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A BRIEF REVIEW ON DEMENTIA -INFLUENCE OF HYPERTENSION ON IT

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ABSTRACT

Dementia is world's fifth leading cause of mortality. It is an term for several diseases affecting memory, other cognitive abilities and behavior. There are mainly three types of dementia are seen commonly allover the world, there are Vascular dementia, Alzheimer disease and Mixed dementia. Vascular dementia cover 40% in the whole dementia, Alzheimer's disease occupy nearly 60% of dementia but Mixed dementia is more prevalent it is due to other types of dementia are less prevalent. dementia is influenced by several factors like hypertension,age, obesity etc… but main risk factor is hypertension and it is also differ based on age as mid life hypertension seen in people of middle age 40-65years and late life hypertension see in people of 75years or above. In this article we come over about dementia, types of dementia with etiology, pathophysiology and diagnosis of each type and influence of hypertension on dementia with recent evidences through studies on it along with world wide and India wide future projections on incidence of dementia up to 2050 and recent age standardization death rates worldwide.

KEYWORDS: Alzheimer's disease, Cognitive, Dementia, Hypertension, Hypoperfusion, Vascular.

INTRODUCTION

Dementia is referred as acquired global impairment of intellect,memory,ability to comprehend and recognize people,loss of orientation and other cognitive functions, in the absence of gross clouding of consciousness or motor dysfunction.It has a physical, psychological, social, and economic impact, not only on people with dementia, but also on their career, families at-last in the society.

Around 50 million people have dementia, and there are nearly 10 million new cases are seen every year worldwide. It is one of the major causes of disability and dependency among older people. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment but it does not affect the consciousness.The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior.

It is caused by a number of diseases of the brain like pick's disease,creutzfeldt-jakob disease,karasakoff's syndrome, lewy bodies, brain injury, brain tumor and other causes like metabolic toxic, vitamin deficiencies, mass lesions, infections, endocrine disorders finally hypertension.

Stages of dementia

No dementia

STAGE 1

The person functions normally and mentally healthy in this stage. It cannot diagnosed because no signs or symptoms, no memory loss, behavioral problems, or anything else associated with the onset of dementia

STAGE 2

In this stage, surrounding people may start to notice some level of forgetfulness.

Normal forgetfulness for aging.symptoms of dementia are still not apparent to doctors.

STAGE 3

The last stage in this category mild cognitive decline.At this stage,people began to identify signs of cognitive decline as surrounding people experiences increased forgetfulness, decreased work performance, speech difficulty, and difficulty focusing on daily tasks. This stage is also known as mild cognitive impairment and it crucial for recognize the signs of this stage for early diagnosis.

Signs and Symptoms

Decreased work performance.
Increased memory loss.
Trouble in concentrating and problem solving.

Managing complex tasks.
Driving difficulties.
Verbal repetition.

Early dementia
STAGE 4
Early-stage dementia has only one stage – moderate cognitive decline. It lasts an average of 2 years and cognitive issues can be identified during a medical examination.person in this stage will have difficulty in concentrating and forget recent events and even have difficulty in managing finances and traveling. Additionally, they may experience difficulty socializing and begin withdrawing from friends and family. In this stage, surrounding people should make a more effort to actively engage the person with dementia.There have more involved role in this stage and subsequent stages and create a daily care and make adjustments to schedules as needed to provide the necessary level of care.

Signs and Symptoms
Misplacing items in work places.
Forgetting recent conversations.
Struggling to find the right words in a conversation.
Losing track of the daily.
Loss of interest in other people or activities.
Unwilling to try new things.
Increased feelings of anxiety, irritability, or depression.
Trouble remembering names when meeting new people
Increased trouble planning or organizing

STAGE-5
Lasting an average of 4 years, a person in mid-stage dementia now needs assistance to complete activities of daily living.

Signs and symptoms of dementia will be very easy to identify.short-term memory will be mostly lost and confusion and forgetfulness will be more pronounced throughout activities of daily living.

Middle dementia
STAGE-6
A person may start forgetting the names of close loved ones and have little memory of recent events. Communication is severely disabled and delusions, compulsions, anxiety, and agitation may occur.

Signs and Symptoms
Problems sleeping and confusing day and night Behaving inappropriately.

Wandering.
Difficulty with perception delusions and/or hallucinations.
Increased aggression and irritability.
Inability to recall personal history, address, and phone number.
Changes in sleep patterns may begin.

Late dementia
STAGE-7
In this very severe cognitive decline lasts an average of 2-5 years. A person in this stage usually has no ability to speak or communicate and requires assistance with most activities, including walking. During this stage, caregivers will focus mostly on providing comfort and quality of life around-the-clock.

Signs and Symptoms
Difficulty eating and swallowing.
Considerable changes in weight Incontinence.
Gradual loss of speech.
Restlessness.
Angry outbursts due to confusion.
Increasingly vulnerable to infections especially pneumonia.

World Wide Evidences on Demenia

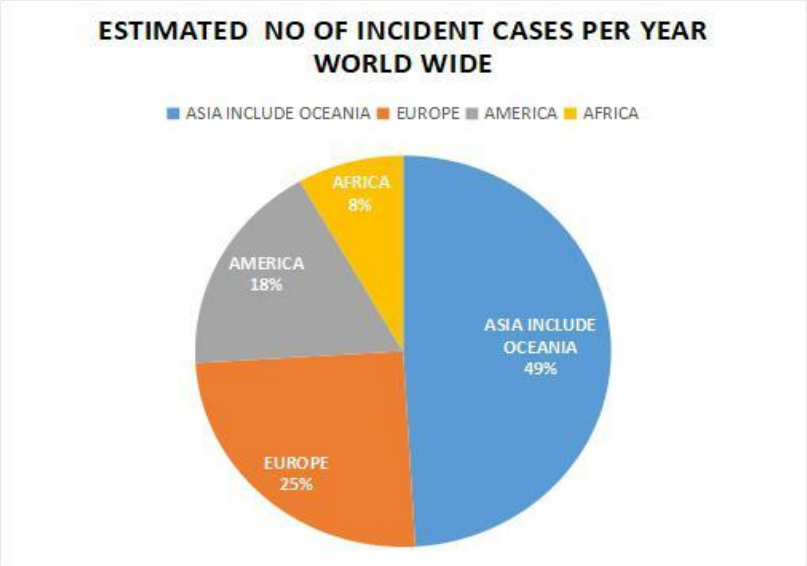


Fig. 1: Dementia incident cases per year as per world Alzheimer report.

It gives the information about the incidence of dementia world in continents.

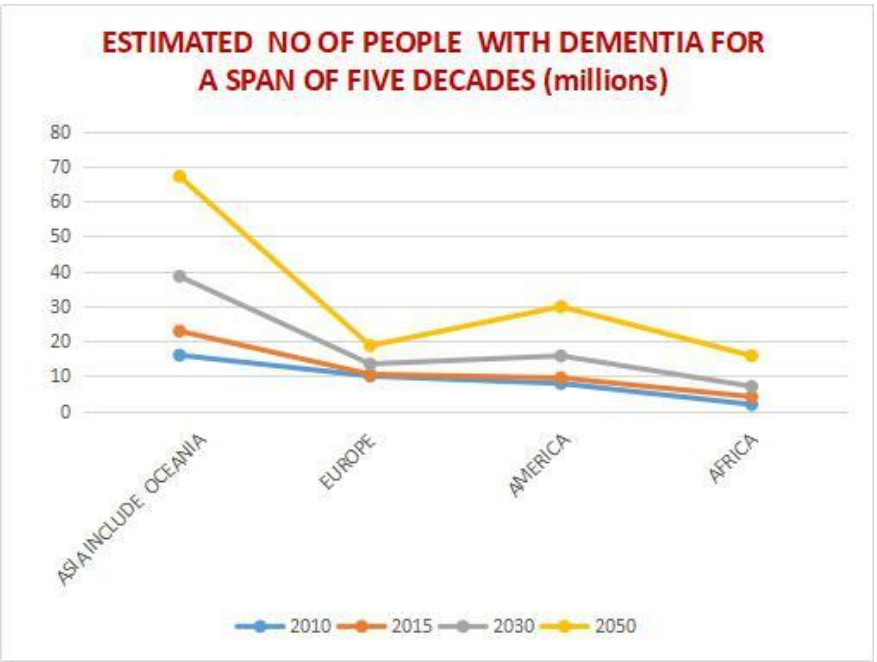


Fig. 2: Estimated projection of no of people with dementia for a five decades as per world Alzheimer reports.

It gives the information about dementia projections worldwide for a decade.

