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"HEMORRHAGIC"&"ISCHEMICSTROKE", A STUDY ON GENETIC FACTORSIN NORTH INDIAN PATIENTS.

Nursing Science

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KEYWORDS

INTRODUCTION :-

Stroke is defined as an "acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain" (Goldstein, 1989). Stroke is the 3rd leading cause accounting for 10% of all death in the world (WHO, 2004). It is a major global health issue that prematurely claims millions of otherwise healthy and productive lives each year. The WHO predicts that the total stroke burden will increase from approximately 38 million Disability Adjusted Life Years (DALYs) in 1991 to 51 million (DALYs) in 2020 (WHO, 2004). Strokes are rare in younger people and become increasingly common with older age but at the age of 45 years, the chances of having stroke in the next 20 years is 1 in 30 (Wolfe, 2000).

There has been a definite increase in the prevalence and incidence of stroke disorder in India over the last 30 years (Banerjee *et al.* , 2005). Stroke represented 1.2% of total deaths in India (Banerjee and Das, 2006). The average annual incidence rate of stroke in India currently is 145 per 100,000 population, which is higher than the western nations and Indians may also be genetically prone for stroke due to high prevalence of metabolic syndrome (Kaul *et al.* , 2009).

The two main types of strokes are ischemic and hemorrhagic which are due to a number of different pathological mechanisms. Hemorrhagic stroke occurs when blood from a ruptured blood vessel compresses and damages normal functioning brain tissue. In an ischemic stroke, a blocked artery prevents blood carrying oxygen and other nutrients from reaching a portion of the brain, leading to dysfunction and death of that brain tissue. Dysfunction of the brain manifests itself by various neurological deficits by various signs and symptoms that are related to the extent and site of the area of brain involved. These include coma, hemiplegia, paraplegia, monoplegia, multiple paralysis, speech disturbances, nerve paresis, sensory impairment etc. Ischemic and hemorrhagic stroke accounts for approximately 85% and 15%, respectively (Hickey, 2003). Stroke is a clinical culmination of many complex processes and interacting pathways, none of which is individually necessary or sufficient to cause the outcome. There is considerable evidence from twin studies and numerous epidemiologic studies have documented that stroke has a significant genetic component (Bak *et al.* , 2002, Tournier-Lasserve, 2002). Studies looking at sibling risk and/or offspring showed significant risk in first degree relatives of stroke patients, with odds ratios that average 1.76 (Flossmann *et al.* , 2004). Family studies have shown an association of hemorrhagic stroke and a positive family history of hemorrhagic stroke, indicating an underlying genetic etiology (Alberts *et al.* , 2002, Polychronopoulos *et al.* , 2002). The cause of most common strokes is multifactorial and involves both genetic variants, environmental trigger such as smoking or diet, and most likely result from that of additive or multiplicative effect of a wide spectrum of pathogenic alleles (a gene dose effect), each of which conferring a small degree of risk but the identification of individual causative mutations remains problematic (Hassan and Markus, 2000). Many common risk factors for stroke like diabetes and arterial hypertension are partly inherited, so many genetic loci contribute more or less to the stroke phenotype (Tonk and Haan, 2007). Risk factors for hemorrhagic stroke have become evident, including heavy alcohol intake and anticoagulant treatment. Less frequent and convincingly proven risk factors are cocaine use and low serum cholesterol (Tonk and Haan, 2007). Many candidate genes for hypertension have been suggested including genes for renin angiotensin converting enzyme, aldosterone, calmodulin, ion ATPases, phospholipase, kallikrein, endothelin, and androgenic receptors. Genome wide linkage surveys have found linkage for blood-pressure loci on almost all chromosomes (Doris, 2002). Several genetic polymorphisms have been also associated with an increased risk for apparently sporadic hemorrhagic stroke. The influence of *APOE* genotype on sporadic cerebral amyloid angiopathy-related –hemorrhagic stroke has been studied intensively, with contradicting results like in ischemic stroke. It is now accepted that the *APOE* E2 allele predisposes to rupture of βA4 laden blood vessels, thus increasing the chance of sporadic cerebral amyloid angiopathy - related-hemorrhagic stroke (McCarron and Nicoll, 2000) Atherosclerosis is a well known risk factor for stroke and the genetic variants of the low-density lipoprotein receptor have already been highly informative for the genetics of atherosclerosis in vascular disease (Hachinski, 2002). Ischemic stroke can be caused by number of monogenic disorders and in such cases stroke is frequently part of a multisystem disorder (Natowicz and Kelley, 1987). Ischemic stroke itself consists of a number of different phenotypes which may each have different genetic profiles (Jerrard-Dunne *et al.* , 2003). Genome-wide linkage study on Icelandic individuals with stroke has indicated that a gene on chromosome 5 may contribute significantly to the risk of stroke (Gretarsdottir *et al.* , 2003). In many of the studies the risk persisted with hypertension, hyperlipidemia, diabetes and smoking. These studies support the notion that stroke, as with all common diseases, occurs at the interface between genes and the environment. However, the significant genetic component to stroke risk is not fully explained by the genetic components driving the known medical risk factors (Gulcher *et al.* , 2005). To relieve the burden of stroke, we need to understand the mechanisms that will form the basis of improved prevention and treatment. In the post genomic era, multiple genes have been termed low-penetrance genes and various studies have focused on different variants of these genes known as polymorphisms. Candidate genes among low penetrance genes are identified based on pathophysiology of the disease. The study of such candidate gene may help to understand the role of these genetic factors in developing the pathogenesis of the disease. Despite the fact that technologies such as genotyping, sequencing and microarray have been available for more than two decades, until recently very little progress was made in defining the molecular genetic determinants of stroke. Three strategies are being used to find stroke genes: positional cloning applied to rare monogenic forms of stroke, candidate gene association studies of common stroke and positional cloning applied to common stroke (Gulcher *et al.* , 2005). The two approaches to identify candidate genes are family based linkage studies which requires multiple affected members in the families and the second is gene- association studies which directly tests the effects of genetic variants of a potentially contributing gene. These case control association studies can be performed relatively quickly and in expensively and may allow identification of genes with small effects. There may be inter individual variation in the studied subjects. Extensive effort has been expended to identify association between single nucleotide polymorphisms (SNPs) in functional candidate genes and stroke (Markus, 2010). However, the candidate gene approach is limited by how much is the underlying mechanism of the disease being investigated.

