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A Study on Risk Factors Associated with Ischemic Stroke among Coronary Artery Disease Patients

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Abstract

Premonitory stroke symptoms are not always found; fewer than 20% of stroke patients have a prior TIA. Focal premonitory symptoms, when present, usually predate infarction rather than haemorrhage. When they occur, they may be so nonspecific that they are not recognized as signs of an impending stroke. Within 90 days after a TIA, the risk of stroke has been reported to be as high as 10% to 20%, and nearly half of these patients will have their stroke in the first 2 days after the TIA. Patients on established coronary artery disease who were on atorvastatin therapy 10 mg for more than 1 year, who developed an ischemic stroke evidenced by CT scan or MRI within 5 years of occurrence of the first coronary event were included. Out of the 50 patients studied 16 were known diabetes patients on treatment accounting to 32% of cases. In our study 38 (74%) CAD patients who developed CVA had positive history of ischemic events in family and 28 (56%) of the controls that were CAD patients and did not develop CVA had positive family history.

Keywords: Risk Factors; Ischemic Stroke; Coronary Artery Disease.

Introduction

The adult brain, measures around 1500 g or 2% of the total body weight, and needs about 150 g of glucose and 72 L of oxygen every 24 hours without any interruption. This amounts to 20% of the body's total oxygen consumption. Since the brain cannot store the substances, severe affect in functioning occurs after only a few minutes of absence of either the oxygen or glucose or their reduction below critical levels. At rest, each cardiac contraction gives about seventy millilitre of blood into the ascending aorta. Ten to fifteen mL is provided to the brain. Every minute, about 350 mL flows through each internal carotid artery, and 100 to 200 mL through the vertebra basilar system, to achieve a total cerebral blood flow of 50 mL/min per 100g [1,2].

Premonitory stroke symptoms are not always found; fewer than 20% of stroke patients have a prior TIA. Focal premonitory symptoms, when present, usually predate infarction rather than haemorrhage.

When they occur, they may be so nonspecific that they are not recognized as signs of an impending stroke. Within 90 days after a TIA, the risk of stroke has been reported to be as high as 10% to 20%, and nearly half of these patients will have their stroke in the first 2 days after the TIA [3].

The statins are the most effective drugs with less adverse events profile for treating patients suffering from dyslipidemia. Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, by competitive inhibition which acts as a catalyst in an early, rate-limiting step in the synthesis of cholesterol [4].

Doses in the high range of the recent drugs with increased potency (*e.g.,* atorvastatin and simvastatin) also decrease triglyceride levels due to elevated VLDL levels.

Statins cause reduction in cholesterol levels by decreasing synthesis of cholesterol by hepatocytes which causes increase in the expression of low density lipoprotein receptor gene. As free cholesterol content within hepatocytes is reduced, membrane bound SREBPs are cleaved by a protease and are trans located into nucleus. The transcription factors bind to the sterol responsive element of the low density lipoprotein receptor gene, increasing

transcription & causing increase in the synthesis of low density lipoprotein receptors. Degradation of LDL receptors also is reduced [5].

Triglyceride levels >250 mg/dl are brought down significantly by statins, & the % reduction achieved is like that of the % reduction in low density lipoprotein cholesterol. Similarly, hypertriglyceridemia occurring in patients who consume high doses of the best potency statins (simvastatin and atorvastatin, 80mg/day; rosuvastatin, 40mg/day) reach about 40% decrease in LDL-Cholesterol and also the same results are seen in triglyceride values.

Many studies conducted for statin effectiveness have particularly eliminated HDL cholesterol levels. While analyzing patients with increased LDL-Cholesterol levels & near normal HDL Cholesterol values (40 to 50 mg/dl in males & 50 to 60 mg/dl in females), an elevation in HDL Cholesterol of 5 - 10% has been reported, in spite of the variations in the dose of statin employed [6].

But the case is not the same when the HDL cholesterol value is low. The reports are variable and need further study.

