IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 10, Issue 7 Series. II (July 2020), PP. 91-100 *www.iosrphr.org*

An overall approach to study Dementia

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Received 10 July 2020; Accepted 26-July 2020

ABSTRACT
Dementia is a syndrome characterized by progressive decline in cognitive functions. The neuropsychiatric symptoms like: apathy, agitation and depression are included in dementia.The root causes of dementia were: various underlying disorders.Age is the main risk factor for dementia. There are three types of dementia: Cortical, subcortical and mixed dementias.

I. INTRODUCTION

Dementia is a progressive, untreatable disease.[1] Dementia is a syndrome characterized by decline in cognitive functions. The neuropsychiatric symptoms included are: Lack of concern, anxiety and depression. The patient becomes dependent on others to perform daily routine activities, as this disorder progresses.[2]The root causes of dementia were various disorders that were characterized by specific signs and symptoms in combination with assumed essential neuropathology.[3] Oxidative stress has been concerned in cognitive defects in disease states like dementia. Oxidative stress is characterized by the production of highly reactive oxidizing factors, such as free radicals and reactive oxygen species (ROS).[4]

Dementia

Dementia is a syndrome characterized by progressive decline in cognitive functions. The neuropsychiatric symptoms like: apathy, agitation and depression are included in dementia. On the progression of disorder, the patient progressively becomes dependent on others for daily routine activities. The root causes of dementia were: various underlying disorders. Alzheimer's disease is considered as the most widespread cause of dementia. Most of the Dementias are progressive,irreversible and incurable ,and it is often not easy to discriminate between the subtypes of dementia. Age is the main risk factor for dementia, prevelance is 2% in those with age 65-69 years while compared with 20% in those with age 85-89.[3] About 4.6 million new cases of dementia were estimated every year ,and is estimated to get doubled in 20years and can reach more than 80million by 2040.[5]

Cognitive functions effected in dementia include: language (aphasia), motor (apraxia), agnosia (failure in recognition) & executive functions (abstract reasoning, judgment and planning).[6]

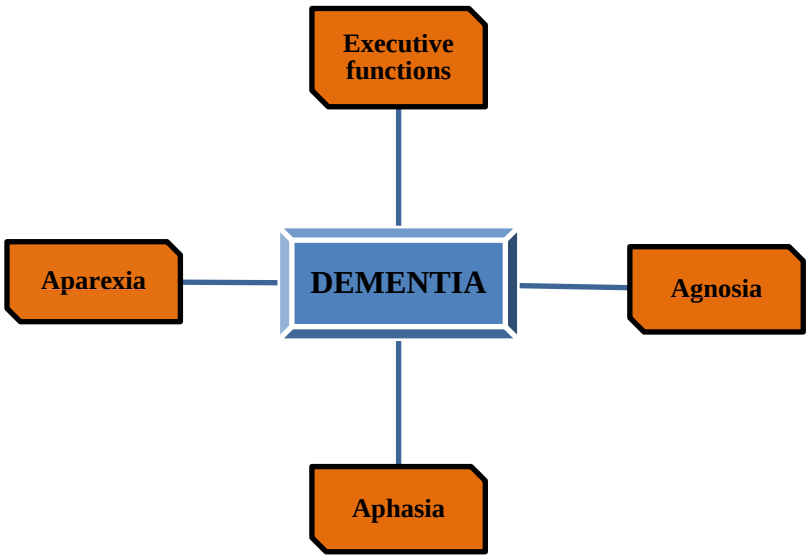


Figure 1- cognitive functions affected in Dementia[6]

Symptoms of dementia may include the following:

- Agitation/ irritability/ mood liability
- Anxiety
- Apathy
- Delusion
- Depression
- Disinhibition
- Euphoria
- Hallucinations
- Loss of appetite
- Sleep disturbances

Fig. 2 symptoms of dementia[7]

Types of Dementia:

Both anatomical and biochemical changes in the brain may occur in dementia according to its causes Dementia is categorized in few subtypes as follows:

