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Association of Poor Drug Adherence and Recurrent Stroke: An Alarm for Better Patient's and Family Education

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1. INTRODUCTION

Stroke is global and chronic health problem and associated with leading cause of death and disability when combined together, and more than 80% of all stroke related deaths are reported from low and middle income countries.[1] If we see for disability caused by stroke about 20% of survivors have to continue institutional care even after 3 months of standard medical care.[2] Other than severe motor disability in one third, stroke is also accountable for epilepsy, depression and dementia in another one third.[3]

It is also obvious that with recurrence of 2nd or 3rdstroke further increases the disability and mortality as compared to first stroke. About 13 to 15 million new cases of stroke occur every year in India and it is associated with case fatality rate of about 41% in Indian population. About 70.45% of death was primarily due to index stroke and 19.27% due to recurrent stroke. [4] Therefore, an effective secondary stroke prevention strategy is as important as we do for the acute management of ischemic stroke. Still we face the problem of recurrent stroke and according to one estimate, among 795000 strokes each year in United States, about 185000 were recurring events which lead to high financial and disease burden.[5]

In previous studies it had been shown that about 55% patients of first ever stroke have good outcome and second stroke is commonly more severe and disabling as compared to first stroke. [6-7] Therefore, in the past efforts had been made to find out tool for early prediction of recurrence after first stroke and older study highlighted that high "CHA_2DS_2VASc score" and "Essen stroke risk score" were associated with good prediction of recurrent stroke, death and cardiovascular events.[8]

Both of these tools only highlighted the disease related factors although we know that other than disease severity, drug adherence is also an important factor to predict recurrence of stroke in countries like India. Currently we don't have any structured primary health care system at community level, to deal with issues like drug adherence and monitoring of disease like diabetes and hypertension.

Our hypothesis is that there are two categories of risk factors for future recurrence of stroke; 1) Patients related risk factors like poor adherence to drugs for secondary prevention of stroke along with 2) disease related risk factors. Since, we could not find any previous study conducted to know the proportion of both categories of risk factors among patients of recurring ischemic or hemorrhagic stroke, we have planned this cross-sectional study on patients presenting with recurrent ischemic or hemorrhagic stroke. Aim was to know the proportion of patients having recurrent stroke due to patients related risk factors like poor drug adherence and disease related risk factors for recurrent stroke.

2. METHODS

This study was a cross-sectional study and was conducted in department of neurology of a tertiary care hospital and medical university in North India. Patient data collection was done for all consecutive patients presenting with recurring stroke during the period of 2 years (June 2020 to June 2022). The project was cleared from institutional research and ethical committee and patient written consent was obtained before enrolment. Data was recorded for type of first stroke, risk factors for first stroke, type of recurrence, factors responsible for recurrence. Factors responsible for recurrence were divided in two groups 1) patient related and 2) non-patient related;

2.1. Definition of Patient Related Factors

When patients are at fault and not taking medicine regularly, not following advice of physician, not doing life style modifications, not doing regular follow-up as advised by physician and had recurrence of stroke.

2.2. Non-patient Related Factors

When patients are regular in their medication, visiting to doctors regularly as per advised, doing all life style modification as advised but still had stroke recurrence.

2.3. Timing of Recurrence

Recurrence was classified as early (within one year of first stroke) or late (after one year of stroke). Index stroke (first stroke) was divided into three categories; 1) large vessel ischemic stroke, 2) small vessel lacunar stroke and 3) primary intracerebral hemorrhage (ICH). Patients with secondary ICH and traumatic stroke were not included. Data was also recorded for the outcome of recurrence and seen how many patients lost their activity of daily living (ADL) after the recurrence.

2.4. Risk Factors Comparison

Risk factors like diabetes, hypertension, cardiac source of embolization or atrial fibrillation, large vessels occlusion > 50%, active smoking and daily alcohol usage were compared between patients admitted with first (single) stroke versus patients with recurrent stroke. For comparison 94 patients of first stroke admitted at the same time were compared with patients of recurrent stroke. Comparison was done only in patients with ischemic stroke and new stroke patients with multiple lesion or old asymptomatic stroke were not taken for comparison.

2.5. Data Availability

Data used in study for analysis and final conclusion can be made available on request of any of the reviewing team members.

2.6. Statistical Analysis

Statistical Analysis was done with the help of SPSS statistics 25 (IBM,USA). Frequency analysis was done for demographic analysis and stroke types. Cross-tab analysis was done to compare early versus late stroke in small vessel and large vessel stroke. Risk Ratio and 95% confidence interval was calculated for comparison of patients with isolated single stroke with patients having recurrent stroke.