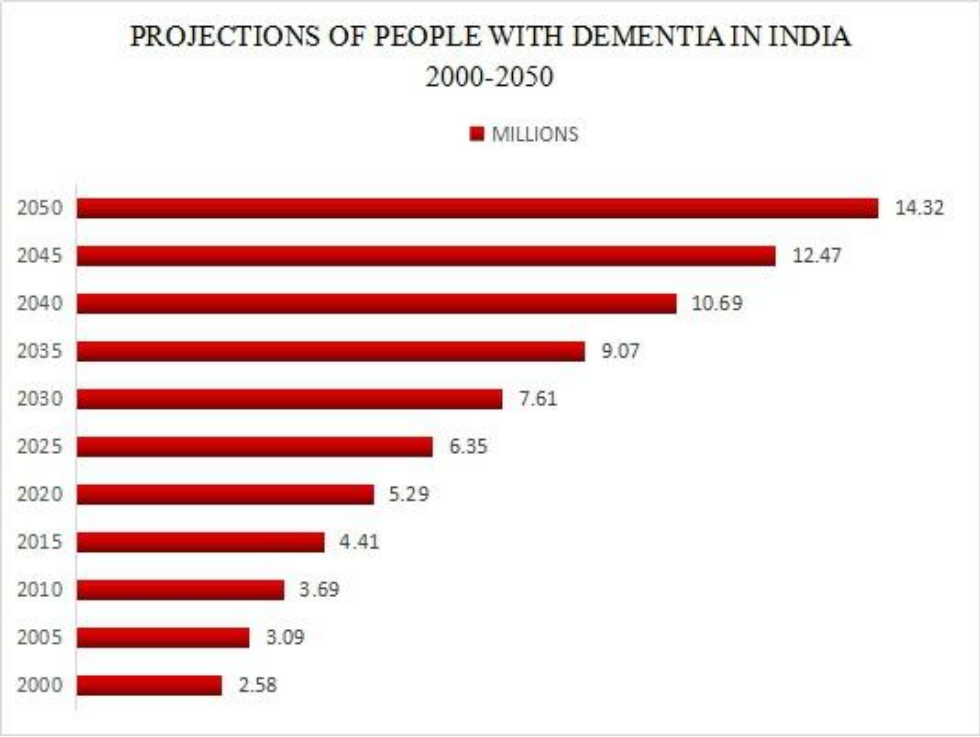


Fig. 3: Projected no of people with dementia for a five decade as per THE DEMENTIA REPORT 2010.

It gives the detail data about the projected number of people with dementia in India up to 2050.

Table 1: Estimated prevalence cases of dementia in India state wise as per THE DEMENTIA REPORT 2010.

STATES	Category
ANDHRA PRADESH	Cat B
ARUNACHAL PRADESH	Cat B
ASSAM	Cat B
BIHAR	**Cat A**
CHHATTISGARH	Cat B
GOA	-
GUJARAT	Cat B
HARYANA	Cat C
HIMACHAL PRADESH	Cat C
JAMMU&KASHMIR	Cat B
JHARKHAND	**Cat A**
KARNATAKA	Cat C
KERALA	Cat C
MADHYAPRADESH	Cat B
MAHARASTRA	Cat C
MANIPUR	Cat B
MEGHALAYA	Cat B
MIZORAM	Cat B
NAGALAND	Cat B
ODISHA	Cat C
PUNJAB	Cat C
RAJASTHAN	Cat B
SIKKIM	Cat B
TAMILNADU	Cat C
TELANGANA	Cat B
TRIPURA	-
UTTARPRADESH	Cat B
UTTARAKAND	Cat B
WESTBENGAL	Cat C

The above table divide the dementia incidence states in India in to three categories i.e cat A,cat B,cat C

Category A referred as the states which the projected incidence people are higher then 500,000.

Category B referred as the states which the projected incidence people are between the 500,000-40,000.

Category C referred as the state which the projected incidence people are between the 40,000-20,000.

So by this categories most prevalent states and less prevalent states are seen.

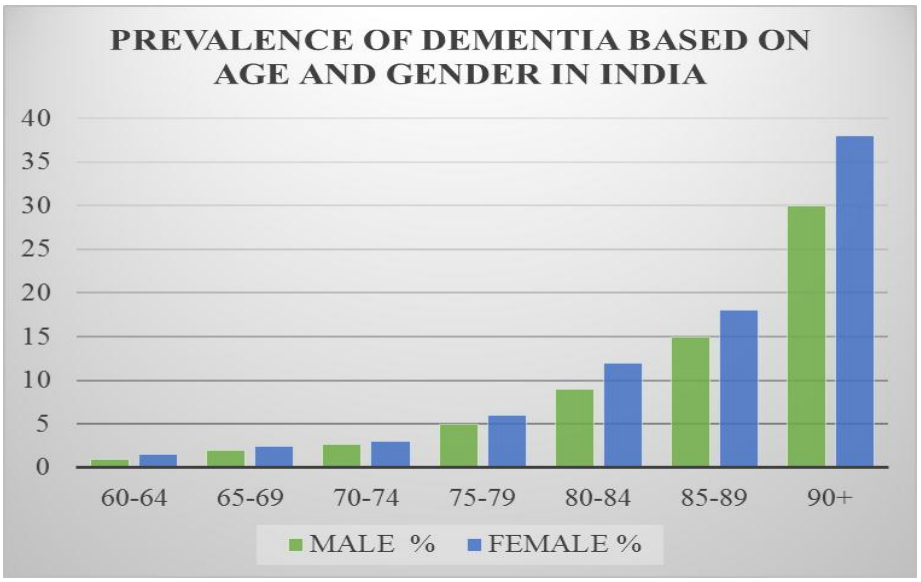


Fig. 4: Prevalence of dementia based on age and gender in India.

The above graph gives information about the prevalence of dementia in different ages from 60 years to 90+ years of both genders in percentages.

AlZHEIMER's DISEASE

Alzheimer disease is the most common form of dementia and may contribute to 60–70% of cases. It was first seen in 51 years women named Auguste D who was having the history of progressive cognitive impairment, hallucinations, delusions, and severely impaired social functioning. Their identified Alzheimer in her brain amyloid plaques, neurofibrillary tangles, and arteriosclerotic changes.[1]

Recent studies tells the features of Alzheimer's disease, such as brain lesions, may already present in midlife but symptoms of the disease do not appear until years later. while the symptoms exposed then it becomes harder for people to remember recent events in their life and to recognize people they know. finally a person with Alzheimer's is likely to need full-time dependent on others for their needs. [2,3]

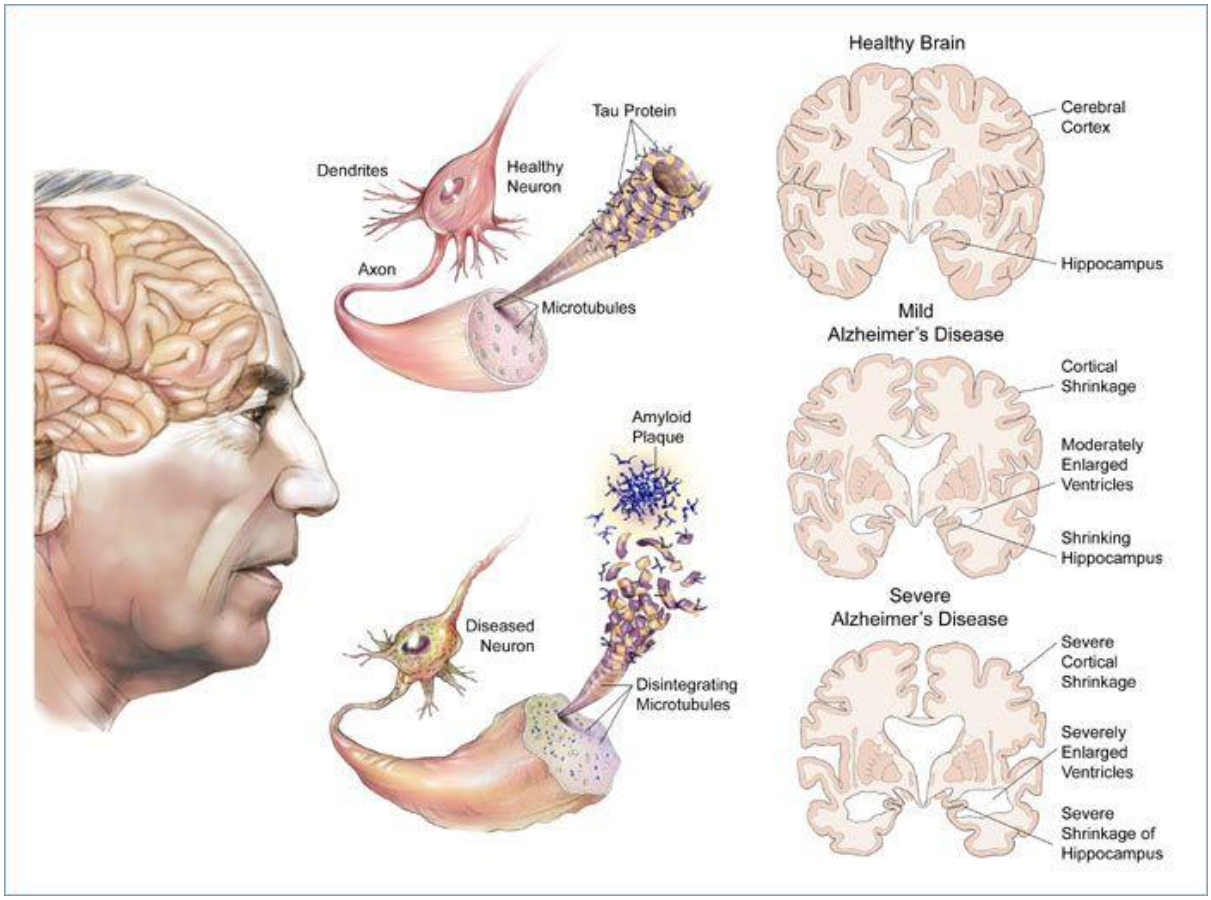


Fig. 4: Gives a brief idea about Alzheimer's disease.