Statin treatment increases endothelial synthesis of nitric oxide which has beneficial action by causing vasodilatation.

Statins affects stability of plaque in many methods. Statins cause inhibition of monocyte entry into the site.

Statins decrease the coronary risk & high values of CRP which is considered an important marker for inflammation in spite of decreasing cholesterol.

Change in morphology of LDL by oxidation has a significant effect in affecting the uptake of lipoproteins by macrophages and also causing cytotoxic effects within lesions.

Statins decrease assembly and aggregation of platelets.

The two well accepted bile acid sequestrants also widely called resins are cholestyramine & colestipol. They are the oldest among hypolipidemic class of drugs & they have safe adverse effect profile as they do not have their absorption at the small intestine. They can be used for patients between 11 to 20 years of age. As statins are good as monotherapeutic agents, they are commonly used as 2nd line agents when statin therapy cannot attain its LDL lowering target successfully [7].

Niacin (pyridine-3-carboxylic acid) is one of the age old dyslipidemic classes of drugs, which has its say on all lipid parameters. In fatty tissues, niacin decreases the lipolysis of triglycerides with the help of hormone sensitive lipase which decreases entry of free fatty acids into the liver and causes reduction of synthesis of triglycerides by the liver.

Fibrates bind to PPAR which is expressed predominantly in the liver and brown adipose tissue & also to a certain degree in kidneys heart & skeletal muscle. Fibrates cause decrease in triglycerides by means of PPAR through increase in fatty acid oxidation increase in lipoprotein lipase synthesis and decrease in expression of lipoprotein lipase. Any increase in lipoprotein lipase levels will increase the removal of triglyceride rich lipoproteins.

Decrease in synthesis of apoC-III by the liver, acts by inhibiting lipolytic processing & receptor mediated clearance, will increase the removal of very low density lipoprotein. Fibrates mediated enhancement in HDL Cholesterol levels are because of PPAR stimulation of apoA-I and apoA-II expression, that enhances High density lipoprotein cholesterol levels. Fenofibrate is more successful in increasing high density lipoprotein levels than gemfibrozil [8].

Methodology:

Inclusion criteria

Patients on established coronary artery disease who were on atorvastatin therapy 10 mg for more than 1 year, who developed an ischemic stroke evidenced by CT scan or MRI within 5 years of occurrence of the first coronary event.

Exclusion criteria

Age less than 40 years.

Patients on irregular statin therapy.

Patients with chronic kidney disease.

Patients with chronic liver disease

Patients who had poor left ventricle function

Study Design

Number of study groups: two

Group 1 Cases: 50 patients with a history of coronary artery disease with ECG or ECHO confirmation and who were on regular atorvastatin therapy 10 mg daily for more than one year who developed a cerebrovascular event in the form of ischemic stroke with CT or MRI Brain evidence within 5 years of occurrence of the first coronary event were included in the study.

Group 2 Controls: A suitable control of 50 patients matching age, sex, smoking, alcohol and diabetes who had coronary artery disease and were also on atorvastatin therapy 10 mg for more than 5 years were included. These patients should have normal CT brain and no prior history suggestive of transient ischemic attacks.

Study size: 50

Study type: case control study

The age ranges from 40 to 80 and the study included both sexes. The study was approved by institutional ethics committee. The risk factors associated with, both modifiable like cigarette smoking, alcohol consumption, hypertension, diabetes mellitus and obesity (BMI) and non- modifiable like age, sex, family history was taken into consideration. The risk factors smoking and alcohol were found out by careful history taking. The risk factors DM and HT were detected by past medical history and laboratory routine investigation and BP measurement.

Total cholesterol HDL Cholesterol and triglycerides were measured in overnight fasting of 10 hrs. at 7 a.m. in the morning using Hitachi 704 Analyser. Low density lipoprotein Cholesterol was calculated by the FRIEDWALD formula LDL-chol = total chol - HDL-chol - Triglycerides/5 which is internationally accepted. Non HDL cholesterol was calculated by deducting HDL from total cholesterol. Both cases & controls were established coronary artery disease with ECG and ECHO confirmation.