3. RESULTS

Our study was not designed to find out the rate of recurrence but among 778 patients admitted for ischemic or hemorrhagic stroke in2 years (retrospectively seen) from January 2021 to December 2022, 118 patients were admitted due to recurrence with prevalence of 15.2%. Among these 118 patients 64% were male and 41.5% were below 60 years age. Details characteristics of these 118 patients are described in table 1& 2. First index stroke in these 118 patients was ischemic in 108 (91.5%) and hemorrhagic in 10 (8.5%) patients. Among 108 patients with first event as ischemic stroke, 74 (68.5%) had large vessel and 34 (31.5%) had small vessel stroke according to TOAST classification.[9] Among the patients with large vessels stroke (N=74) 59 (79.7%) had anterior circulation and rest 15 (20.3%) had posterior circulation stroke and 54 (45.8%) had right hemisphere lesion at the time of first stroke and 48 (40.7%) had left hemisphere lesion. Rest of 16 (13.5%) patients had bilateral weakness at the time of first stroke due to either bilateral cerebral hemisphere involvement or brain stem involvement **(table 1-2).**

Type of Recurrence (Table 1): Among 108 patients who had index event as ischemic stroke, 96 (88.9%) had recurrence with similar type of stroke that is ischemic stroke and 12 (11.1%) had recurrence with hemorrhagic stroke. Among 10 patients with first hemorrhagic stroke, 6 (60%) had recurrence with ICH and rest 4 (40%) had recurrence with ischemic stroke. Thus total 16 (13.6%) had recurrence with change in subtype from index stroke.

Side of Recurrence (Table 1): Among 102 patients who had unilateral (either right or left) first stroke, 65 (63.7%) had same side recurrence while 37 (36.3%) had recurrence on contra lateral side of brain. Among 74 patients with large vessel stroke, 51 (68.9%) had same territorial involvement and 23 (31.1%) had different territory in second stroke.

Timing and Number of Recurrence (Table 3): Among 118 patients, 90 (76.3%) had late recurrence that is after one year of index stroke, while 28 (23.7%) had early recurrence within one year of first stroke. Among patients with late recurrence group 79 (67%) recurrence between 1-5 years of first stroke. Timing of recurrence was not found to be significantly associated with type of first ischemic stroke and with risk factor associated with recurrence. Among 118 patients, 102 (86.4%) had only one

recurrence till the completion of study while 16 (13.6%) patients had more than one recurrence.

Factors for Recurrence (Table 4): Among 118 **patients** with recurrent stroke, 63 (53.4%) had patient's related factor (poor compliance and/or poor control of risk factors) and 55(46.6%) had non-patients related risk factors (Table 3). Most common patient's related factors were poor adherence of drug 53.4% and poor monitoring/ control of diabetes and/or hypertension in 22.9% patients. Along with the poor drug adherence and poor control of risk factors 12.7% patients continued to smoke.

Comparison of Risk Factors in Patients with First Stroke Versus Recurrent Stroke (Table 5): hypertension and diabetes was found to have higher relative risk factors for recurrence of ischemic stroke. Poor control of blood pressure (RR =1.298, 95% CI = 1.095-1.53) and diabetes (RR = 1.329, 95% CI = 0.969 – 1.824) was more common in recurrent stroke. Active smokers were significantly more common in patients with first stroke as compared to recurrent stroke (p = 0.001).

4. DISCUSSION

Recurrent stroke needs to be addressed as large number of patients with minor stroke and TIA can suffer from major disabling stroke next time if proper safety not taken. Disability related to stroke is huge and in year 2019 there were 143 million disability adjusted life years (DAILYs) lost due to stroke. [10] It is known that about 20% of survivors have to continue institutional care even after 3 months after first stroke.[11] Recurrence of stroke further adds to the challenges in recovery and duration of hospital stay and leads to prolong hospitalization, worsened functional outcome and increased mortality.[12] Even patients with minor first stroke can have recurrence with major stroke or myocardial infarction to cause high mortality in these patients. Patients who had minor stroke or transient ischemic attack have 10 years stroke recurrence risk of 19% and 10 years risk of stroke, myocardial infarction and vascular death of 43% [13]. In our study 36.3% patients had recurrence of stroke on contra lateral hemisphere that leads to severe disability for both motor and cognitive functions. Similarly 31.1% patients had changed the territory in second stroke like posterior circulation stroke in patients with first anterior circulation stroke or vice versa. Patients had become cortically blind or became persistent vegetative due to bilateral posterior circulation stroke and patients became dependent on nasal tube feeding due to pseudo-bulbar palsy in bilateral anterior circulation stroke. Therefore treatment of first stroke and prevention of recurrent stroke both are very important to reduce stroke related disability in patients of ischemic stroke or ICH.