Alzheimer disease genetics has been divided into two broad categories:-

Early-onset alzheimer disease (EOAD)

EOAD only accounts for less than 10% of all people with AD at age of < 65 years,but clear genetic foundations have been shown to cause EOAD. In other word, there is a clear genetic ground for EOAD. According to the previous studies, associated genes with EOAD introduced separately.[4]

EOAD cases are inherited in an autosomal dominant pattern. In this form, dominant mutations in genes like APP, PSEN-1 and PSEN-2 associated with alzheimer disease.[5,6]

Late Onset Alzheimer Disease

There are several genes that investigated in relation with late onset Alzheimer disease. Twenty important genes associated with Alzheimer disease.

Etiology

Risk factors for Alzheimer's disease and their relationship to its pathogenesis.

Genetic Factors - APP mutations ,Presenilin 1 and 2,Apolipo protein ε4.

Biochemical Factors - Inflammation,Free radical,Nerve growth factor deficit,Estrogen deficit.

Unmodifiable Risk Factors - Age, Head size, Education level, Sex.

Modifiable Risk Factors - Smoking,High blood pressure and cholesterol, obesity and lack of physical activity.

Pathogenesis

Alzheimer's disease causes by different factors like genetic,biochemical,modified and unmodified factors.It is characterized by a gradually developing pathogenic process that kills neurons and destroys synaptic connections.This process are not clear at initial stages.It is described by the presence of neuritic plaques and neurofibrillary tangles throughout the cortex and loss of cholinergic neuron.hence its is difficult to understand.

In case of genetic factors like APP,PEN_1 etc… are leads to formation of plaques which are seen between the dying brain cells,and there are made of protein known as β-amyloid.It core is surrounded by dystrophic neurites and abnormal synapses, with activated microglia and fibrous astrocytes present on the periphery.The mutations in the amyloid precursor protein gene along with early-onset AD gives strength to the concept that β-amyloid plays a predominant pathogenic role in AD.

In case of bio chemical factors tangles seen within the nerve cells,and there area also made from another protein known as tau.neurofibrillary tangles consist of paired helical filaments and are composed significantly abnormally phosphorylated tau protein joined with other lesser components in normal conditions,tau binds to micro tubules and stabilizes them therefore an important element of the neuronal cytoskeleton.In case of AD, abnormally phosphorylated tau is no longer able to bind to micro tubules, which may lead to destabilization in micro tubules.The presence and extent of tangle deposition in the brain are more related with cognitive decline in AD.[7,8]

Age and other factors like obesity, hypertension, smoking are also plays important role pathogenic process. In recent studiesAPOE-e4s is acts as the high risk factor for developing of alzheimer's in people with age of 55 years.apo E is a protein with roles in lipid metabolism and tissue repair.It has been used to mediate neuronal protection, repair and remodeling by number of mechanisms include antioxidant effects, interactions with estrogen.Three different APOE alleles (e2, e3 and e4) found in human brain.among them e3 allele is seen more frequently in adults then allele e2 and e4 allele is crucial risk factors for alzheimer's disease.[9]

The below fig 5 gives idea about pathogenesis by flow chart manner for easier understanding.[10]

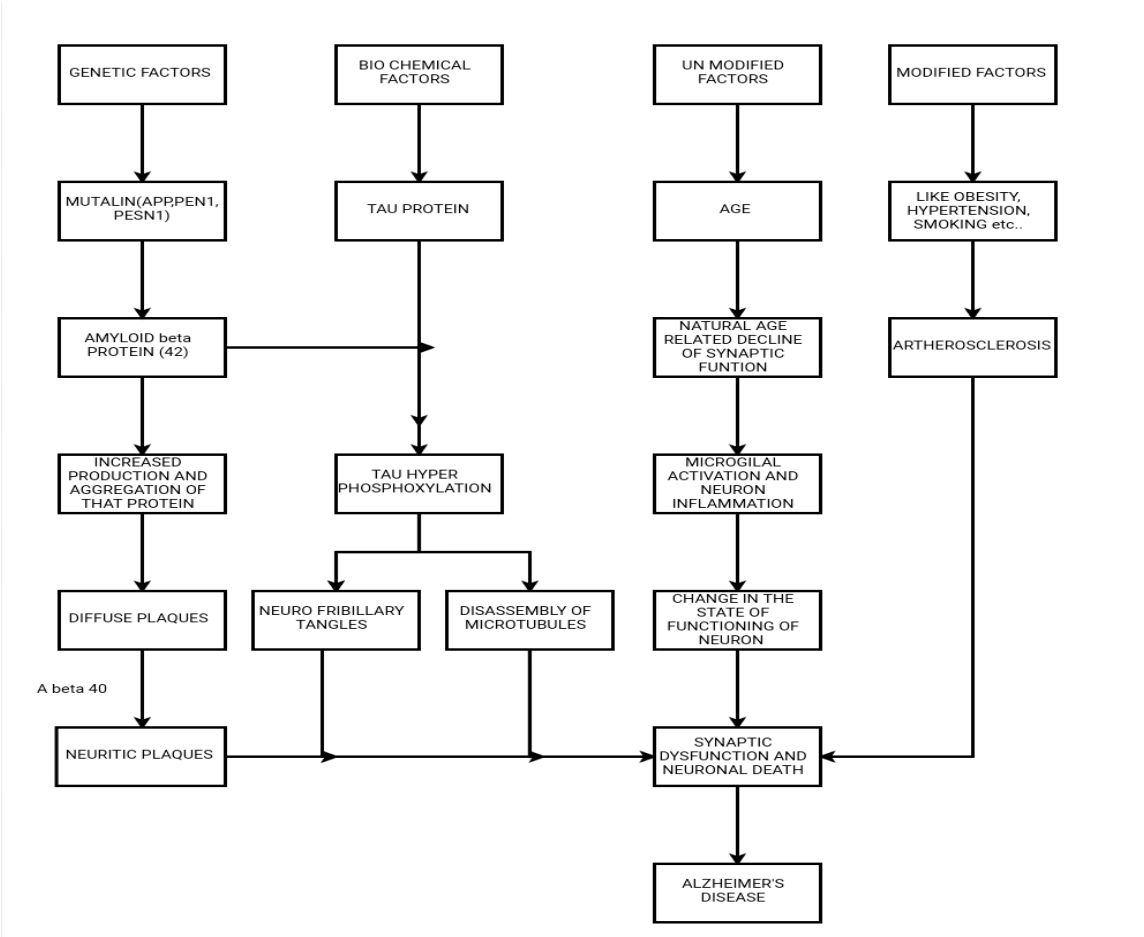


Fig. 5:

Diagnosis

It is diagnosed by evaluating the patient's mental status, including orientation, learning, naming, drawing, and judgment skills with a standardized instrument, such as the Mini-Mental State Examination (MMSE). This 30 point test can be administered in a clinic or office in approximately five minutes. Whereas test results may be affected by the level of education, adjusted norms that take this factor into consideration are available.In adults the median score was 29 for those with at least nine years of education, but the score dropped to 26 for those with five to eight years of schooling and was only 22 for those with zero to four years. Among patients 80 years of age or older, the median score was 25. Therefore, a score of less than 26 in a patient with a high school education should potential presence of AD.[11]

Treatment

There is no known cure for Alzheimer's. The death of brain cells cannot be reversed. However, there are therapeutic interventions that can make it easier for people to live with the disease.

Vascular Dementia

Vascular dementia is the second most common type of dementia after Alzheimer's disease,It occupies about 40 percent of dementia cases in older adults. It is also called a Vascular Cognitive Impairment It is caused by reduced blood flow to the brain—usually from a stroke or series of stroke.In 1960s was the first time that concluded by Tomlinson article After a careful analysis that a stroke of considerable volume of less then 100ml of blood in blood vessels of brain was accompanied by a great risk of dementia development. it is a brain disorder that is characterized by memory loss and difficulty thinking, such as solving problems and making decisions.small infarction's in the brain clearly can affect cognitive function,simply by damaging areas important for cognitive function.However, there are many, more complex interactions between vascular disease and cognitive function.[12]

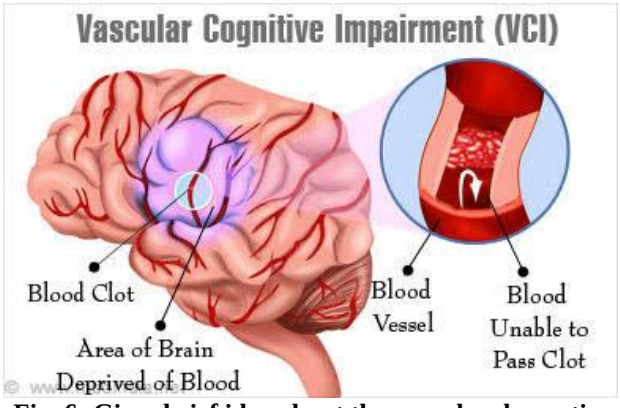


Fig. 6: Gives brief idea about the vascular dementia.

There are different types of vascular dementia are given below.

Lacunar state (Etat Lacunaire)

Chronic hypertension Patients are at risk for the development of "lacunar" strokes, small infarcts deep in the white matter of the cerebral hemispheres, the internal capsule, the basal ganglia, and the brain-stem. These strokes are frequently multiple and lead to the syndrome of "lacunar state".[13]

Cadasil (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

It is seen people with migraine-like headaches, multiple small territory ischemic strokes, and dementia are typical of Cadasil. dementia appears to be correlated with brain atrophy and with the burden of sub cortical infarction.[14]

Binswanger's Disease.