In the present study, we have employed targeted candidate gene analysis to look for association of genetic variants with risk of stroke

and their clinical subtypes. Candidate genes were chosen a priori on the basis of assumed biological relevance. The recent advances in the identification of *PDE4D* and confirmation that genetic component of diseases such as stroke may be found. It gives hope to the idea that little by little, we may understand how our genetic makeup and our environment interact to cause stroke. A definitive genome wide association study in ischemic and hemorrhagic stroke has yet to be completed. Various risk factors like blood lipids, hypertension, proteolytic enzymes, endothelial dysfunction, and hyperhomocystenimia contribute in developing the pathogenesis of stroke through variouspathways. This background knowledge indicates a possible role of common polymorphisms of *ACE, ADD, APOE, PDE4D, ACT, MTHFR* genes in stroke susceptibility. Thus the current study involves the analysis of SNPs in these genes to elucidate any association with stroke in North Indian stroke patients.

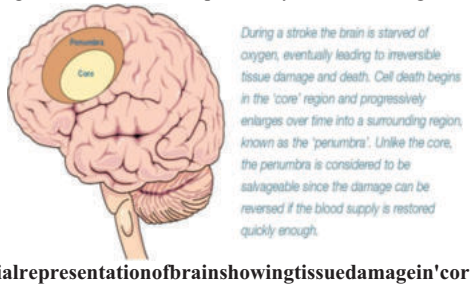
Review of Literature:-

History of stroke

"Stroke" was originally short for 'stroke of apoplexy'. 'Apoplexy' is derived through French and Latin from the Greek word "apoplexia", meaning a sudden loss of feeling and motion. Earliest studies on the understanding of brain pathology came with studies of apoplexy. Gregor Nymman of Wittenberg published the first monograph on apoplexy in 1619 (Garrison, 1969). The most important progress in the investigation of apoplexy came from precise studies by John Jakob Wepfer (Donley, 1909, Meyer, 1962). Cerebral hemorrhage was little known before the publication of *Wepfer's Treatise on Apoplexy*, Jakob Wepfer put across the opinion initially that extrinsic compression of the internal carotid or vertebral arteries or occlusion or narrowing of the lumen by small fibrous bodies in the vascular wall would impede a sufficient supply of blood from reaching brain. He was the first to appreciate that apoplexy resulted from cerebral hemorrhage. But the actual demonstration of the mechanism of paralysis on the side opposite from the brain lesion in apoplexy was made by Domenisco Mistichelli (Thomas, 1910).

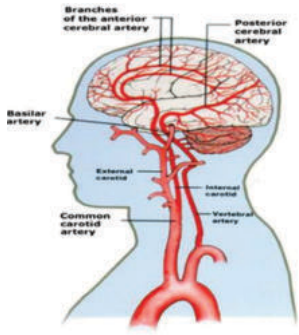
How Stroke Affects The Brain?

Brain cells require a constant delivery of oxygen and glucose from the blood and in ischemic and hemorrhagic stroke, the blood supply to the tissues is disrupted. Disruption in blood flow is caused when either a blood clot or piece of plaque blocks one of the vital blood vessels in the brain (ischemic stroke), or when a blood vessel in the brain bursts, spilling blood into surrounding tissues (hemorrhagic stroke). Both hemorrhagic and ischemic strokes affect brain in the same way as they starve the brain of oxygen and nutrients causing the brain cells to die. The damages that are occurring to the brain tissue and the blood vessels supplying blood to the brain are pictorially shown in the figure.



Pictorialrepresentationofbrainshowingtissuedamagein'cor e'and' penumbra'

Source:(SAFE)http://www.safestroke.org/facts/the-burden-of-stroke.aspx

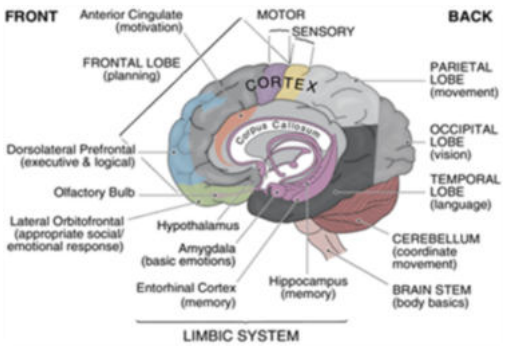


Pictorialrepresentationofbloodvesselssupplyingbloodtobrain

Source: http://www2.mhsi.us/education_stroke.html

The brain is a highly complex organ that controls many of the body's functions. The consequences of stroke are wide-ranging because they depend on the region of the brain affected. Location wise control of function of the brain is shown in fig. 2.3. Depending on the part of the brain affected and how widespread the damage is, stroke can lead to

- ❖ Hemiplegia and muscle weakness of the face
- ❖ Apraxia (altered voluntary movements)
- ❖ Visual field defect
- ❖ Memory deficits (involvement of temporal lobe)
- ❖ Hemineglect (involvement of parietal lobe)
- ❖ Disorganized thinking, confusion,
- ❖ Anosognosia
- ❖ Hemiparesis, bladder and bowel control
- ❖ Dysarthria (motor speech disorder resulting from neurological injury)
- ❖ Reduction in sensory or vibratory sensation
- ❖ Weakness in tongue (inability to protrude and/ or move from side to side)