In current study 15.2% had recurrent stroke and in published data recurrence of both ischemic and hemorrhagic stroke varies from 5% to 23% during longitudinal follow-up. In one study on 2584 patients of stroke on dual anti platelet drugs, 212 (8.2%) had recurrent ischemic stroke.[14] Another study by Hier DB et al., showed 14.1% risk of recurrence of ischemic stroke in 2 years post-stroke.[15] Association had been seen with duration of follow-up period and rate of recurrent stroke. One community based study in China reported that annual rate of recurrent stroke during first 5 years after the index stroke and it was 5.6% after 1 year and 22.5% after 5 years of first stroke.[16] One study followed up 1872 stroke survivors for 3 years and found cumulative recurrence rate of14.2%.[17] Another study found rate of recurrence in ischemic stroke was 1.2% in first 30 days, 3.4% in 90 days, 7.4% in 1 year, and 19.45% in 5 years of index stroke event.[18]In our cohort of 118 patients 9.3%had stroke after 5 years of index stroke suggest the chronicity of disease and risk of cumulative burden over the years.

As mentioned earlier, the best ways to prevent the recurrence of ischemic stroke are good monitoring and control of underlying risk factors like diabetes, hypertension, lipids, smoking, and obstructive sleep apnea along with use of appropriately selected blood thinner for secondary prevention (anti platelet or anticoagulant).[19] Other then hypertension and diabetes systemic medical illnesses like chronic kidney disease was found as independent risk factor for recurrence (5 to 30 times higher) of both hemorrhagic and ischemic stroke.[20]

In our study the most common risk factor responsible for the recurrence of stroke was poor adherence to treatment (53.4% patients) and poorly controlled systemic diseases like diabetes and hypertension (22.9% patients). According to one report from Mayo Clinic, it was suggested that the full benefits of pharmacological treatment on chronic illnesses are often not realized because approximately 50% of patients do not take their medication as prescribed.[21]

It can be seen in current study that adequate drug adherence to treatment can prevent about 50% of recurrence in stroke patients and we should find out the strategy to improve the drug adherence for secondary prevention of stroke like antihypertensive, anti-diabetic, anti platelet or anticoagulant can one of the major steps to prevent recurrence. We have asked the patients about the reason to leave their medication and there were two types of people; 1) if they improve completely (20.4%) they think why to take medicine and 2) if they had permanent residual deficit (33%) then they like to choose complementary-alternative medicine for having better outcome. Few patients also have recurrent stroke when they stopped blood thinner due to some procedure or surgery (4.2%). Therefore, first and foremost part is to educate patients and patient's family about the adherence to treatment in diseases like stroke and coronary artery disease which are associated with high mortality and morbidity. In countries like India, along with poor patient's knowledge, there are other factors needs to intervene to counter the poor drug adherence in chronic disorders. These factors are related with the cost, availability and adverse effects of prescribe treatment and these factors should be closely observed by clinicians.[22]

After drug adherence second (22.9% patients) second most common patient's related factor for recurrence of stroke was poor monitoring and control of underlying modifiable risk factors like hypertension, diabetes and life style related issues (table 4). It is known that adequately control even a single parameter of hypertension at community level can lead to 30-40% reduction of stroke recurrence. [23-25]If additionally adequate monitoring and control of diabetes is combined to hypertension then we can further prevent about 9.1% of recurrence. [26-27]So, strict monitoring and control of hypertension and diabetes at primary health care level would be able to prevent about one third of recurrent strokes. Good monitoring and adequate control of modifiable risks factors of stroke is a major challenge in country like India. The larger disease burden and non-existence of quality primary healthcare system and poor doctor population ration in India create challenge in monitoring of non-communicable diseases and need to be addressed at policy level.[28] It has also been stated by Kocaman G et al., that only a stronger primary health care system can take care of patient's education for better drug adherence and control of risk factors together to prevent recurrent stroke [29].

Till now we have seen that the two most common interventions for prevention of recurrent stroke are related to patient's education and attitude; 1) adequate drug adherence and 2) adequate control of modifiable risk factors.

After discussion of above two patients related factors, now we will see the recurrence of stroke in patients taking care of drug adherence and risk factor control. Aggressive or severe underlying diseases contributed to 28.8% of recurrent stroke in our series which included patients with severe carotid stenosis, advance heart failure, fluctuation in INR on regular VKA, High cerebral microbleed load on MRI brain, metabolic syndrome malignant hypertension and refractory diabetes. "Stroke on aspirin" raised the concern for other underlying mechanisms rather than atherosclerosis like cardio-embolic stroke, atrial fibrillation, and large vessels occlusion (LVO). Cryptogenic stroke produces another challenge for clinicians in selection of best molecule for stroke prevention.[30] Stroke with occult or obvious malignancy is also a cause of high risk for recurrent stroke on aspirin.[31]