Binswanger's Disease is also called as sub cortical vascular dementia,it is caused by narrowing of the blood vessels called atherosclerosis, which is the same build up of fatty material in blood vessels that can lead to heart attacks. Therefore, the factors associated with heart disease are also associated with vascular dementia.[15]

Multiple large infarcts (Multiple large infarcts)

Dementia develops in ischemic stroke patients, depending to the location and amount of infarcted tissue; even single strokes in strategic sites may cause major cognitive impairment, it association with age-related brain pathology. Most of such strokes are clinically obvious; occasionally, infarcts may occur in silent areas of the brain.[16,17]

Etiology

It doesn't have clear causes but there are different risk factors given below.

Strokes which are "silent"

These are occur due to interruption of flow of blood in blood vessels which are connected to brain. In elderly silent strokes are major risk factor for loss of cognitive decline we cannot even recognize them because their are asymptomatic.[18]

Vascular risk factors

1. Hypertension-Blood pressure more than 140/90mmHg.
2. Diabetes mellitus- Random serum glucose greater than or equal 2g/l.
3. Dyslipidemia-Total cholesterol greater then 2g/l or LDL value greater then 1g/l or HDL value greater then 0.40g/.
4. Alcohol consumption - daily intake is greater then 40g/l.
5. Obesity body mass index greater then 30 is obesity.[19]

Transient ischemic attacks

A transient episode of neurologoic dysfunction caused by focal brain, spinal cord or retina ischemia,without acute

infractions.It occur when blood flow to the brain is temporarily blocks. The other causes are a blood clot,narrow blood vessels and restricted blood flow from the carotid arteries.[20]

White matter ischemic

Ischemic white matter disease or "leukoaraiosis" a complex risk factor. These lesions do not represent definite strokes, but these are related to age, vascular risk factors, and cognitive impairment. Ischemic white matter changes also characterized with disturbance of executive function.may be the neuropsychological patterns in vascular dementia differ considerably, such that no specific pattern is seen. it is rare for vascular dementia to present with isolated memory loss,and most patients with vascular dementia have executive function deficits.therefore MRI scans can detect ischemic white matter changes in patients.[21]

Pathophysiology

Vascular dementia can be caused by vascular factors like atherosclerosis of the cerebral arteries, cerebral small vessel disease, ischemic attacks and white matter lesions are other factors for vascular dementia. The cerebral vasculature damage is the initial step in the case of vascular dementia.

In case of vascular risk factors atherosclerotic plaques commonly develops in large to medium size arteries,but also present in small penetrating vessels in the form of micro atheroma.These Plaque rupture causes stroke through local thrombosis leading to ischemia.The small artery damage lacunar infarction and ischemic white matter lesions are most commonly found in association with lipohyalinosis affecting the small penetrating arteries.

Cerebral small vessel disease is common in the elderly which are having hypertension and diabetes.due to cerebral haemorhage cerebral microbleeds and retinal microvascular changes are commonly seen in people with dementia.In some studies also that ischemic white matter disease consists of demyelination, loss of axons, gliosis,widening of perivascular spaces and loss of blood–brain-barrier integrity. Therefore the presence of severe brain injury, white matter lesions,micro-bleeds and brain atrophy has been linked to aging and vascular risk factors,especially hypertension below fig 7 gives brief idea about pathogenesis [22]

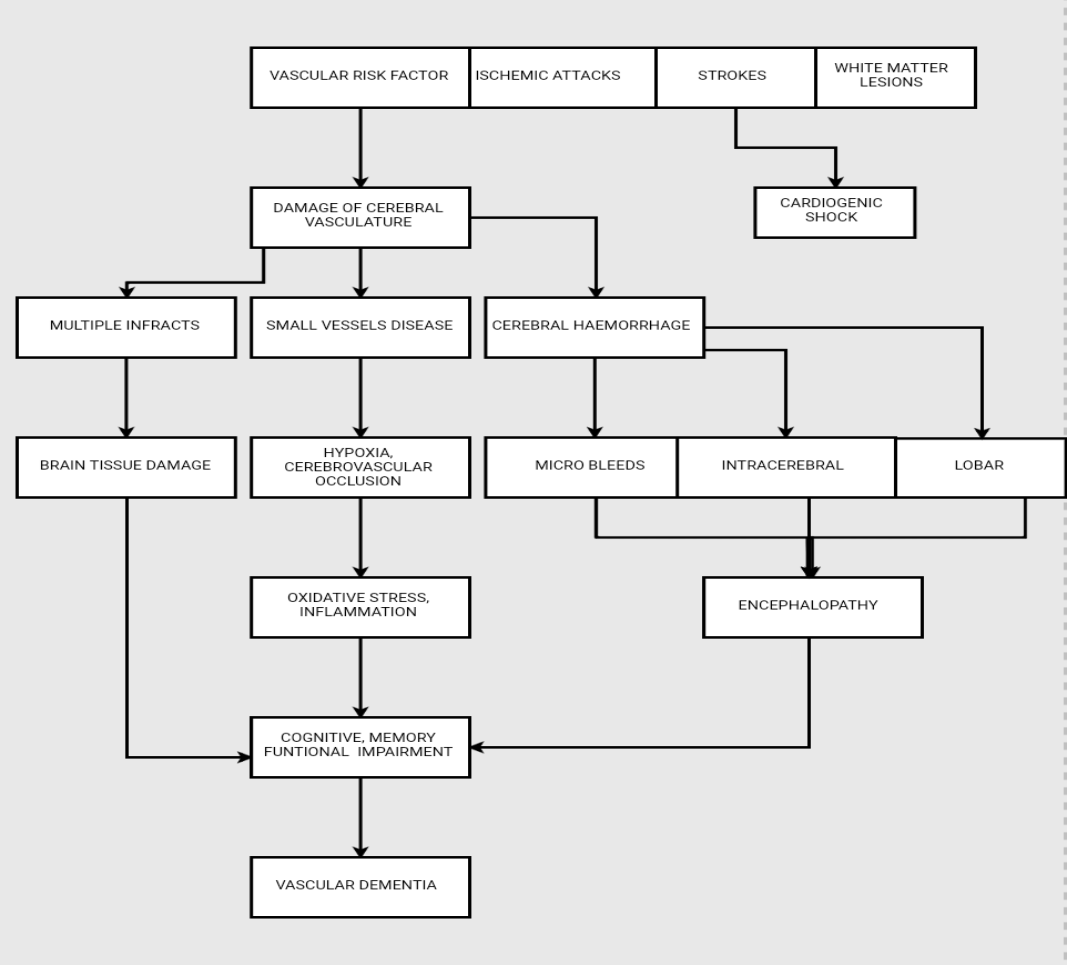


Fig 7: The cardiovascular risk factors associated with vascular dementia may disturb hemodynamic flow by inducing cerebral hypoperfusion long with disruption of the microstructural integrity and cortical-subcortical circuitry.

Diagnosis

Hachinski ischemic scoring system.

Table 2: Patients with a total score of ≥ 7 are considered to have multi-infarct dementia and patients scoring ≤ 4 have primary degenerative dementia.[23]

Feature	Score
Abrupt onset	2
Step-wise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

California criteria for ischemic vascular dementia

These factors support the diagnosis of ischemic vascular dementia

1. Dementia established by clinical examination.
2. Progressive worsening of cognitive function.
3. Evidence of ≥ 2 strokes by clinical or neuroradiologic criteria.
4. Evidence of ≥ 1 hemisphere infarct by CT or MRI (T1-weighted).
5. Diagnosis of definite IVD requires neuropathology.

History of transient ischemic attacks, hypertension, or other risk factors for cerebrovascular disease; early gait disorder; extensive deep white matter disease; and focal abnormalities on positron emission tomography or single-photon emission CT functional brain imaging.[24]

National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria

1. Documented dementia
2. Evidence of cerebrovascular disease by clinical history, clinical examination, or brain imaging.
3. The dementia and cerebrovascular disease must be "reasonably related"

The diagnosis of vascular dementia, by these criteria, also must include a decline in memory and at least two other domains of intellectual ability, with resultant impairment of activities of daily living. Single strokes are permitted if the other criteria apply.

It also emphasize typical clinical features of impairment of multiple cognitive domains, usual presence of focal neurologic signs, gait abnormalities, mood changes, psychomotor slowing, and extrapyramidal signs.[25]

Treatment

There is currently no cure for vascular dementia, the earlier any brain damage is caught, the better your chance of preventing dementia, or at least slowing down the progression of the disease. By treating the risk factors that led to vascular dementia, such as high blood pressure or diabetes, you may even be able to reverse some of the symptoms.

Mixed Dementia

Mixed dementia combination of two types of dementia Although it is rarely diagnosed during life, up to 45 percent of people with dementia are believed to have mixed dementia,In this case more than one type of dementia occurs simultaneously, normally vascular dementia and Alzheimer's disease. It shows a greater impact on the brain than others. It is often indicated by cardiovascular disease and dementia symptoms that get worse slowly over time.