Pictorialrepresentationofdifferentlobesofthebrainshowingvariousfunctions

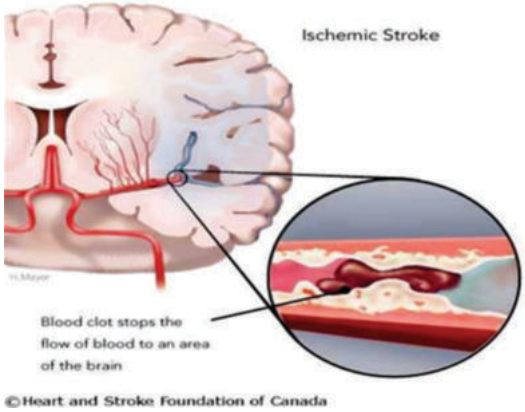
Source: http://www.brainwaves.com/brain_new.html

Classification Of Stroke

Stroke is broadly classified in to two major groups: Ischemic stroke (IS) and hemorrhagic stroke (HS). The distinction between ischemic and hemorrhagic stroke in radiological routine is based on computerized tomography (CT) and Magnetic resonance imaging (MRI).

Ischemic Stroke (IS)

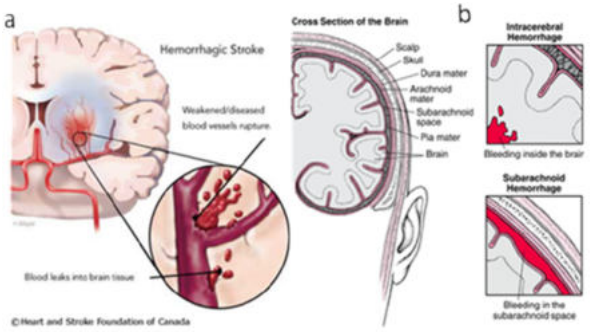
Ischemic stroke occurs when adequate blood supply to a region in the brain is interrupted (fig 2.4). The common cause of interrupted blood flow is an occlusive thrombus though interruption can result from various conditions, eg. a sudden lowering of systemic blood pressure in combination with a carotid stenosis or a dissection of pre-cerebral artery. Thrombus formation may be a local process in a cerebral artery or it may originate from the heart or from atherosclerotic plaque lesions in the aorta or carotid arteries. In the later cases, when a thrombus is transported with the blood stream in to a cerebral artery, it is defined as embolus.



Source: http://www.heartandstroke.com/atf/cf/%7B99452D8B-E7F14BD6-A57D-B136CE6C95BF%7D/stroke_isc_web.jpg

Hemorrhagic Stroke (HS)

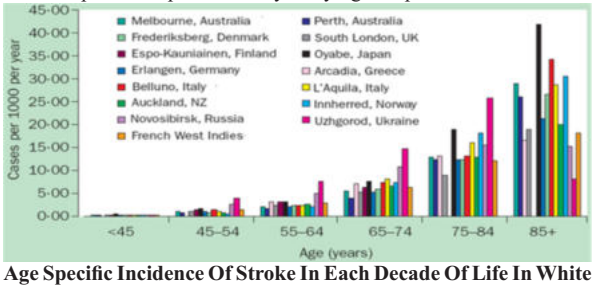
Hemorrhagic stroke include bleeding within the brain termed as intracerebral hemorrhage (ICH) and bleeding between the inner and outer layers of the tissue covering the brain; termed as subarachnoid hemorrhage (SAH) (fig 2.5). Hemorrhagic strokes also involve bleeding inside the skull involving epidural and subdural hematomas, which are usually caused by a head injury. Hemorrhagic stroke represents 15% of all strokes, including a large population of fatal or severe cases. Blood from a ruptured blood vessel compresses and damages normal functioning of brain tissue. This rupture may occur because of underlying damage to the blood vessel from years of high blood pressure or from an underlying abnormality in a blood vessel, such as an aneurysm (abnormal bulging of a blood vessel). Blood pressure is a major risk factor for intracerebral hemorrhage (ICH) than for ischemic stroke (Park *et al.* , 2001), but the difference is modest (Lewington *et al.* , 2002). The other possible causes include alcohol abuse, drug abuse (especially cocaine), and cigarette smoking. A subarachnoid hemorrhage is considered stroke when it occurs spontaneously which is usually due to sudden rupture of an aneurysm in a cerebral artery. Hypercholesterolaemia as a risk factor for intracerebral hemorrhage (ICH) remains a topic of discussion and epidemiological data have suggested that very low cholesterol levels are also a risk factor (Iso *et al.* , 1989).