Cortical Dementias: Dementias which involves the principal involvement of dysfunction is in cortex region.
Subcortical dementias: dementias which involves the principal involvement of white and grey matter structures such as basal ganglia, thalamus and frontal lobe projections.
Mixed dementias: these dementias usually involves those dementias which includes both cortical and subcortical regions.[8]

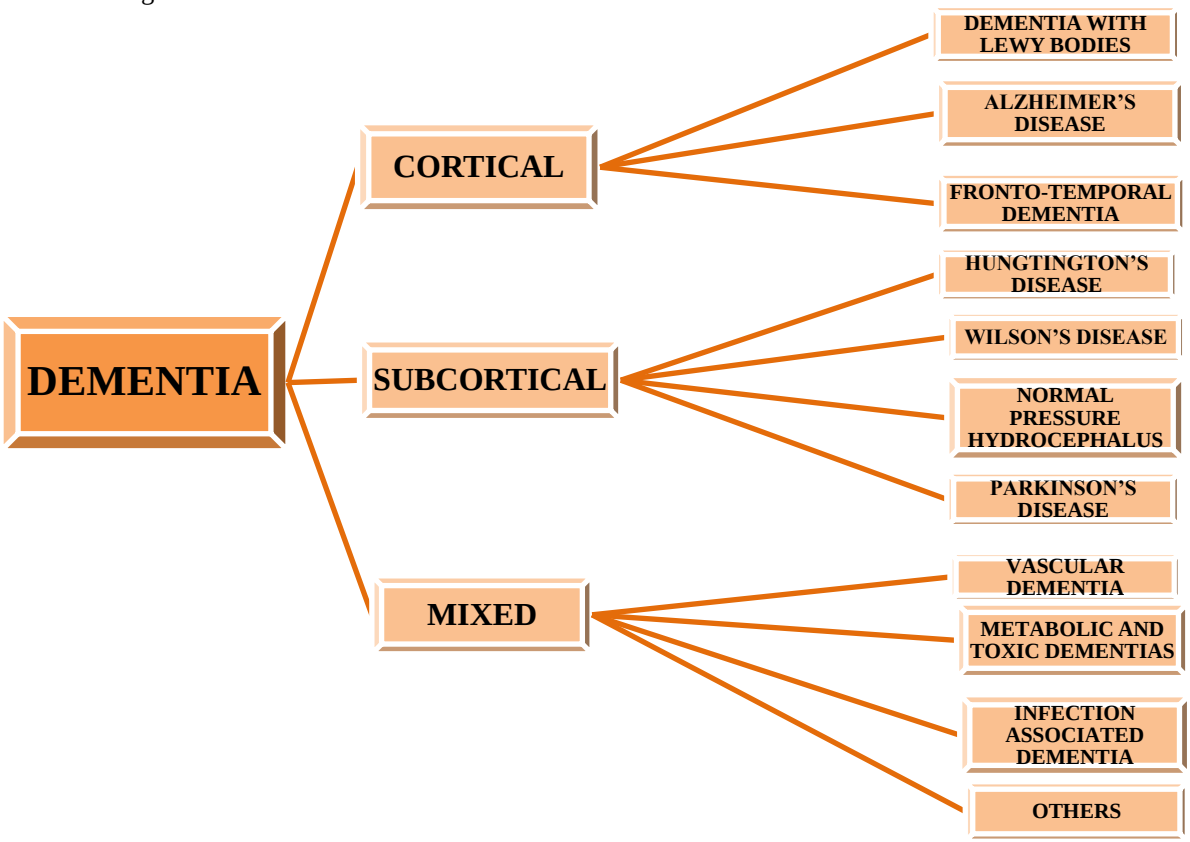


Figure 3: Types of Dementia[3]

Cortical dementias:

i. Alzheimer's Disease:

Alzheimer's disease is a unbearable and progressive neurodegenerative disease, and is considered as the most common cause of dementia and amongst the older people it is considered as the leading cause of disability and death.[9] Gradual neurodegeneration affecting the short-term memory was precipitated by Alzheimer's disease followed by long-term memory memory loss.[10] AD is a senile or presenile onset condition that may be progressive and neurodegenerative and it depends upon whether the disease occurs before or after the age of 65 years. Sleep disturbance, anxiety , aggression and agitation are mostly accompanied in Alzheimer's disease.[11]The neuropathological features like accumulation of misfolded proteins are accompanied in alzheimer's disease. These protein aggregates are formed as amyloid- beta (Aβ) and phosphorylated tau protein in the form of neurofibrillary tanges (NFTs)[12]. Oxidative and inflammatory damage, which may result in energy failure and synaptic dysfunction is caused by the misfolded proteins aggregates.[13] Neurofibrillary tangles are mainly made up of phosphorylated tau proteins and are microscopic paired helical filaments. Some neurotransmitters and neuromodulators are affected biochemically in AD.[14]

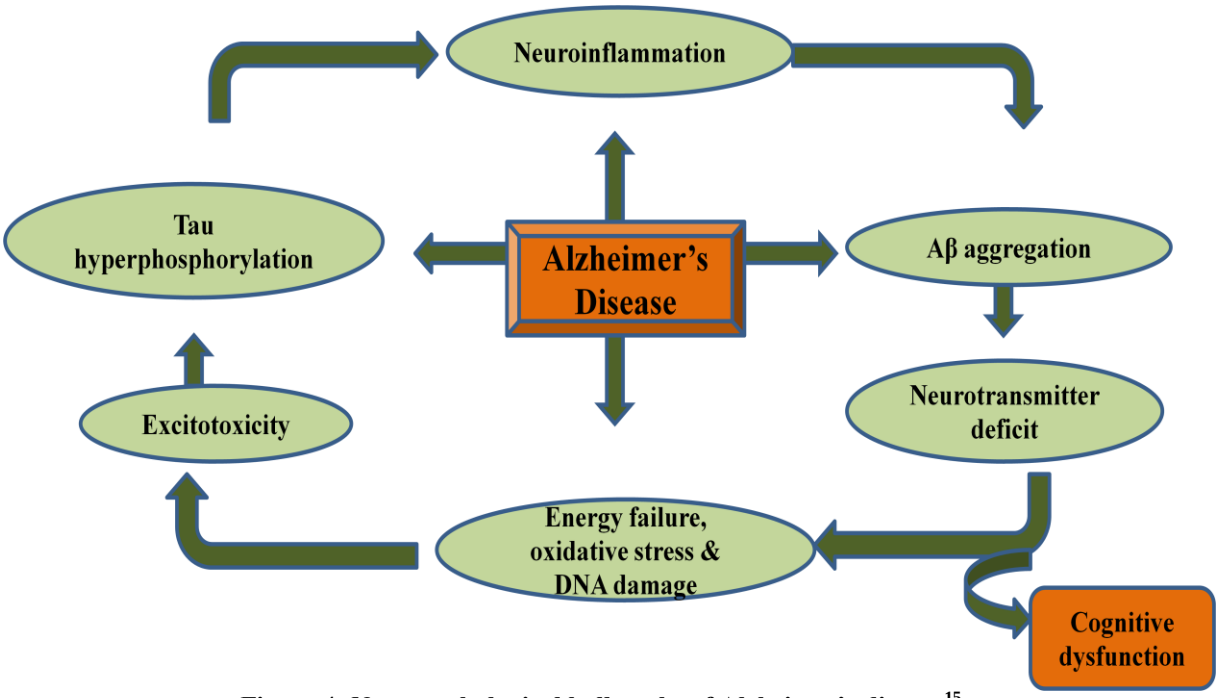
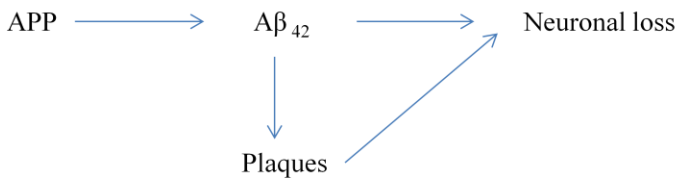
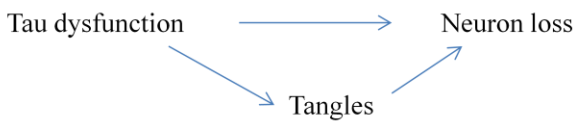


Figure 4: Neuropathological hallmarks of Alzheimer's disease[15]