Common pathway for all types of dementia is given below:-

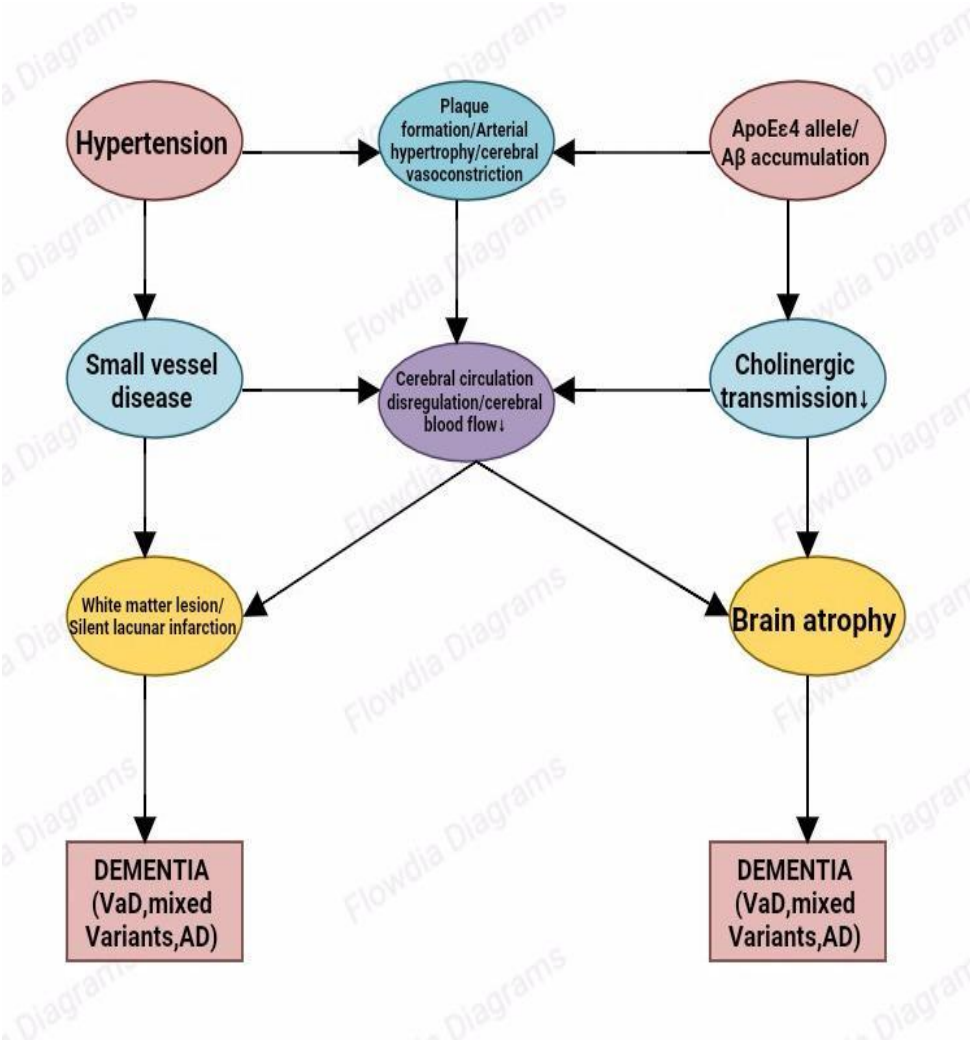


Fig. 8:

The below flow chart tells about information about the different factors that cause the dementia are interlinked by the way that hypertension causes the small vessel disease along with it also causes formation of plaques and tangles these both are results of hypertension. From other way Apolipo protein ε4 is also leads to development plaques and tangles and decrease in cholinergic transmission. These decrease transmission and small vessel disease together with plaque causes vascular re modulation and auto regulation of blood flow. therefore there three factors united to cause the white matter lesion and brain atrophy finally leads to the dementia.

World Wide Recent Age Strandardized -Death Rate

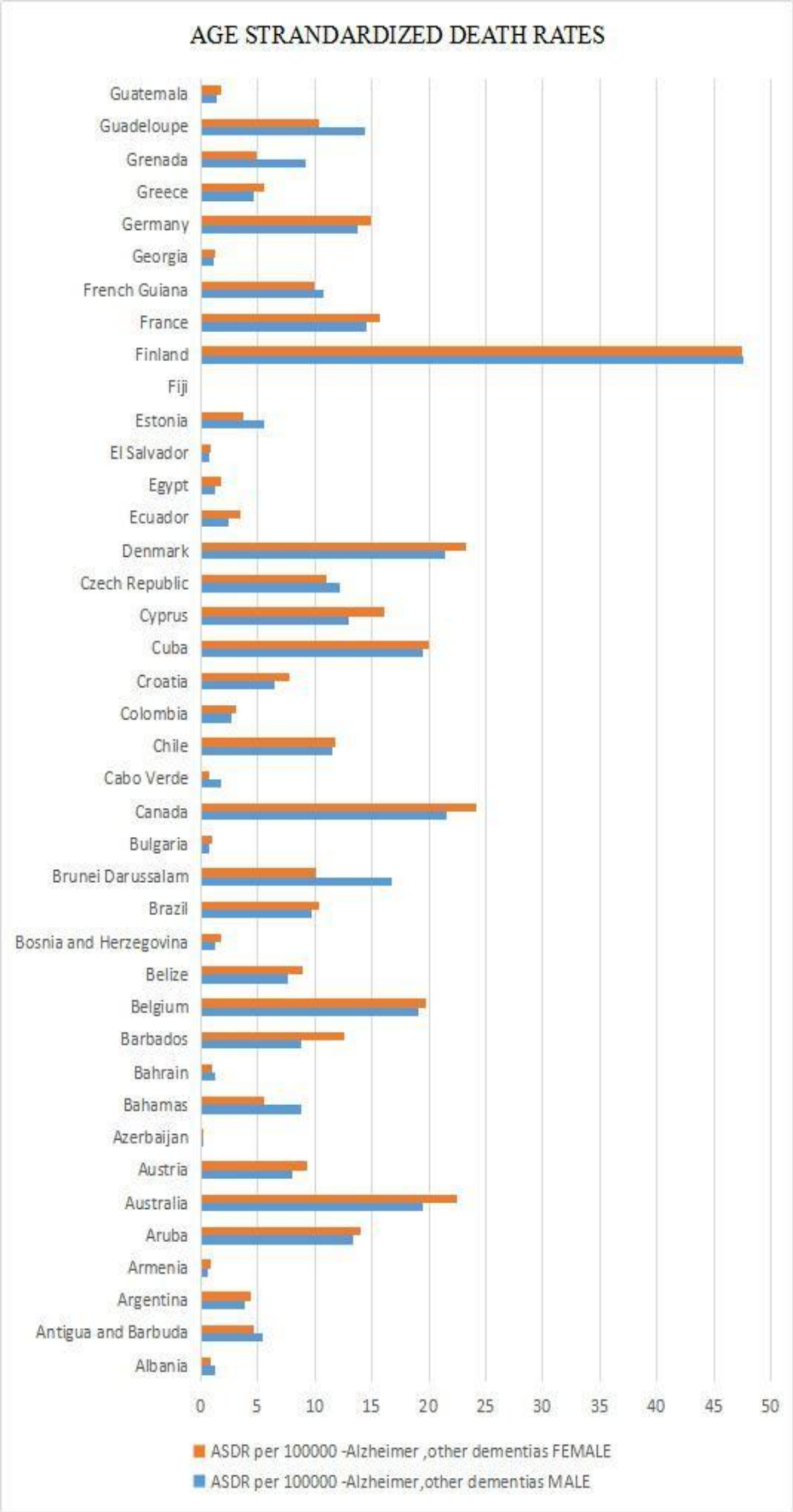
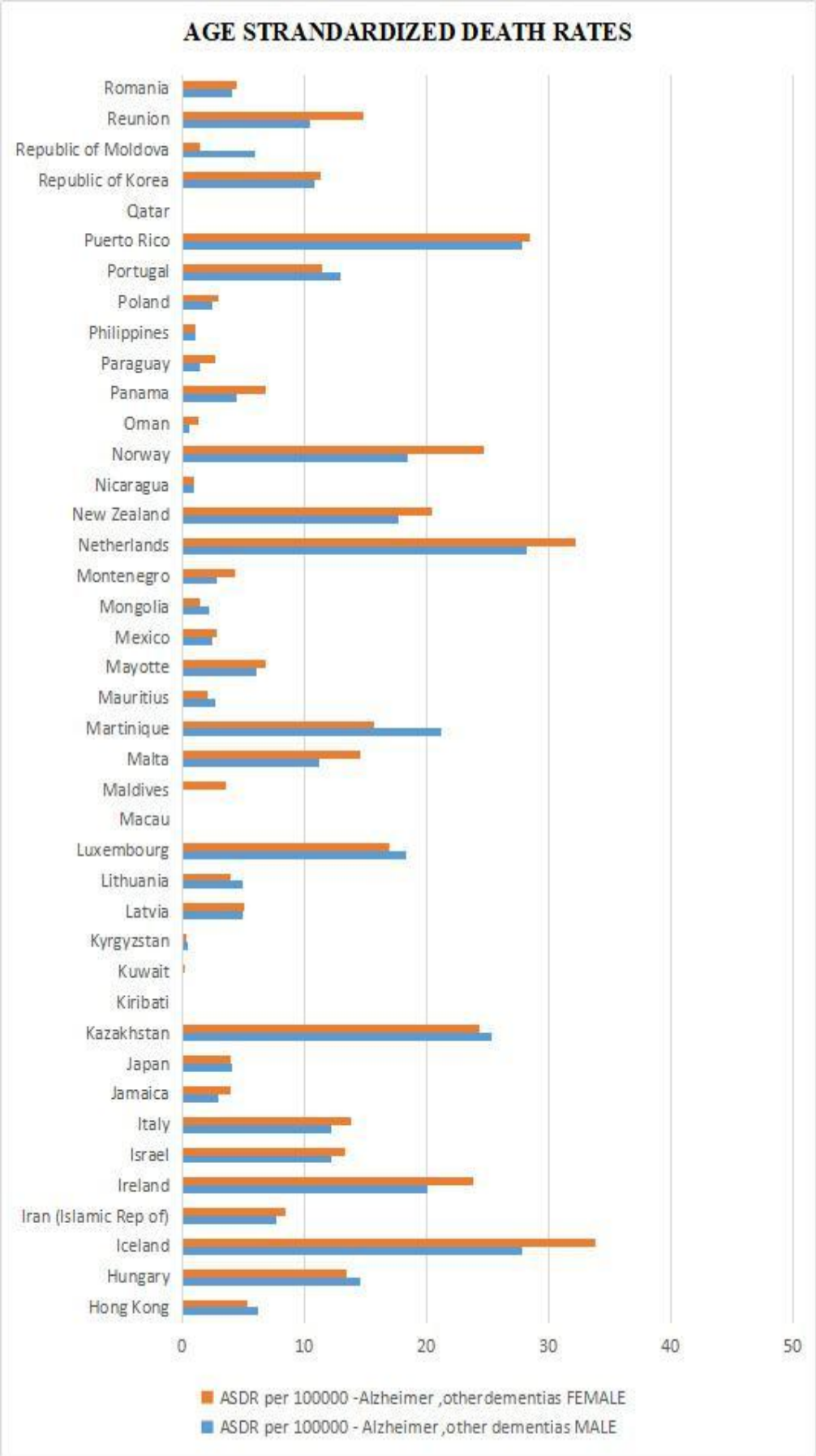


