

Apparent Treatment - Resistant Hypertension in Hypertensive Stroke Patients

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Abstract

Background: The amount of data available to evaluate the traits of apparent treatment-resistant hypertension (ATRH) in stroke patients is scarce, and little is known about the associated factors. We aimed to find out the prevalence and factors associated with ATRH among stroke patients. **Methods:** This cross-sectional study was conducted between November 2017 to December 2019 and involved two tertiary care hospitals in New Delhi, India. Standard protocol was used to measure clinic-based blood pressure, and antihypertensive medications were assessed via a review of medical records. The patients who achieved target blood pressure 140/90 mmHg on more than or equal to four drugs are considered as controlled ATRH. Patients who were aphasic and not able to respond verbally were excluded from the study. **Results:** Out of 91 stroke patients, 21.4% had ATRH. Stroke patients with ATRH had poor adherence to treatment ($p=0.006$), a higher prevalence of chronic kidney disease (CKD) ($p=0.002$) and a higher probability for intracranial hemorrhage ($p=0.025$). ATRH was found more commonly among males ($p=0.216$), smokers ($p=0.011$) and overweight ($p=0.020$) patients. In this study, no significant association was found between depression, cognitive impairment, coronary artery disease (CAD), diabetes mellitus (DM), chronic obstructive pulmonary disease, multiple strokes with ATRH stroke patients. **Conclusions:** In our study, it was found that a significant proportion (18.4%) of stroke population had ATRH. It was also observed that that majority of the patients were not adherent to their anti-hypertensive therapy. It reinforces the role of aggressive adherence improvement in these patients before other etiologies of ATRH are sought after. Also, statistically significant association of ATRH with CKD was found in our study. No association was found between ATRH stroke patients and CAD, COPD, DM, depression, cognitive impairment in subject population. Significant association of ATRH with factors like smoking and obesity lays stress on the importance of healthy lifestyle measures that are both effective and economically viable in a resource scarce country like India.

Keywords: Resistant hypertension, stroke, prevalence, associated factors, Indian population

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Introduction

One of the most important risk factors for primary and secondary stroke prevention is hypertension. Arterial hypertension stands among the leading global risks for mortality, being responsible for 8.5 million deaths worldwide in 2010 [1]. Resistant hypertension is an entity that has gained much attention in recent years, with some western studies suggesting prevalence as high as 10-15% in treated

hypertensive patients [1]. In a study by Mandal et al. in Kolkata, among 300 hypertensive subjects, 23.33% were identified as ATRH [2].

American Heart Association has defined ATRH as blood pressure that remains above goal i.e., BP $\geq 140/90$ mmHg, despite the concurrent use of three anti-hypertensive agents of different classes or is controlled using four or more anti-hypertensive medication. Ideally, one of the agents should

be a diuretic, and all agents should be prescribed at optimal dose amounts [2]. Control of BP following stroke is a substantial challenge. Studies done in risk factor management in stroke patients have revealed the low prevalence of blood pressure control in this cohort.

ATRH population as a whole carries an elevated risk of stroke and associated morbidity and mortality. This is supported by the fact that among patients with a history of stroke, the prevalence of hypertension is as high as 82% [1], whereas ATRH was found to be 24.9% [3]. Amongst multiple goals of secondary stroke prevention, the treatment and control of hypertension is by far the most important. To achieve this goal in stroke survivors has proven to be particularly challenging. The various factors contributing could be multifactorial and include medication non-adherence/ non-persistence/ non-fulfillment due to costs, side effects, complexity of treatment regimen, medical care(irregular), treatment-resistant hypertension, and lack of healthy behaviors such as adequate physical activity, etc. [2].

ATRH is a common clinical problem both primary physician and specialists face. As literature reveals, apparent treatment-resistant hypertension is even more important in stroke as it widely influences the disease's management and outcome. Despite this, the literature published in this area is sparse. The high prevalence of the disease and the paucity of literature globally make it a pertinent topic for further research. This study aimed to estimate the proportion of ATRH among patients with a history of stroke and to determine the risk factors associated with it.

Methodology

The present cross-sectional study was conducted from November 2017 to December 2019 in the Department of Medicine at University College of Medical Sciences (UCMS) and associated Guru Teg Bahadur (GTB) hospital, Delhi and Department of Neurology, Indian Institute of Human Behavior and Allied Sciences (IHBAS), Delhi.