All the basic blood investigations were done and their body mass index was calculated and the presence of metabolic syndrome was analysed. Those who had elevated renal parameters or abnormal liver function tests were excluded from the study.

Results

In our study 38 (74%) CAD patients who developed CVA had positive history of ischemic events in family and 28 (56%) of the controls who were CAD patients and did not develop CVA had positive family history. Chi squared equals 8.117 with 1 degrees of freedom.

The two-tailed p value equals 0.0044

By conventional criteria, this difference is considered to be very statistically significant.

Table 1: Family history

	CAD With CVA	CAD Without CVA
+ Family History	38	28
No Family History	12	22

$$\text{Relative Risk} = \frac{\text{Incidence of CAD with CVA in patients with family history}}{\text{Incidence of CAD with CVA in patients with negative history}}$$

$$= \quad a/(a+b) \div c/(c+d)$$

$$= \quad 1.6$$

Thus a positive family history can be associated with a 1.6 fold increase in the risk of developing CVA in established CAD patients. It is important to remember that earlier onset of both coronary and cerebrovascular events were observed in patients with positive family history (Table 1).

Table 2: Smoking

Total	Smokers		Nonsmokers	
50	males	females	males	Females
	20	0	9	21

Out of the 50 patients 20 were smokers which accounts to 40%. All the 21 females were nonsmokers. But 17 of the females were exposed to passive smoking (Table 2).

Table 3: Alcoholism

Total	Alcoholics		Non alcoholics	
	Males	females	males	Females
	19	1	10	20

Out of the 50 patients 20 were alcoholics which accounts to 40%. Out of the 21 females one was an alcoholic. She works as a cleaner in a bar shop and developed the habit of tasting the left over wines and became addicted to it. The controls were matched for smoking and alcoholic. Except that the lone female alcoholic could not be suitably matched (Table 3).

Table 4: Diabetes Mellitus

	Diabetes		Non Diabetics	
50	Males	Females	Males	Females
	10	6	19	15
Total	16		34	

Out of the 50 patients studied 16 were known diabetes patients on treatment accounting to 32% of cases. The controls were matched for diabetes (Table 4).

Table 5: Socio Economic Status

Low socioeconomic group	Middle socio economic group	High socio economic group
25	20	5

50% of patients belonged to lower socio economic

group, while 40% were from middle income group and only 10% were from upper group. Existence of coronary artery disease in the lower socio economic group of people in the urban areas has changed considerably due to change in lifestyle. The more number of patients in low socio economic group could be because of more number of low socio economic group people visiting government hospital in general (Table 5).

Table 6: Hypertenison

Total	Hypertensives		Nonhypertensives	
	Males	Females	Males	Females
	12	6	17	15
Total	18		32	

Out of the 50 patients 36% were hypertensive. The controls were matched for hypertension (Table 6).

Discussion

In our study 38 (74%) CAD patients who developed CVA had positive family history for ischemic events and 28 (56%) of the controls who were CAD patients and did not develop CVA had positive family history. This was similar to the study conducted by hoseini et al. [9]. The very high prevalence of family history is reported in Indian population so also the earlier onset of ischemic event by a decade due to genetic factors.

In our study 40% were smokers. Controls were matched for smoking. This indicates a high prevalence of ischemic events in people who smoke. This has been proved number of times in various studies examples include study done by Jeremy et al. [10].

In our study 40% were alcoholics. Controls were matched for alcohol intake. This indicates a high prevalence of ischemic events in people who consume alcohol. This has been proved number of times in various studies examples include study done by michael et al. [11].

Some patients especially men though they have only slight increase in waist circumference have other points in favour of the detection of metabolic syndrome. They have strong genetic influence for the development of metabolic syndrome. They should be advised diet and lifestyle changes

The main goal in the therapy of metabolic syndrome is proper education and counselling regarding the hazards of faulty diet habits and physical inactivity. Half an hour of physical activity a day increases their life span by 6 to 7 years. The ATP 3 guidelines also stresses upon these factors.