A. Amyloid hypothesis



B. Tau hypothesis



C. Unknown trigger hypothesis

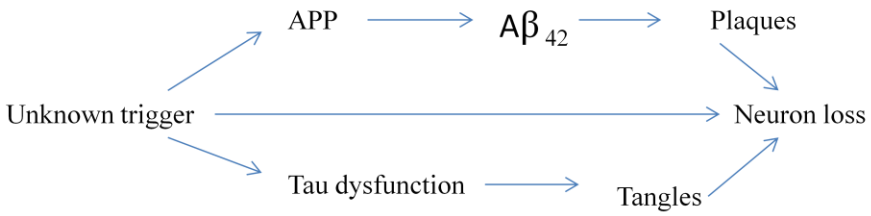


Figure 5: hypothesis to explain neurobiology of alzheimer's disease[15]

ii. Dementia with Lewy bodies:

About 15 to 20 percent of dementia cases were considered with dementia with lewy bodies. The disease seems to be positioned somewhere between AD and parkinson's disease.[3] DLB has some characteristic features like spontaneous parkinsonism, recurrent visual hallucinations, fluctuating cognition, rapid eye movement sleep behavior disorder (RBD), severe sensitivity to antipsychotic medications and decline in striatal dopamine transporters on single photon emission computed tomography (SPECT) or positron emission

tomographty (PET).[16] DLB has distinct microscopic features: Lewy bodies and amyloid plaques in the subcortical and cortical regions of the brain. Heavily phosphorylated alpha- synuclein becomes cross- linked to form the insoluble complexes that are lewy bodies. Lewy bodies contain a variety of inflammatory markers (interleukins), proteases, BA and Lipids. Lewy body development is accompanied by neuronal loss with specific deficits in cholinergic and dopaminergic neurotransmission.[5]

iii. Frontotemporal dementia:

FTD is also called as fronto-lobar degeneration (FTLD) sometimes and it is considered as the second commonest cause of dementia in younger people (< 65 years), focal atrophy of the frontal and anterior temporal lobes, with associated cognitive features. The presenting feature of the disease are the behavioural changes and it dominates the clinical picture during the disease course, whereas the qualitative changes in language and cognitive impairments in executive function may also takes place.[17]
Two major presentations are documented:

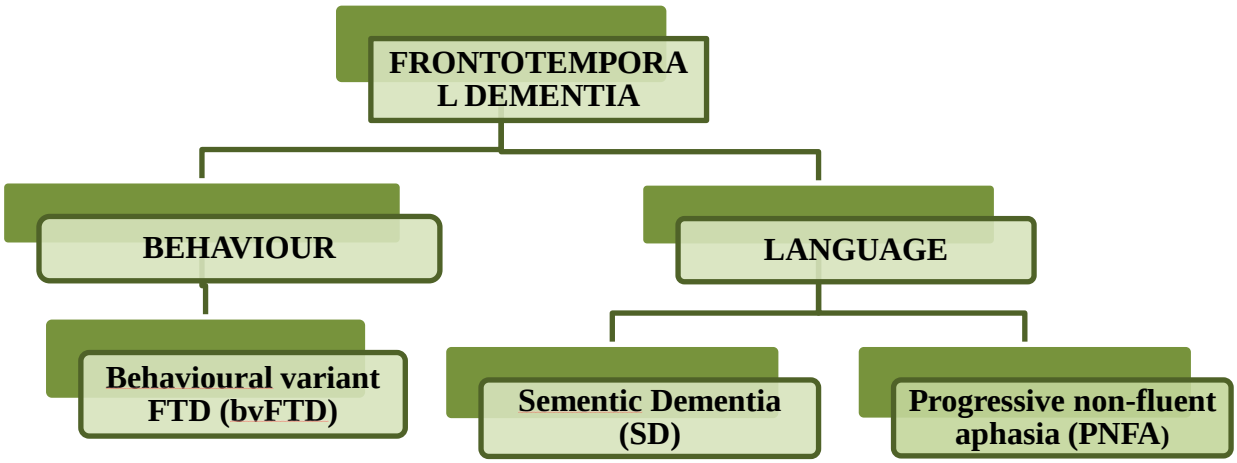


Figure 6: Classification of frontotemporal dementia[18]