Adult (Age >18 years) hypertensive patients who had been diagnosed with stroke in the past (documentary evidence) and were on regular treatment for at least six months after the first episode of stroke were enrolled. The patients who achieved target blood pressure 140/90 mmHg on more than or equal to four drugs are considered as controlled ATRH [4]. Patients who were aphasic and unable to respond verbally were excluded from the study.

All enrolled patients gave consent for the study. Case record form was filled for each subject included socio-demographic profile, treatment history, relevant clinical and laboratory data. Socio-economic status was calculated by Dr. B G Prasad scale (per capita monthly income) [5]. Detailed treatment history was recorded in terms of drugs prescribed and their frequency.

Class of anti-hypertensive with their respective doses, over-the-counter drugs, and side effects were recorded.

The doctor interviewed patients for Adherence to Refills and Medications Scale (ARMS). There are 12 questions, each carrying 1-4 points depending on the patient's response. The total score on the ARMS ranges from 12 to 48, with a lower scale indicating a better adherence [6]. The presence of depression was assessed as per Patient Health Questionnaire (PHQ-9 scale). The minimum score is 0, while the maximum score is 27 [7]. A cognitive evaluation was done using the six items Cognitive Impairment Test (CIT-6). The total score ranges from a minimum of zero to a maximum of 28 [8].

Statistical Analysis

The statistical analysis was done by SPSS 20.0. Chi-square test was used to test the difference in categorical measures and an independent-sample t-test for difference in means. Fischer's exact test was used when the variable size was small. The level of significance was considered as a p-value less than 0.05.

Results

In this study, 91 patients were screened; seven were aphasiacs, therefore excluded from the study. Among 84 stroke patients recruited, 18 (21.4%) had ATRH, and out of these 18, 13 (72.2%) were uncontrolled ATRH. There were 34 (40.5%) females, and 50 (59.5%) males, and mean age of the patients was 58.6 years. Male patients (26%) were more likely to have ATRH in comparison to females (14.7%) (p 0.216). The mean BMI was calculated to be 25.74 kg/m². The mean BMI (p 0.022) and waist size (p 0.143) was higher in patients with ATRH.

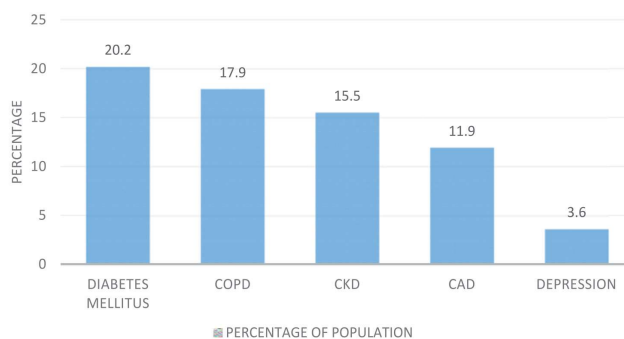


Figure 1: Self-reported co-morbidities in subject population

Co-morbidities like DM were reported in 20.2% of cases, followed by COPD in 17.9% and CKD in 15.5% (Figure 1). No statistically significant association was found between patients suffering from DM (p 0.369), COPD (p 0.507), CAD (p 0.862), and ATRH stroke patients. Although, ATRH patients were strongly associated with CKD (p 0.002).

Patients with hypertensive stroke who suffered from intracerebral hemorrhage (ICH) had more chances of suffering from ATRH than patients with ischemic stroke ($p 0.025$).

Socio-economic profile and tobacco/alcohol intake

In our study population, 63 (75%) cases were married 39 (46.4%) were members of nuclear families. In most cases, 59 (70%) were financially dependent on their family members. Patients with ATRH had fewer family members than patients without ATRH ($p 0.104$), while they were more likely to be financial dependent on their families ($p 0.339$).

Overall literacy ($p 0.033$) and mean years of schooling ($p 0.072$) were higher in subjects with ATRH when compared to non-ATRH patients. Participants were higher in patients with ATRH, but the result failed to reach statistical significance ($p 0.130$).

Smokers predominated the study as 34 (40.5%) while 18 (21.4%) were alcoholics. Ten (11.9%) patients used tobacco in chewable form. ATRH patients were strongly associated with smoking habit ($p 0.011$).

Although ATRH patients were more likely to be alcoholic when compared to non-ATRH patients, the result did not reach statistical significance ($p 0.926$).

Anti-hypertensive Drugs and their burden: Patients of ATRH were on various classes of anti-hypertensives drugs, among them calcium channel blockers (83.3%), followed by beta-blockers (44%) and thiazide diuretics (31%) were common (Table 1).

