases synaptic plasticity; aids neurogenesis; reduces cell death; benets some cognitive processes	None if done within one's physical capabilities; little research specically on AD patients
Cognitive training	Improves many cognitive functions	More research indicated
Socialization	Preserves cognitive functioning; may improve reduce mood stress and depression	Little research
Music	improves cognition, perhaps by aiding the destruction of dysfunctional cells, increasing melatonin levels, facilitating neurogenesis, and increasing plasticity	Little research
Psychological factors	A positive attitude may stimulate patients to exercise and engage in activities that are beneficial	No research specific to AD

AD: Alzheimer's disease

trials stopped for the reasons indicated above showed evidence of plaque reduction. Immunization of AD patients provides a novel means of specifically targeting the neurotoxic effects of Aβ peptide and thereby targeting disease progression. Recently, it has been shown that antibodies against Aβ are present in human immunoglobulin preparations (IVIG), which specifically recognize and inhibit the neurotoxic effects of Aβ.

Stimulatory therapies

Physical exercise, cognitive training, and socialization are generally thought to facilitate cognitive functioning. Physical exercise increases the blood supply to the brain and regulates chemicals such as insulin that are necessary for a healthy brain as given in Table 2. Recent reviews of studies on exercise indicate that exercise may facilitate learning and memory, improve vascular function, reduce inflammation, improve metabolism, elevate mood, delay age-related memory loss, speed information processing, increase brain volume, aid hippocampal neurogenesis, increase synaptic plasticity, increase brain-derived neurotrophic factor, increase dendritic spines, enhance the glutamatergic system, and reduce cell death.[68]

Mechanisms that might underlie such benefits include increased natural killer cells that destroy dysfunctional cells and increased serum melatonin levels. A recent paper hypothesized that music increases steroid production that facilitates neurogenesis, repairs cells, and increases neural plasticity.[69]

CONCLUSION

Although evidence has been presented to suggest that Aβ is central to the pathogenesis of AD, there are many complex secondary events that all contribute to final outcome of neurodegeneration. Tremendous progress has been made in developing strategies to treat AD. Some of these strategies include antiamyloid, anti-inflammatory, anticholinergic, antihypertensive, secretase inhibitor and some natural nutrients, hormones, vitamins, immunotherapy, and stimulatory therapies. Currently, Food and Drug Administration-approved drugs treat AD symptomatically and provide temporary relief form dementia. However, these drugs are frequently associated with adverse drug effects and do not cure the disease by modifying its pathology. There remains an urgent need to develop effective and safe alternative approach for the treatment of AD.

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How to cite this article: Upadhyay P, Panjwani D, Yadav AK. Neuropathology staging and treatment strategies of Alzheimer's disease: An update. Int J Nutr Pharmacol Neurol Dis 2014;4:28-42.

Source of Support: Nil. **Conflict of Interest:** None declared.
Received: 13-6-2013, **Accepted:** 18-09-2013