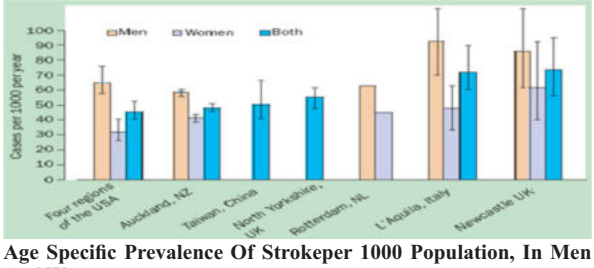
Source: http://www.heartandstroke.com/atf/cf/%7B99452D8BE7F1-4BD6-A57D http://www.merckmanuals.com/media/home/figures/MMHE_06_086_04_eps.gif

Epidemiology

The WHO recently identified stroke as a major public health problem for developed and developing countries. According to the WHO, stroke is associated with fourth highest burden of disease worldwide (Millán and Dávalos, 2006). The incidence of new cases of first-ever stroke, is about 200 per 100,000 in the few Caucasian population studied (Sudlow *et al.* , 2006). A review which analyzed the published reports on white population-based studies on the incidence, prevalence, mortality, and case-fatality of stroke from 1990 onwards, reported that the age- specific incidence of stroke increased progressively with each decade of life (Feigin *et al.* , 2003) The same review reported the prevalence by studying nine prevalence studies.



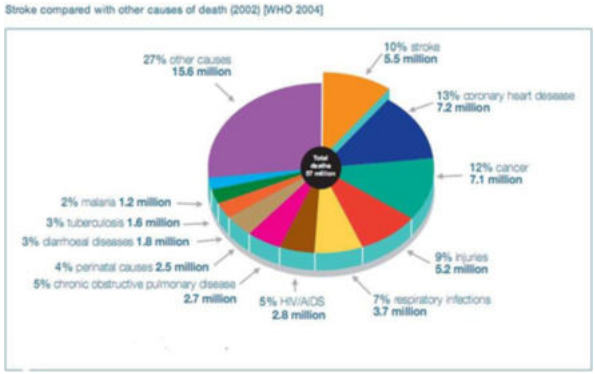
Age Specific Incidence Of Stroke In Each Decade Of Life In White Population.



Age Specific Prevalence Of Strokeper 1000 Population, In Men And Women.

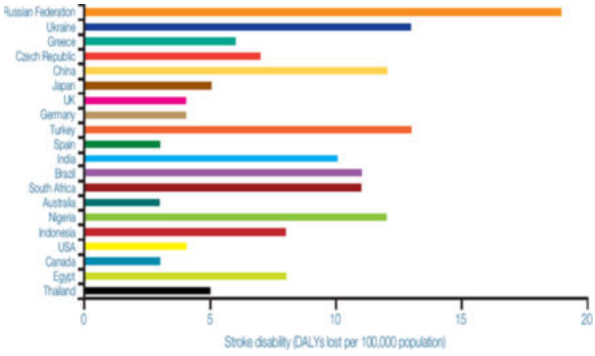
Zone	Place	Rural/ urban	Year	Population	Crude prevalence rate per 100,000
North	Rohtak, Haryana	Urban	1971-74	79,046	44
	Kuthar Valley, Kashmir	Rural	1986	63,645	143
West	Mumbai, among the Parsis	Urban	1985	14,010	842
	Mumbai	Urban	1997	145,456	220
East	Malda, West Bengal	Rural	1989-90	37,286	126
	Baruipur, West Bengal	Rural	1992-93	20,842	147
	Kolkata	Urban	1998-99	50,291	147
South	Vellore	Rural	1969-71	258,576	57
	Gowribidinur, Karnataka	Rural	1982-84	57,660	52
	Bangalore	Rural	1993-95	51,055	165
	Bangalore	Urban	1993-95	51,502	136