Fig. 9:


AGE STRANDARDIZED DEATH RATES
Romania
Reunion
Republic of Moldova
Republic of Korea
Qatar
Puerto Rico
Portugal
Poland
Philippines
Paraguay
Panama
Oman
Norway
Nicaragua
New Zealand
Netherlands
Montenegro
Mongolia
Mexico
Mayotte
Mauritius
Martinique
Malta
Maldives
Macau
Luxembourg
Lithuania
Latvia
Kyrgyzstan
Kuwait
Kiribati
Kazakhstan
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Jamaica
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Israel
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ASDR per 100000 -Alzheimer ,otherdementias FEMALE
ASDR per 100000 - Alzheimer ,other dementias MALE

Fig. 10:

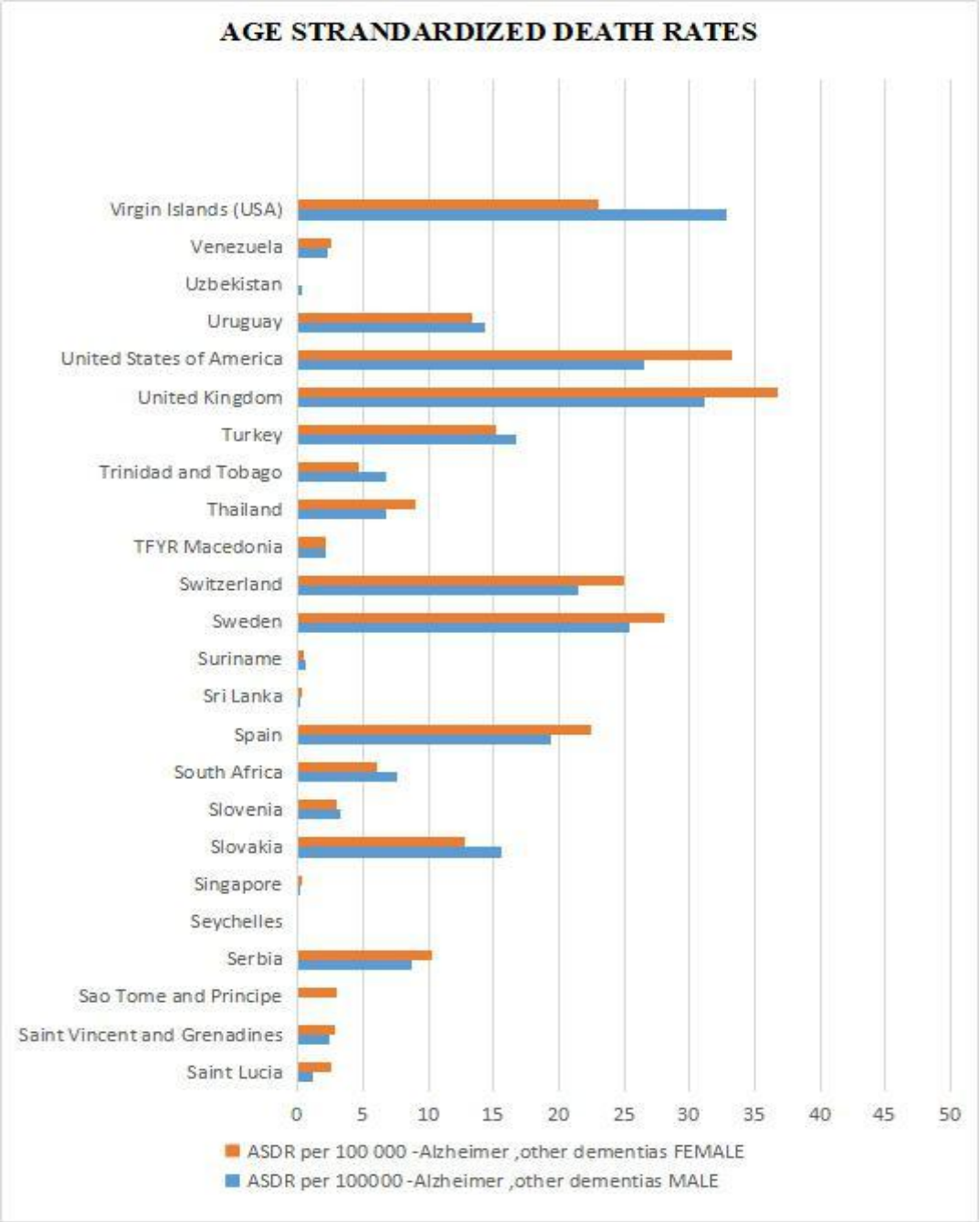

Fig. 11: The above fig 9,10,11 gives the information about world wide statistics on death rates and which country have maximum and minimum death rates.

Influence of hypertension on dementia

Hypertension is the medical term for high blood pressure. This means that the blood applies too much force against the walls of blood pressure. according Medical guidelines defined hypertension as blood pressure higher than 130 over 80 millimeters of mercury and The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure classified hypertension as a systolic BP > 140 mmHg and/or a diastolic BP > 90 mmHg.

Hypertension is a highly prevalent condition, occurring in one-third of the world's adults and two-thirds of adults over age 65. Around 85 million people have high blood pressure. It is already an established risk factor for cardiovascular and cerebrovascular disease,evidence suggests that hypertension may also play an important role in the development of cognitive decline, Alzheimer's disease, and vascular dementia. Because hypertension is a modifiable risk factor, it represents a potentially important mechanism through which the prevention or delay of age-related cognitive disorders may be possible. For this reason, understanding hypertension's role in the development and progression of age-related cognitive decline and dementia has been a research priority over the last two decades.[26]

Normal B.P is 120 over 80 mm of mercury, but hypertension higher than 130 over 80 mm Hg.

Table 3: Ranges of B.P.

Systolic pressure (mm/Hg)	Diastolic pressure (mm/Hg)
Normal B.P - less than 120	Normal B.P - less than 80
Elevated-Systolic pressure between 120 -129	Elevated - Diastolic pressure less than 80
Stage 1:- It ranges between 130 and 139.	Stage 1:- It ranges between 80 and 89
Stage 2 :- hypertension at least 140.	Stage 2:- hypertension at least 90
Hypertensive crisis - over 180	Hypertensive crisis - over 120

- Acute causes high B.P include stress,but it can happen on its own,or it can result from an underlying condition such as kidney disease
- Un managed hypertension can lead to heart attack and stroke.

Midlife hypertension:- It is differ from hypertension based of the age so it is kind of hypertension seen in middle age of 40-64 is called as midlife hypertension.

Late life hypertension:- It is also same as midlife hypertension based of age factor so it is hypertension seen in age of 65-75 or above.

Pathophysiology of hypertension as it relates to cognitive decline

Vascular dementia linked with hypertension

Hypertension has also been associated with vascular dementia and cerebral small vessel diseases defining features like WMH volume, WMH (white matter hyperintensities) progression, lacunar infarcts, and cerebral micro bleeds. Supporting the relationship between high blood pressure and white matter some studies and clinical trials suggest that treatment of hypertension reduces WMH progression. High SBP has been associated with smaller regional and total brain volumes and reductions in brain volume. The relationship between high DBP and brain volume is less agreeable hence In elderly patients low SBP and low DBP is associated with reduced brain volume and cortical thickness therefore the relationship between BP and brain volume may be dependent on age.[27]

Auto-regulation and cerebral perfusion linked with hypertension

Cerebral auto-regulation is a action that the brain's ability to maintain steady low-pressure blood flow in the conditions of changing systemic blood pressure. This action is discontinued as a result of chronic hypertension and perfusion is nothing but passage of blood through blood vessels. due to long time exposure to high blood pressure and elevated pulsatility, a modification occurs in the brain's auto-regulatory capacity as a result higher systemic BP is required to maintain the same level of cerebral perfusion.

Hypertension modify cerebral auto-regulation through causing changes in arteriole endothelial and vascular smooth muscle cells that falls cerebrovascular reactivity and raises myogenic tone.not only that vascular changes modify the cerebral auto-regulatory curvature in a manner which also reduces resting cerebral blood flow,but the brain also becomes more sensitized to hypoperfusion during time intervals of low systemic BP or during periods of normal blood pressure in chronically hypertensive people.