Table 1: Anti-hypertensives usage in study population

Class	Percentage of use
Calcium channel blockers	83.3
Beta blockers	44
Thiazide diuretics	31
ACE inhibitors	25
Angiotensin receptor blockers	22.6
Central anti-adrenergics	15.2
Loop diuretics	1.2
Combined alpha and beta blockers	1.2

In this study, the average pill burden was seven pills per day. The minimum pills were estimated at 1, while the maximum was 15 per day. The average number of pills taken by each patient was 10 per day. During their treatment, 15.5% of the subjects suffered from some side effects of the anti-hypertensive treatment.

Medication adherence

Knowledge about medicine was assessed by asking

questions to the subjects, and most of the subjects did not know the name (11.9%) and dose (10.7%) of the drug (Table 2).

Table 2: Knowledge about medicine in study population

Aspect of knowledge about medicine	Percentage of participants having known
Name of medicine	11.9
Dose	10.7
Frequency of dosing	59.5
Indication	20.2
How and when to take	58.3

Adherence was calculated for the study population using the ARMS scale. Cases were divided into two categories; group 1 consisted of subjects with a score of 12, which depicts good adherence, while group 2 had subjects with a score of >12 depicting poor adherence. Nearly half of the study population had poor adherence to anti-hypertensive drug therapy (51.2% vs. 48.2%). It was observed that patients with ATRH had poor medication adherence to the patients without ATRH ($p 0.006$) (Figure 2).

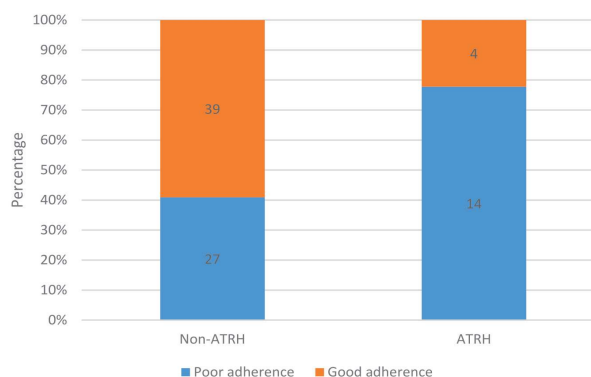


Figure 2: Association of adherence with ATRH status

Clinical depression and cognitive impairment

Only 27.4% of the patients were likely to have clinical depression when calculated by the PHQ-9 depression scale. The relative frequency of each class in the study population is tabulated below (Table 3).

Table 3: Frequency of various depression classes in study population

PHQ-9 (Depression class)	Frequency	Percent (%)
Minimal	61	72.6
Mild	9	10.7
Moderate	7	8.3
Moderately Severe	5	6.0
Severe	2	2.4
Total	84	100.0

In our study population, 52.4% of subjects had cognitive impairment. The frequency of various classes is tabulated below (Table 4). There was no association between depression ($p=1.000$) or cognitive impairment ($p=0.761$) with ATRH stroke patients. Association with various factors has been tabulated in table 5 and 6

Table 4: CIT-6 score frequency in study population

Cognitive impairment class	Frequency	Percent (%)
0 (Normal)	39	46.4
1 (Mild impairment)	8	9.5
2 (Severe impairment)	37	44.0
Total	84	100.0

Table 5: Associations of various variables with ATRH

Sr. No.	Variable	ATRH	Non-ATRH	T- test	P-Value
1.	Age	58.4 years	58.7 years	0.110	0.193
2.	BMI	27.03kg/m ²	25.01kg/m ²	2.341	0.022
3.	Waist	93.44cm	89.71cm	1.479	0.143
4.	Education	6.44 years	3.97 years	1.825	0.072
5.	No. Of family members	7	6	1.643	0.104

Table 6: Association of various factors with ATRH

Variable	Chi-square	P-Value
Sex	1.533	0.216
Literacy	4.525	0.033
Adherence	7.694	0.006
CKD	9.600	0.002
CAD	0.862	0.862
DM	0.807	0.369
COPD	0.507	0.507
ICH	7.320	0.025
Side effects	0.848	0.347
Multiple stroke	0.848	0.357
Alcoholic	0.009	0.926
Smoker	6.522	0.011
Cognitive impairment	0.093	0.761

Discussion

The current study revealed that 21.4% of the subjects had ATRH. Various studies have reported the association of ATRH with stroke; only a few have tried to study the proportion of ATRH in stroke and factors affecting them. Howard et al., conducted a study on data derived from REGARDS cohort and concluded that 18.2% of the stroke population had ATRH [9], which was lesser than the results obtained in our study.