Atrial fibrillation (AF) needs special attention as a risk factor for recurrent stroke because secondary prevention is best done by anticoagulation rather than antiplatelet drugs and stroke can recur on regular aspirin intake. In our study 14.4% found to have recurrence of stroke as underlying AF was missed at the time of first stroke. Previous study also showed that after diabetes mellitus, atrial fibrillation was significantly associated with high chances of recurrent stroke.[32] High recurrence of ischemic stroke has been reported in patients in whom clinicians had missed the paroxysmal atrial fibrillation (PAF) and it is better to do 24-72 hours Holter monitoring is if stroke recur on regular use of anti platelet drugs.[33]After AF, another important cause of recurrent stroke on aspirin can be due to severe carotid artery stenosis (70-99% of lumen) which should be evaluated at the time of first stroke and can be better managed by vascular interventions on symptomatic side.[34]

Since primary ICH is less frequent than ischemic stroke (15% versus 85%) therefore recurrence rate is also less as only one risk factor (blood pressure) has to be monitored to prevent primary ICH. In our study only 10

patients with first stroke as ICH had recurrence of stroke and recurrent hemorrhage was positive only in 6 (5%) patients. Aggressive treatment and strict monitoring of blood pressure was globally recommended to prevent recurrence of ICH.[35]In patients with first stroke as primary intra cerebral hemorrhage (ICH), recurrence rate was reported to be 8.9% after one year and 13.7% after 5 years.[35]Five (83%) out of 6 patients with recurrent ICH had poor blood pressure control at the time of recurrence in our study.

Change in subtype of index stroke at the time of recurrence is known and ischemic stroke can reoccur with ICH and vice versa. In our study we found only 13.6% patients having change in subtype of index stroke. In one study, change in subtype of index stroke was very high(45.5%) and that was more common with lacunar stroke.[36]The incidence of ICH within one year of ischemic stroke was found to be about 15 times higher as compared with reference population.[37]

Intra-cerebral hemorrhage in patients of index ischemic stroke is commonly seen in patients on VKA with unstable INR, patients of chronic kidney disease with stroke and in patients with high cerebral micro bleeds (CMBs) load. Unstable INR (International Normalized Ratio) in patients on VKA for mitral valve disease or mechanical valve replacement create challenges for clinicians and patients are at risk of recurrence with ischemic (with low INR) or hemorrhagic strokes (with high INR).Currently, there is a shift towards usage of NOAC over VKA in prevention of stroke with AF or underlying cardiac source and now choosing NOAC over VKA can be a better option for those patients of valvular heart disease who are finding difficulty in monitoring and maintaining their INR on VKA.[35]

High cerebral micro bleeds (CMBs) load is known to be associated with high recurrence rate of both hemorrhagic and ischemic stroke.[38-40]CMBs load was labeled when there were more than 5 spots of micro bleeds on MRI brain.[39]It was also documented that there is a difference in pattern of recurrent stroke in Western and Asian people with high CMBs load.[38]In patients with high CMBs load, recurrence with ICH was significantly higher in Asian while recurrence with ischemic stroke was significantly higher in Western cohorts.[38] Patients with lacunar stroke with high CMBs load, have higher risk of recurrence with ICH, if prescribed dual anti platelet drugs due to any reasons. Among our study group, among 12 patients who had recurrence with ICH on the top of old ischemic stroke on anti platelet drugs 5 (41.7%) patients had high CMBs load.

Timing of recurrence in stroke was also addressed in some studies and it was divided into two times zone; 1) early, if stroke was recurring within one year of index stroke or 2) late if recurrence was after one year of first stroke[41]. The author in this article reported that that large vessels stroke was associated with early recurrence while small artery stroke were associated with late recurrence.[41]However, our data could not establish the same relationship of recurrence with type of stroke, as drug compliance was major factor for recurrence in our cohort. Total 18 out of 34 (52.9%) patients with small vessel stroke had disease related recurrence as compared to 30 out of 74 (40.5%) with large vessel stroke but it was statistically not significant (p=0.228).

To conclude, patients after first index stroke can have recurrence at any time which can increase the disability after first ischemic or hemorrhagic stroke. It is important for clinicians that their patients with stroke should be well explained about prevention plan, drug compliance, monitoring of underlying risk factors and life style modification. The plan discussion is more important in patients with TIA and minor stroke. Patients should regularly follow the family physicians near to home for monitoring and minor modifications. Family should always be educated by physicians about recurrence risk and prophylactic medications. Every effort should be made to rule out paroxysmal atrial fibrillation and critical carotid artery stenosis at the time of first stroke or TIA. Patients with stroke should be seen for high CMBs load and should be kept under strict observation if blood pressure is uncontrolled, or associated with CKD or receiving dual anti platelet. More than 50% chances of recurrence can be avoided with small precautions and it will ultimately lead to less disabled people in society.

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