These hypertension induced changes to cerebral autoregulation and perfusion may explain about the individuals with chronic hypertension in midlife and low BP in late-life show significant reductions in brain volume and greater levels of cognitive deficits like dementia.[28]

Vascular remodeling linked with Hypertension

The extended elevations in blood pressure may cause cerebral vessel remodeling in a manner which increase chance pathological changes in brain along with cognitive decline A rearrangement in vessel wall material in the form of hypertrophic remodeling of the media and vascular smooth muscle cells occurs due to maintain the steady low blood pressure blood supply to periphery and then protect end organ micro-circulation from pulsatile stress along with hypertension.This rearrangement leads enlargement in media size causes a reduce in lumen diameter then lead to increase vascular resistance and vessel wall stiffening. Arterial stiffening will increases arterial pulse wave velocity and pulsatile pressure if it taken place of long time causes rarefaction of downstream capillaries followed by inward remodeling of vessel walls.

Hypertension may increase the chase of intracranial atherosclerosis in large intracranial arteries and arteriolosclerosis in smaller arterioles which are supplied to subcortical white matter and deep gray matter brain structures.arteriolosclerosis also increase microvascular resistance as a results of thickening of the vessel wall.because of this brain requires high levels of continuous perfusion throughout systole and diastole leads to increases in vascular resistance leave cerebral arterioles open to hypoperfusion when systemic BP is reduced. due to hypoperfusion along with several neurovascular changes,which together may prevent the cognition may be dementia.[29]

Endothelial dysfunction, altered functional hyperemia & Oxidative stress

Due to increase in endothelial dysfunction, hypertension is also involved in disruption of the coordinated coupling among neurons, glia, and cerebral blood flow in the microvasculature. Uncoupling of this neurovascular unit can impair the homeostatic process of functional hyperemia in-turn increases in cerebral blood flow occur in associated with increases in neuronal activity to control the delivery of adequate levels oxygen and glucose long with facilitate the removal of metabolites some animal studies evidences that hypertension-induced vascular oxidative stress resulting from up-regulation of reactive oxygen species producing enzyme NADPH oxidase which impairs the endothelium-dependent expression of vasodilators and vasoconstrictors which are necessary to maintain neurovascular coupling.

Alzheimer's disease linked with hypertension

The association between hypertension and incidence of Alzheimer's disease has also been found by examination of Alzheimer's disease biomarkers by comparing directly to the brain of normal individual which are having history of hypertension from this shows greater levels of β-amyloid plaques, atrophy, and neurofibrillary tangles. Relatively, hypertension has been identified as a risk factor for cortical fibrillar β-amyloid deposits and reduced glucose metabolism in Alzheimer's disease-specific brain regions through positron emission tomography in the brains of cognitively normal middle-age and older adults. from this evidences a study found that individuals with abnormal plasma β-amyloid levels and elevated blood pressure at midlife have an high risk of developing Alzheimer's disease later in life.

Some studies on relationships between incidence of dementia due to hypertension:-

A study that Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study.Hypertension in 2011 a population-based prospective study in Japan reported that both midlife and late-life hypertension correlates with vascular dementia, but not AD. Although this study was based on a limited number of blood pressure measurements over the years, the data suggest that dementia is not universally associated with a reduction in blood pressure it have shown that midlife hypertension is a risk factor for AD. Although the mechanisms of the association remain unclear,there is evidence that hypertension may promote the accumulation and aggregation of the amyloid-β peptide in brain which is cause of alzheimer disease.[30]

Attenuation of brain damage and cognitive impairment by direct renin inhibition in mice with chronic cerebral hypoperfusion.in 2011 Hypertension found that inhibition of renin, the enzyme that converts angiotensinogen into angiotensin I, protects the brain from white matter injury and associated cognitive impairment.but the evidence that hypertension treatment prevents dementia is not conclusive.

Longitudinal studies such as blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years.Hypertension in 2012, demonstrated that in women with hypertension, the development of dementia is preceded by a reduction in blood pressure, an effect that correlated with a reduction in the body mass index.The reduction in body mass index suggests a reduced metabolic state, which may be responsible for the blood pressure decline in the late phases of the dementia However,there is no consensus on the association between late-life dementia and low blood pressure, and there might be differences between AD and vascular dementia.[31]

Other study in 2012 Endothelin 1-dependent neurovascular dysfunction in chronic intermittent hypoxia. Hypertension investigated the impact of chronic intermittent hypoxia, a model of sleep apnea, on the regulation of the cerebral circulation in mice. Chronic intermittent hypoxia increased blood pressure, induced cerebral endothelial dysfunction, and suppressed the increases in cerebral blood flow produced by neural activity, a vital homeostatic response that matches the delivery of energy substrates with the energy demands of the active brain.although it remains to be established whether the elevation in blood pressure induced by chronic intermittent hypoxia is necessary or sufficient to induce the cerebrovascular dysfunction, the findings highlight the importance of endothelin-1–induced cerebrovascular damage in the pathophysiology of risk factors for cognitive impairment.

Effects of angiotensin II on the cerebral circulation: role of oxidative stress.Front Physiology in 2012 is a other study that the angiotensin II an octapeptide involved in the mechanisms of hypertension, has also been implicated in the vascular dysfunction underlying the effects of hypertension on the brain and leading to cognitive impairment.using a mouse model of cerebral hypoperfusion, which summarize selected features of vascular cognitive impairment.

A study in 2014 Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span.Hypertension their concluded that incident hypertension increases the risk of dementia later in life, but the cognitive decline develops ≥1 year after the hypertension, making it well suited to therapeutic interventions. successful treatment of hypertension tended to dampen the cognitive decline, with partial success, whereas untreated or uncontrolled hypertension had the greatest negative impact on cognition.

Other study association between ambulatory 24-hour blood pressure levels and brain volume reduction: a cross-sectional elderly population-based study. Hypertension in 2012 demonstrated that hypertension leads to reduced gray matter volumes selectively in the left frontal lobe,a finding linked to executive dysfunction

and independent of major confounders such as age, sex, education level, and total brain volume. Although the possibility that these changes were related to local or distant micro-vascular pathology, for example, microinfarcts, cannot be ruled out, the data suggest a potential mechanism for the executive dysfunction associated with hypertension. As discussed in the next section, hypertension can also influence cognition by modulating the brain levels of amyloid-β, a peptide involved in the pathobiology of AD.

The recent on 2017 describe Association between systolic blood pressure and dementia in the Whitehall II cohort study and role of age, duration, and threshold used to define hypertension examine the associations of diastolic and systolic blood pressure (SBP) at age 50, 60, and 70 years with incidence of dementia, and whether cardiovascular disease (CVD) over the follow-up mediates this association their concluded that the Hypertension is a known risk factor for cardiovascular dementia , It is also highly prevalent; number of persons with elevated SBP continues to increase globally and may affect dementia risk either directly or via processes related to cardiovascular dementia their shows mainly the detrimental effects of mid-life hypertension at age 50 years and increase in risk at levels below that used to treat SBP.[32]

Dementia incidence in midlife hypertension

There are different studies examined the relationship between elevated blood pressure in midlife and the onset of dementia and AD later in life.

The Honolulu Asia Aging Study at 2000 studied this relationship in 3703 Japanese-American men aged 45-68 years at their midlife examination, who were followed them for 26 years in the Honolulu Heart programme. It was evaluated by The Cognitive Abilities Screening Instrument and VaD and AD were diagnosed according to the DSM-III-R.

Among men untreated for high blood pressure 57% of the sample, There was a strong association between midlife hypertension and both AD and VaD when 160/95 mmHg was used as the BP cut-off. But non significant, risk was also associated with BP cut-offs of 140/90 mmHg.but patients receiving antihypertensive treatment, shows no identifiable association between elevated blood pressure and dementia.

Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia Aging study. Neurobiol Aging Study on 2000 with 243 participants elevated SBP in midlife was associated with vasculopathic changes, a lower brain weight and greater numbers of neuritic plaques in both the neocortex and the hippocampus.

Elevated DBP was associated with greater numbers of neurofibrillary tangles in the hippocampus. Neurofibrillary tangles and neuritic plaques, while they can occur as neuropathological features of aging, are classically associated with AD.

The Kuopio and Joensuu studies on 2001 also found that both elevated systolic and/or diastolic blood pressure in midlife was associated with an increased of both AD and VaD, independent of APOE genotype.

According to Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study on 2002 the high SBP was combined with an elevated total cholesterol level, the risk for AD or VaD was greater than when either were present alone.The Adult Health Study in Japan on 2003 was the only study that linked midlife systolic hypertension to late life VaD, but not AD.

A neuroimaging study on 2004 demonstrated an association between midlife untreated hypertension and hippocampal atrophy Although hippocampal atrophy can occur in the presence of either VaD or AD, it is considered as a hallmark for AD.

Finally there is substantial evidence of a risk effect of midlife high blood pressure on the development of late-life dementia.[33]

Dementia incidence in late life blood pressure studies

Several longitudinal studies have addressed the issue, only two Swedish studies identified an association between hypertension in late-life and dementia.

In the Kungsholmen project, a community-based on 1270 participants aged less than 75 years were followed up for a period of 6 years, 339 subjects had a diagnosis of dementia according to DSM-IV criteria, 256 with AD.