Prevalence Rates Of Stroke Determined From Majore Pidemiological Surveys In India. (BanerjeeandDas,2006)



Percentage of stroke death compared with other causes of death

Source:(SAFE)http://www.safestroke.org/facts/the-burden-of-stroke.aspx



The Disability Adjusted Life Years(DALYs) due to stroke in different population

Source:(SAFE) http://www.safestroke.org/facts/the-burden-of-stroke.aspx

Genetics of Stroke

Historically, the two most common approaches in finding genes involved in disease have been linkage and candidate gene association studies. Association studies have become an increasingly common approach to mapping variants that affect ischemic and hemorrhagic stroke, especially as a result of lower power in family studies and advances in high-throughput genotyping**.** Numerous candidate gene pathways and genes have been studied and most of them were involved in inflammation, lipid metabolism, nitric oxide release, coagulation and renin- angiotensin-aldosterone systems, hemostasis.

Aim(s)And Objectives

Aim

To identify the genetic factors associated with ischemic and hemorrhagic stroke susceptibility using genetic association study in cases and healthy controls from North India.

Objectives

To find association of candidate gene polymorphisms with ischemic

and hemorrhagics trokes. To investigate the role of candidate gene in large vessel disease, small vessel disease, non lobar and lobar subgroups of stroke.

MATERIAL AND METHODS

The study population consisted of 85 ischemic and 85 hemorrhagic stroke patients. Based on inclusion/exclusion criteria, patients were recruited from the Neurology outpatient and inpatient clinic of Jaiswal Hospital and Neuro Institute & Government Medical College Kota Rajasthan India. Simultaneously, 5 healthy controls (HC) were recruited for the study after taking into consideration the mean age of selected patients. Healthy controls were recruited at a similar time and geographical location as the case group to avoid potential bias of population heterogeneity and stratification. The study groups were personally questioned whether their grandparents, parents or themselves were north Indian natives. Also, question regarding the language they speak, the food they eat, determined the ethnicity. The study was ethically approved by institutional ethics committee.

RESULTS WITH CONCLUSION:-

Stroke is an acute neurologic event leading to death of neural tissue and often resulting in the loss of motor and cognitive function. It is the third leading cause of death and the leading cause of severe long-term disability. Most strokes (80%–90%) are caused by an acute interruption of the brain arterial blood supply due to vascular occlusion, leading to brain tissue ischemia. A minority of strokes (10%–20%) are caused by blood vessel rupture, leading to hemorrhage. Ischemic stroke results from various pathophysiologic mechanisms such as large artery atherosclerosis, cardio embolism, small vessel disease, other determined and undetermined causes. Intracerebral hemorrhage contributes more than 80% of the hemorrhagic stroke with hypertension as an important known risk factor. There is substantial evidence supporting a genetic contribution to stroke susceptibility. Studies in twins showed significantly greater concordance rates of stroke in monozygotic twins than in dizygotic twins, and a positive family history was a significant risk factor for both ischemic and hemorrhagic strokes.

The Clinical Characteristics Of The Study Are Summarized As Follows:

- Majority of the stroke patients were male in our study group and hypertension was found in 55.3% of ischemic and 66.3% hemorrhagic stroke patients.
- 55.40% of the ischemic stroke patients were under large vessel disease subgroup.
- 88% of the hemorrhagic stroke patients had non lobar hemorrhages in which 52% had putaminal bleed.
- 27% of the hemorrhagic bleed was thalamic and only 12% constituted lobar hemorrhages.
- In our patient group 15% were smokers, 19.4% chewed tobacco and 17% had alcohol consumption.
- Family H/o stroke was present in 15.54% of the total patients.
- History of TIA/stroke was observed in 11.65% of the total study subjects.

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