Uncontrolled hypertension in stroke is a well-known predictor of increased mortality in these patients, mainly due to increased stroke recurrence. The present study showed that one in every five patients with stroke had ATRH. This clearly emphasizes the magnitude that this problem poses and the potential complications that it may lead to if not appropriately managed. Hence it becomes imperative for physicians to understand the importance of this entity and effectively manage it to improve the general outcome of this population.

Multiple reasons are responsible for the slightly higher prevalence of ATRH in India when compared to the western population. Poor medication adherence is one of the primary reasons responsible for this. Factors like low health

awareness, multiple co-existing co-morbidities, and weak health infrastructure are some of the other reasons that are responsible.

In this study, patients that had ATRH were found to be of a similar age when compared to patients without ATRH (58.39 years vs. 58.70 years). Hung et. al., conducted a similar study and found a higher prevalence of ATRH in the elderly (>60 years) [10]. Our results were discordant with western studies probably because of the lower socioeconomic status and poor health care facilities in our country because of which patients generally go untreated and present earlier with advanced stage of disease.

Multiple studies have shown male gender as an independent predictor of ATRH in stroke. Howard et al. demonstrated that the development of ATRH in stroke was significantly more in men [9]. This study also revealed that males are more likely to have ATRH as compared to females (72.2% vs. 28.8%), but the results failed to reach statistical significance (p 0.216). The higher prevalence of ATRH in men calls for strict lifestyle interventions and aggressive screening strategies for this subset of the population.

The mean BMI in patients with ATRH was more than in patients without ATRH, which was statistically significant (p 0.022). Similarly, ATRH patients were more likely to be overweight (BMI>25) than their non-ATRH counterparts (p 0.020), a similar study was conducted by Weitzman et al [11].

Also, ATRH subjects had a larger waist circumference (93.44 cm vs. 89.7 cm) when compared to non-ATRH patients. Although these findings did not reach statistical significance, they were seconded to Thomas et al., on CRIC subjects in the USA, which showed a similar association between waist circumference and ATRH [12].

Extensive western literature has shown a strong causal relationship between obesity and a myriad of non-communicable diseases the DM, HTN, CAD and stroke [13].

Obesity has already reached epidemic proportions in developed nations and soon will be a major concern in developing countries like India. On the brighter side, obesity is one of the most easily modifiable lifestyle factors that drastically decrease the risk of conditions. A healthier diet and increased physical activities may help manage resistant hypertension. Lifestyle play a considerable role in the etiopathogenesis of hypertension and stroke. It has been proved that smoking and chronic alcohol use are associated with increased DM, HTN, stroke, and metabolic syndrome.

In this study, smoking is associated with a statistically significant incidence of ATRH in stroke patients. Alcoholism was also associated with a higher incidence of ATRH, but it did not reach statistical incidence. Howard et al. showed a positive correlation between smoking and ATRH [9]. On the contrary, Faceira et al., demonstrated similar prevalence in smokers and non-smokers [4]. The variability in these results could be in part due to different pack-years, different methods of smoking, sociodemographic characters of the population on which the study was done, other co-morbidities, etc.

The present study showed that ATRH patients were more likely to be literate (p 0.033) and had higher per capita income. The BG Prasad scale was used to calculate the urban population's socio-economic status, and it was higher in ATRH patients, although it did not reach statistical significance (p 0.111). This contradicts a previous study reported by Thomas et al [12]. One of the possible reasons for this could be the unhealthy lifestyles, poor diet, and decreased physical activity rampant in the socially affluent in India. As previously stated, the urban population in India was more likely to have hypertension than rural ones. Moreover, increased health awareness in higher socioeconomic strata leading to earlier diagnosis could be another cause.

ATRH patients were more likely to be financially dependent on their families than their counterparts, but statistically, the result was non-significant (p 0.339). Dependent patients are more likely to have erratic hospital visits and irregular medication supply leading to frequent BP fluctuations. There is no other literature found for demonstration of this relationship.

Co-morbidities associated with ATRH have been extensively researched in western countries but with variable results. Only a few of them are associated with ATRH stroke patients specifically. In the current study, it was observed that DM (20.2%) was the most common self-reported co-morbidity in our sample group, but no statistically significant association was found between DM and ATRH (p 0.369). Hung et al., Weitzman et al., Faceira et al., and Romano et al., all reports are contrary to our result [4,10,11,14].