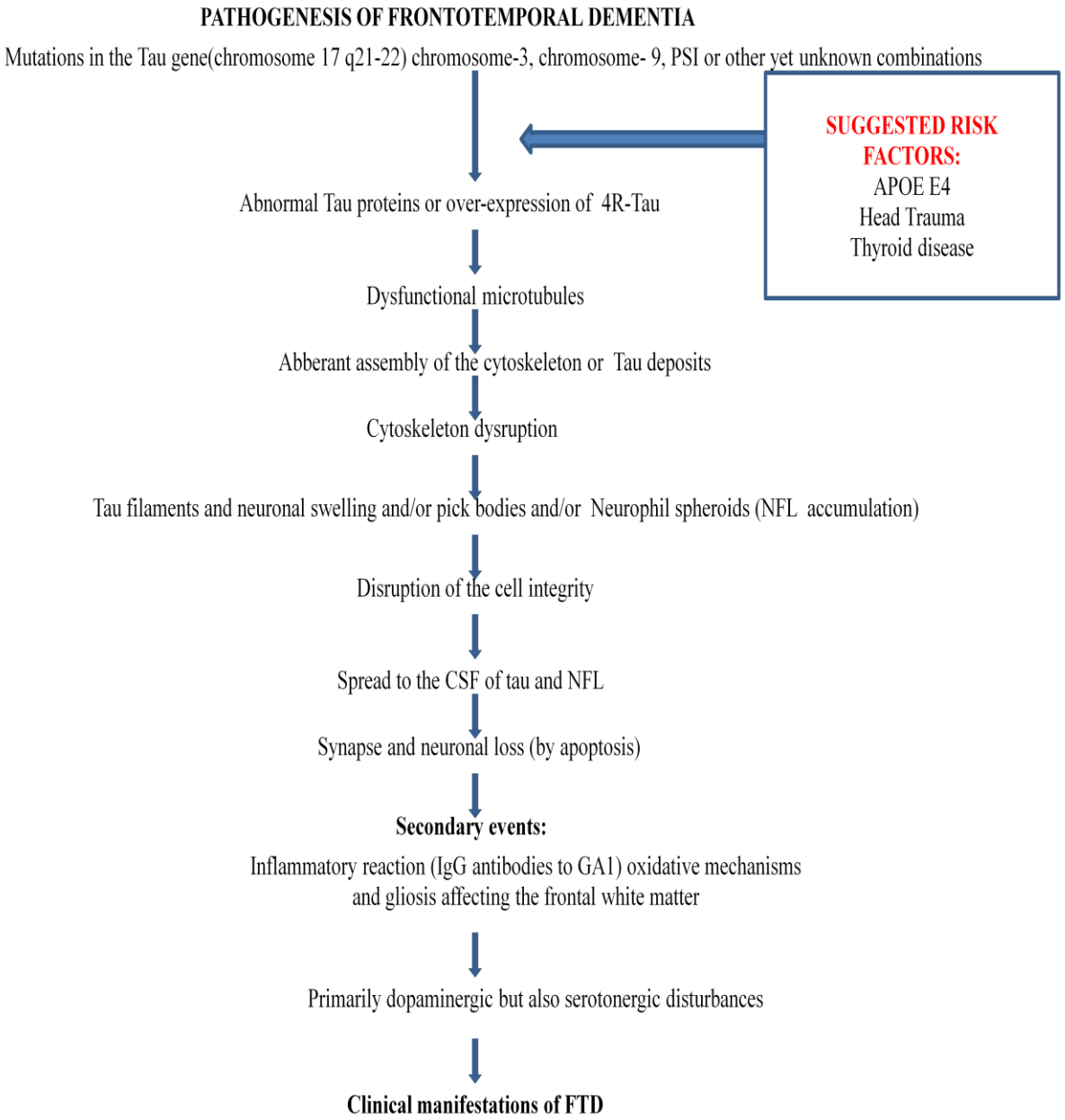


Figure 7: Pathogenesis of Frontotemporal Dementia[19]