The only one study Skoog et al on 1996 described an association between both elevated systolic and diastolic blood pressure and a subsequent diagnosis of AD or dementia.

In this there are 382 subjects age of 70 years followed for 15 years, participants who developed dementia at age 79-85 had higher SBP and DBP at age 70 than those who did not develop dementia. Higher DBP at age 70 and 75 years was associated with a higher incidence of both AD and VaD. Finally this study also described that blood pressure declined in the years preceding the onset of dementia, and was then similar to, or lower than that in non demented individuals.[34]

Recently Study Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study 2007 describe the association between BP and the risk for both AD and dementia across a spectrum of older ages and examined BP changes before dementia onset. The 2356 participants were all free of dementia and 65 years, but

for analyses were grouped into three age categories 65-74 years, 75-84 years and greater then 85 year and during 8 years, Cognitive Abilities Screening Instrument is used for evaluation of Cognition BP was measured at enrollment.. The risk estimates were similar although not statistically significant for this group and the development of AD. The risk estimates for both AD and dementia associated with SBP declined with advancing age.

Investigation on effects of anti hypertensives on dementia through Randomized control Syst-Eur

The systolic hypertension in Europe studied discuss about the effect of antihypertensive treatment on elderly patients with recorded systolic hypertension led to a change in stroke morbidity and mortality. In this study the effects of a calcium channel blocker commonly 10–40 mg/day nitrendipine. some times nitrendipine was combined with an enalapril maleate and/or a diuretic. due to active treatment using a calcium channel blocker resulted in 60% reduced in risk of dementia and out of 64 cases of dementia 80% are alzheimer's disease finally this study suggests using aa calcium channel blocker to lower BP and reduce the risk of dementia, particularly alzheimer's disease,in elderly patients.[35]

Progress

The perindopril protection against recurrent stroke study with 6105 patients, all of them with stroke or may be with transient ischemic attack. Patients are given active treatment perindopril along with indapamide for people with neither an indication nor a contraindication to a diuretic if not matching placebo is implemented finally the the effect of perindopril on cognitive decline is insignificant.

Shep

The systolic hypertension in the elderly program (SHEP) study was Conducted for a span of average 5-yearand followed by 6 academic clinics.out of 447.921 candidates aged 60 years and older 4736 were taken for the study. In this Systolic blood pressure ranges from 160 to 219 mm Hg,and diastolic blood pressure was less than 90 mm Hg. The active anti hypertensive drug therapy or a matching placebo group is done. Active treatment consists of a diuretic at step 1 and a beta blocker at step 2. If atenolol was contraindicated reserpine was used .This study of using the active anti hypertensive drug is insignificant.

Scope

The study on cognition and prognosis in the elderly (SCOPE) was a study conducted between 1997 and 2002. In this study 4964 patients of age 70–89 years having ranges of Systolic blood pressure from 160 to 179 mm Hg and diastolic blood pressure ranging from 90 to 99 mm Hg. In this study patients were given the angiotensin II receptor blocker or a placebo,with active anti hypertensive therapy their result is insignificant.but in subgroup analysis of SCOPE performed later, a significant positive effect on some cognitive decline which is reported by using testing methods which are more sensitive than the MMS.

HYVET-COG

The Hypertension in the very elderly trial—cognitive function assessment examined anti hypertensive medication for patients ≥80 years of age. Eligible of patients was no dementia, Systolic blood pressure was 160 to 200 mm Hg and diastolic blood pressure was below 110 mm Hg. patients were given 1.5 mg slow release diuretic with an option of enalapril maleate or a placebo it is less significant.[36]

CONCLUSION

We summarized from the above information about the dementia its incidence rates and age-standardized death rates allover the world wide along with a brief idea about the influence of hypertension on it. from the incidence projections to 2050 tells Asia includes Oceania as high cases of incidence per year, In India wide prevalence of dementia female are more commonly seen in states like Jharkhand, Bihar and In countries Finland as high mortality rates up to recent statistical data.

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REFERENCES

1. Nussbaum RL, Ellis CE. . Alzheimer's disease and Parkinson's disease. N Engl J Med, 2003; 348: 1356–64.
2. Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ, Browne P, et al. Atorvastatin for the treatment of mild to moderate Alzheimer Disease: Preliminary results. Arch Neurol, 2005; 62: 753–757.
3. Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF. Mortality with dementia: results from a French prospective community-based cohort. Am J Epidemiol, 2001; 154: 642–8.
4. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature, 1995; 375(6534): 754–760.
5. Schellenberg GD, Bird TD, Wijsman EM, Orr HT, Anderson L, Nemens E, et al.Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. Science, 1992; 258(5082): 668–71.
6. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science, 1995; 269(5226): 973–7.
7. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated

protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci, 1986; 83: 4913–4917.
8. Wood JG, Mirra SS, Pollock NJ, Binder LI.Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axona microtubule associated protein tau Proc Natl Acad Sci, 1986; 83(24): 9773.
9. MARTIN R. FARLOWEtiology and pathogenesis of Alzheimer's disease Am J Health-Syst Pharm, 1998; 55(Suppl 2): S5-10.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975; 12: 189-98.
11. Folstein M, Anthony JC, Parhad I et al. The meaning of cognitive impairment in the elderly. J Am Geriatr Soc., 1985: 33: 228-35.
12. Elias MF, Goodell AL, Dore GA. Hypertension and cognitive functioning: a perspective in historical context.Hypertension, 2012; 60: 260–268.
13. Roman GC: On the history of lacunes, etat crible, and the white matter lesions of vascular dementia. Cerebrovasc Dis, 2002; 13(Suppl 2): 1–6.
14. Dichgans M, Mayer M, Uttner I, et al.: The phenotypic spectrum of CADASIL: clinical fi ndings in 102 cases. Neurology, 1998; 44: 731–739.
15. Sneddon IB: Cerebro-vascular lesions and livedo reticularis. Br J Dermatol, 1965; 77: 180–185.
16. Vermeer SE, Prins ND, den Heijer T, et al.: Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med, 2003; 348: 1215–1222.
17. Kalaria RN.Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. Stroke, 2012; 43: 2526–34.
18. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. Lancet Neurol, 2012; 11: 272–82.
19. Solomon A, Kareholt I, Ngandu T: Serum cholesterol changes after mid-life and late-life cognition: twenty-one year follow-up. Neurology, 2007; 68: 751–756.
20. Bos MJ, Van Rijn MJ, Witteman JC, et al.: Incidence and prognosis of transient neurological attacks. JAMA, 2007; 298: 2877–2785.
21. Pohjasvaara T, Mantyla R, Salonen O, et al.: How complex interactions of ischemic brain infarcts, white matter lesions, and atrophy relate to poststroke dementia. Arch Neurol, 2000; 57: 1295–1300.
22. Dennis chang,Jianxun liu,Kellie billnski,Li xu,Geneviveve Z.steiner,Sai w.seto,Alan bensussan Herbal medicine for the treatment of vascular dementia:An overview of scientific evidence. Hindawi publishing corporation, 2016.
23. Hachinski VC, Iliff LD, Zilkha E, et al.: Cerebral blood fl ow in dementia. Arch Neurol, 1975; 32: 632–637.
24. Chui HC, Victoroff JI, Margolin D, et al.: Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology, 1992; 42: 473–480.
25. Roman GC, Tatemichi TK, Erkinjuntti T, et al.: Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Work Group. Neurology, 1993; 43: 250–260.
26. Elias MF, Goodell AL, Dore GA. Hypertension and cognitive functioning: a perspective in historical context. Hypertension, 2012; 60: 260–268.
27. Martinez-Lemus LA, Hill MA, Meininger GA. The plastic nature of the vascular wall: a continuum of remodeling events contributing to control of arteriolar diameter and structure. Physiology, 2009; 24: 45–57.
28. Wang X, Xing A, Xu C, Cai Q, Liu H, Li L. Cerebrovascular hypoperfusion induces spatial memory impairment, synaptic changes, and amyloid-β oligomerization in rats. J. Alzheimer's Dis., 2010; 2: 813–22.
29. Keenan A. Walker1, Melinda C. Power2, and Rebecca F. Gottesman Defining the relationship between hypertension, cognitive decline, and dementia: a review Curr Hypertens Rep., 2017 March; 19(3): 24.
30. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, Kanba S, Iwaki T, Kiyohara Y. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. Hypertension, 2011; 58: 22–28.
31. Joas E, Bäckman K, Gustafson D, Ostling S, Waern M, Guo X, Skoog I. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. Hypertension, 2012; 59: 796–801.
32. Sean P. Kennelly, Brian A. Lawlor, and Rose Anne Kenny Blood Pressure and Dementia – a Comprehensive Review Ther Adv Neurol Disord, 2009.Jul; 2(4): 241–260.
33. Korf E.S., White L.R., Scheltens P., Launer L.J. Midlife blood pressure and the risk of hippocampal atrophy: The Honolulu Asia Aging study. Hypertension, 2004; 44: 29–34.
34. Skoog I., Lernfelt B., Landahl S., Palmertz B., Andreasson L.A, Nilsson L.et al. 15-year longitudinal study of blood pressure and dementia. Lancet, 1996; 347: 1141–1145.
35. Michiya lgose,katsuhiko kohara,tesuromiky:The associationbetween hypertension and dementia in elderly: Inter journalof hypertension, 2012; 6.
36. Peters R, Beckett N, Forette F, Tuomilehto J., Clarke R., Ritchie C. et al.Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial Cognitive Function Assessment: a double-blind, placebo controlled trial. Lancet Neurol, 2008; 7: 683–68