In this study, no statistically significant association was

found between patients with ATRH and COPD (p 0.399) and CAD (p 0.348). Smith et al., Muntner et al., and others showed a higher prevalence of CAD in ATRH [15,16]. Scarce diagnostic modalities could explain the discrepancy in our results in the Indian setting, leading to decreased CAD diagnosis. Also, premature deaths of patients with CAD in Indian health setup play an important role in decreasing the prevalence of CAD in Indians.

Consistent with the previous data [12], ATRH patients had an increased incidence of CKD which was statistically significant. Interestingly our study did not show any correlation between side effects and development of ATRH in stroke (p 0.372). History of multiple strokes also did not prove to be a factor associated with increased incidence of ATRH in stroke (p 0.357).

In this study, it was observed that patients with ATRH had poor adherence compared to those without it. (p 0.006) The majority of the ATRH population (78%) was non-adherent to their medication. Although no Indian studies on medication adherence among ATRH, foreign studies showed the prevalence from 9.9 to 68%. In the latest meta-analytic study conducted by Durand et al., the prevalence of non-adherence varied between the studies, ranging from 3.3% to 86.1% [17]. The variation in prevalence may be due to different sociodemographic profiles of the population and differences in clinical practice and different methods of testing adherence used in various studies. The reason for the very high prevalence of low adherence in our patients may be due to poor education status, socioeconomic class, their lack of knowledge about disease and medicine itself.

The established link between medication adherence and blood pressure control effectively highlights the importance to evaluate compliance in hypertensive patients. There are serious negative outcomes to uncontrolled hypertension such as poor clinical outcomes and increased health care expenditures. Majority of patients will not need to undergo extensive clinical tests that are required to diagnose true ATRH, if the compliance to antihypertensive medications is evaluated diligently. This is seconded by the fact that medication knowledge was low in the study population. The most challenging part was remembering the name of the drug and the dose. Only 60% of the patients knew about the frequency of the drug intake.

Patients with hypertensive stroke who suffered from ICH had more chances of suffering from ATRH than patients with infarct (p 0.025). Most intraparenchymal bleeds are due to uncontrolled hypertension; therefore, its association with ATRH is not surprising. This reemphasizes the importance of strict BP monitoring in these patients to avoid stroke recurrence.

No association was found between depression (p 1.000) and

ATRH stroke patients in this study. However, a higher incidence of ATRH was found in patients with fewer family members (5.94 vs 7.08) ($p = 0.104$). This result reflects the family's social support, which plays a massive part in ensuring adherence to anti-hypertensive therapy in patients with ATRH. Shallcross et al. conducted a study ($n=1392$) from data of Jackson heart study to explore psychosocial correlates of ATRH. He found no association with depression or stress with ATRH. The only social factor that impacted ATRH was increased social support by the patient's family members [18]. Cognitive impairment was calculated using the six items cognitive impairment scale. Our study was also not found to be associated with ATRH. No study comparing cognitive impairment and ATRH could be found.

There are certain limitations in the current study which should be mentioned. Firstly, the small sample size in the analysis may not accurately represent the overall population. Furthermore, the samples were recruited from two tertiary care hospitals in New Delhi which may introduce a selection bias in the study. Lastly, the study's cross-sectional nature does not allow us to determine a causal relationship of various factors associated with ATRH.

Despite the limitations, our study is unique as no similar studies are available in the Indian population. The systematic approach ensures that the existing literature has been accurately represented, and the statistical techniques employed attempt to explain the considerable variability within this literature.

The current study represents the first attempt to systematically study ATRH in hypertensive stroke patients in an Indian population. The high prevalence of ATRH in stroke strongly emphasizes its importance in the Indian clinical scenario. The strong association of multiple co-morbidities with ATRH in stroke, as shown in this study, reiterates the importance of early recognition and swift management of this entity. Therefore, it is advised that physicians take a personalized approach to assess and manage blood pressure levels, including additional tests for associated co-morbidities and incorporating advice related to lifestyle changes.

Conclusion

Treatment of hypertension has long been regarded as one of the most important goals in stroke management. In our study, it was found that a significant proportion (18.4%) of stroke population had ATRH. It was also observed that that majority of the patients were not adherent to their anti-hypertensive therapy. It reinforces the role of aggressive adherence improvement in these patients before other etiologies of ATRH are sought after. Also, statistically significant association of ATRH with CKD was found in our study. No association were found between ATRH stroke patients and

Coronary artery disease, COPD, Diabetes Mellitus, depression, cognitive impairment in subject population.

Significant association of ATRH with factors like smoking and obesity lays stress on the importance of healthy lifestyle measures that are both effective and economically viable in a resource scarce country like India.

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