I. A behavioural variant (bvFTD)- Major change in personality and social behavior, with apathy or disinhibition, emotional blunting, stereotyped behaviours, loss of empathy, changes in appetite and food preference with limited or no insight are the few characteristic features of bvFTD. These changes show involvement of orbital and mesial frontal lobes.[19]

II. Language variant – It can be divided into two different patterns:

- Sementic dementia: philosophical loss in conceptual knowledge, leads to anomia and impaired understanding of words, objects or faces are being accompanied in senile dementia.
- Progressive non-fluent dementia (PNFA): steady loss of expressive language abilities with impairments in phonological (sound-based) and grammatical aspects of language production were accompanied in PNFA.

Repetition of multisyllabic words and phrases were impaired in PNFA but in comparison with SD , word comprehension and object detection are well conserved.[18]

Subcortical Dementias:

iv. **Parkinson's disease:**

Out of all Parkinson's disease patients about one-third patients are found to be prone to subcortical and progressive dementia. The neurodegeneration is not only restricted to substantianigra but is also found to extend to other subcortical nuclei as well as limbic system and the cerebral cortex. The losses of cholinergic,dopaminergic and nonadrenergic interventions are the fundamental neurochemical deficits of parkinson's disease.[20] As compared to the general population, the patients with Parkinson's disease were found to have a higher rate of cognitive decline[21].

v. **Huntington's disease:**

Huntington's disease is an autosomal dominant disorder with an average track of about 15 to 20 years that affects patients between the age of 30 to 50 years[22]. "Fidgety" movements (chorea) isthe main and primary symptom of Huntington's disease but cognitive decline, attention deficit and depression were also being followed in this disease. In patients with HD, development of bipolar disease and schizophrenia is most common. A polymorphic trinucleotide repeat in chromosome 4p has been recognized as the responsible gene mutation of Huntington's disease[23].

vi. Wilson's disease:

In the patients with wilson's disease, distinctive extrapyrimidal signs were seen. The common symptoms of the disease were: depression, disinhibition, personality changes and reduced impulse control, while the mild symptoms of the disease were: cognitive defects[3]. Abnormal and vicious deposition of copper in the basal nuclei, which is due to an inherited defect in the copper- carrying serum protein ceruloplasmin were found to be mainly responsible for the psychopathological features of the disease[24].

vii. Normal pressure hydrocephalus:

Motoric and psychopathological features i.e. an early abnormal gait (resembling the steps of spastic paraparesis); subcortical dementia with particularly severe apathic features and urinary ncontinence were the characteristic triad of clinical symptoms of this neuropsychiatric syndrome. With the beginning of the incident, the cognitive deficits may emerge[24]. The tissue destruction by stretching may lead to the neuropsychiatric deficits and as a result may lead to the chronic hydrocephalus.[3]

Mixed dementias and dementia in disseminated brain diseases:

Vascular dementia: Vascular dementia (VaD) is a progressive disease that affects cognitive abilities and reduced blood flow may leads to vascular dementia. Common symptoms of vascular dementia are: slowed thinking, forgetfulness, depression and anxiety, disorientation, and loss of executive functions like problem solving, working memory, thinking, reasoning, judgment, planning and execution of tasks, with performance declining with increasing task complexity[25]. VaD is the second most common form of dementia (upto 20% of the cases) inn the elderly after AD.[26]

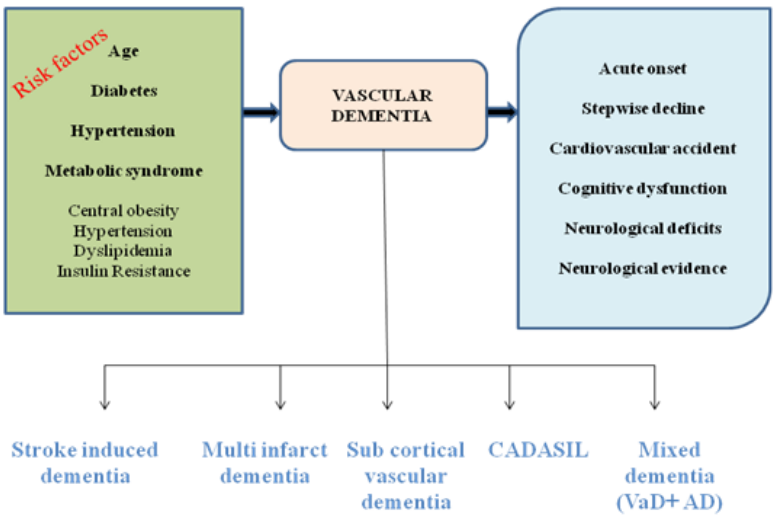


Figure 8: risk factors,subtypes and characteristics of Vascular dementia[27]