Establishing proper glycaemic status reduces micro vesicular complications more than macro vesicular complications of diabetes. Hence early detection of diabetes and following patients periodically is important. It may even result in adverse events. So the ultimate goal is in correction of diabetic dyslipidaemia and other factors.

Multiple drug trials are being conducted keeping in mind the specific dyslipidaemia problems of diabetes. Statin therapy has been shown to have very high benefit beyond doubts. Other factors beyond tight glycaemic control are being looked upon.

Since the benefit of HMG CO Areductase inhibitors for diabetic populations are proved by meta-analysis. The American diabetic association recommends statins to all patients with total cholesterol above one hundred and thirty five. Metformin is the only oral hypoglycaemic agent which is found to be cardio protective. Statins are not useful in chronic kidney disease especially in end stage.

A large number of markers of coronary event risk have been identified in recent years. Markers estimated by using peripheral arterial blood include size of low density lipoprotein particles & levels of blood homocysteine, Lipoprotein a, fibrinogen, C reactive protein, plasminogen activator inhibitor protein 1, tissue myeloperoxidase & lipoprotein related phospholipase A_2.

But still there is no substitute for careful history taking and analysis of serum lipid profile and fasting blood glucose [12].

With the existing clinical data we are not in a position to recommend imaging studies as a screening test in detecting underlying disease. Such methods include the usage carotid Doppler to study carotid intima media thickness, calcification, MR angiography and CT angiography. If these tests are used universally the patients may panic and this may increase the economic burden of the society

Conclusion

- It is important to remember that earlier onset of both coronary and cerebrovascular events were observed in patients with positive family history
- Existence of coronary artery disease in the lower socio economic group of people in the

urban areas has changed considerably due to change in lifestyle. The more number of patients in low socio economic group could be because of more number of low socio economic group people visiting government hospital in general.

References

1. Nilson J. Atherogenesis regulated by immune mechanisms: prospects for the development of preventive medicines. Arteriosclerosis Thromb Vascular Biol 2005;25:18–28. [PMID: 15514204].
2. Pasterrkamp G. Expansive arterial remodeling: Location, location, location. Arterioscler Thromb Vasc Biol. 2004 Apr;24(4):650-7.
3. Rana JS. The role of non-HDL cholesterol in risk stratification for coronary artery disease. Elsevier Ireland Ltd Nov 16:2012.
4. Sigdel M. Study on cholesterol. B. BMC Res Notes. 2012 Nov 17;5(1):640.
5. Wood D. preventive methods for coronary heart disease in daily life. What the Second Joint Task Force of European and Other Societies on Coronary Prevention has recommended. European. Heart Journal., 1998;19:1434–1503.
6. Yuan J. Differences in structural & prevalence of variation among low density lipoprotein subtypes in in patients with high triglycerides & high cholesterol in individuals during treatment with gemfibrozil.1994;110:1–11. PMID.
7. Yuv Pravin et al. Role of non HDL cholesterol on CVA. Bangladesh Journal of Medical Science 2010 Jul;9(3).
8. Kruth HS. Sequestration of aggregated low density lipoproteins because of macrophages. Curr Opin Lipidol 2002;13:483.
9. Hoseini K, Saedeghian S, Mamoudian M, Hamiidian R, Abasi A. Family history of cardiovascular disease as a risk factor for coronary artery disease in adult offspring. MonaaldiArchieve Chest Disease. 2008 Jun;70(2):84-7.
10. Jeremy A. Kelley. Coronary Artery Disease and Smoking Cessation Intervention. Online Journal of Health Care, 2009;9(2).
11. Michal G Marrmota. Alcohol and heart disease. Int. J. Epidemiology. 2001;30(4):724-29.
12. Michel Miler. What Are the Effects of Statins on Triglycerides and What Are the Results of Major Outcomes Studies? JAMA. 2012 Mar 28;307(12):1302-9.