Mechanisms implicated in Vascular dementia:

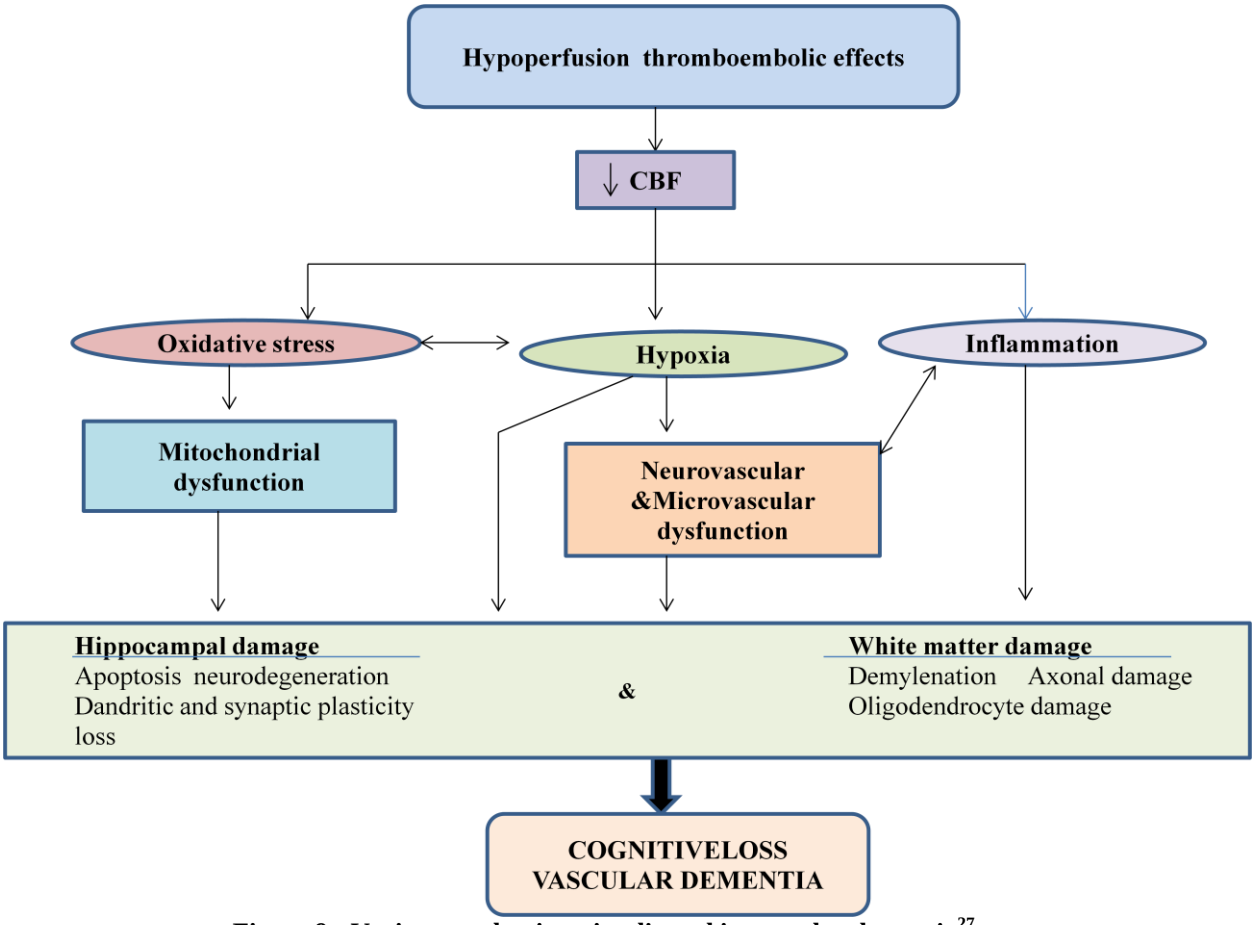


Figure 9: Various mechanisms implicated in vascular dementia[27]

Vascular dementia may be categorized into several subtypes, depending upon the nature, extent and site of neuropathological lesions as follows:

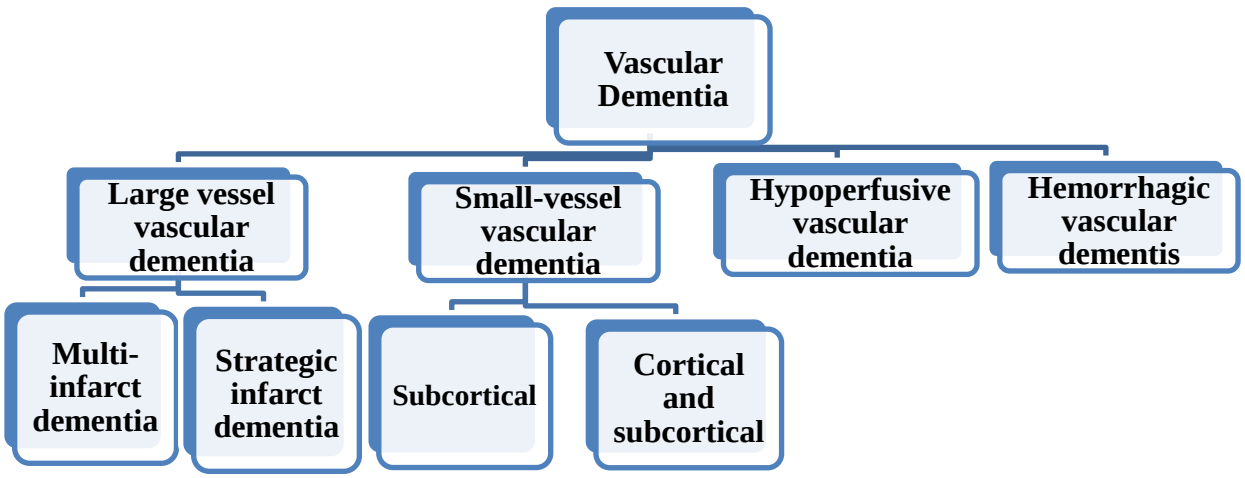


Figure 10: Subtypes of vascular dementia.[3]

Infection associated dementia:

- HIV dementia: HIV dementia: It is likely to become more common, considering the rise in HIV infection. It is estimated that up to 30 percent of patients with HIV will develop HIVD. HIVD is a subcortical dementia where patients have poor cognitive flexibility, reduced response times, apathy and emotional lability.[28]
- Creutzfedlt- jakob disease: it is a dementia with rapid course, caused by transmissible infectious agent, the prion. The cognitive deterioration is progressive, widespread and accompanied by pyramidal and extrapyramidal signs i.e myoclonic jerks, ataxia and muscle rigidity.[29]
- Neurosyphillis: It may evolve into different types of dementia if left untreated. The dementia may be easily recognized in advanced state by characteristic signs, such as papillary abnormalities, dysarthria, tremor of tongue and hypotonia.[30]
- **Metabolic and toxic dementias-** Dementia in these conditions has predominantly subcortical features but may have mixed characteristics.[31]It may be a result of associated malnutrition, especially of B vitamins and particularly thiamine
- **Neoplastic- associated dementia-** Neoplastic diseases essentially may produce any kind of neuropsychiatric symptoms.[32]
- **Dementia following traumatic brain injury-** Traumatic brain injury may cause variety of cognitive difficulties. The severe trauma with loss of consciousness is called as post- traumatic amnesia.[3]
- **Psychiatric diseases associated dementia-** The relationship between dementia and depression is complex. Dementia syndrome of depression occurs during episodes of severe mood disorders.[33]

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