Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

Vascular cognitive impairment in India: Challenges and opportunities for prevention and treatment

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ARTICLE INFO

ABSTRACT

The burden of vascular contribution to cognitive impairment and dementia is substantially high in India. There are approximately 5.3 million dementia patients in India and nearly 40% are estimated to be due to vascular dementia. Several factors pose unique challenges to reducing the burden of vascular dementia and vascular cognitive impairment (VCI) in India. Wide heterogeneity in vascular risk factor profile, diversity in socioeconomic, ethnic and dietary factors, as well as regional and rural-urban differences impact uniform implementation of preventive and therapeutic strategies. There is limited evidence on the natural history of vascular disease from longitudinal cohorts in India. Additionally, the lack of advanced brain imaging and genetic information pose challenges to understanding pathophysiology and treatment response to VCI in India. Efforts are now being made to implement programmes to reduce cardiovascular risk and VCI at the population level. Cognitive and functional measures appropriate to the diverse linguistic and educational context have been developed to diagnose VCI across India. Multicentric clinical and research cohorts of stroke are also being established. Filling research gaps and developing intervention strategies for the Indian context are crucial to address the growing burden of VCI.

1. Introduction

Of the 47 million people living with dementia globally, 63% live in low and middle-income countries (LMIC) [1, 2, 3] and the numbers are projected to increase to 152 million by 2050 [4, 5]. In India, there are at least 5.3 million people with dementia and this number is expected to double by 2035 [2]. While Alzheimer's disease is the most common cause of dementia, vascular contributions to dementia are increasingly being recognised. Vascular dementia (VaD) is the second leading cause of late-life dementia and accounts for about 30% of dementia in LMICs including India [6, 7]. Hospital based studies have shown that while Alzheimer's disease is the most common cause, vascular dementia is the second most common cause and mixed dementia is increasingly being encountered especially among older people [8]. Vascular cognitive impairment (VCI) that includes milder forms of cognitive impairment due to cerebrovascular disease [9] is also very common and up to two-thirds of stroke survivors in India are found to have varying degrees

of cognitive impairment [10,11]. Most importantly, unlike in high-income countries (HIC) where the burden of dementia is stable or even declining, LMIC are facing a rising burden of dementia [12,13]. Recent evidence suggests that vascular risk factor and lifestyle modification can reduce the risk of dementia by up to 40% [14]. These observations offer hope that preventive interventions targeting vascular risk factors might yield large reductions in dementia in LMIC.

Efforts are underway in India to develop both population-based and individualised preventive and treatment strategies for vascular cognitive impairment (VCI). However, several challenges will need to be overcome for effective implementation in the Indian context. In this article, we discuss the population at risk for VCI that stands to gain from treatment, the advantages to including a diverse population characteristic of India in clinical trials, challenges unique to India in instituting preventive and therapeutic measures, the existing knowledge gap and emphasize the need to conduct clinical trials to develop evidence with an aim to reduce burden of VCI in India.

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2. Challenges for VCI prevention and treatment in India

To determine whether treatment strategies for VCI need to be specific to India it is important to systematically evaluate factors specific to India that impact development and implementation of treatment strategies. Evidence suggests that there are significant variations, especially in vascular risk factor profiles, stroke burden and subtypes, proportion of population at risk and also disparities in health care availability. The research gap is also wide and VCI treatment strategies developed elsewhere, especially those developed in high-income countries, may not be directly applicable to India.

2.1. A high burden of vascular risk factors

Vascular risk factors especially in midlife, are strongly associated with the development of both vascular dementia as well as Alzheimer's disease [15,16,17] and their effective control is crucial to reduce burden of VCI. Wide regional and ethnic variations in the relative importance of vascular risk factors in stroke have been demonstrated [18]. Indians are recognised to have a disproportionately higher prevalence of vascular risk factors, compared to other ethnic groups and are therefore likely to be at a greater risk of developing VCI. The reasons for a higher prevalence of risk factors in India may be due to its demographic transition, urbanization, dietary habits and genetic predisposition.

Hypertension is one of the most important risk factors for cerebrovascular diseases. India ranks among the top five countries with the highest levels of disability due to high blood pressure (BP) [19]. In a systematic review, overall prevalence of hypertension in India was 29.8%, defined according to the American Society of Hypertension guidelines [20]. Differences in hypertension prevalence were noted between rural (27.6%) and urban (33.8%) areas in India [21]. Regional estimates for the prevalence of hypertension also varied significantly across North, East, West, and Southern India. Overall estimates for the prevalence of treatment, and control of hypertension were also variable across different regions of the country. Overall hypertension control among both urban and rural parts of India have been very poor (6.5–15% in rural and 11.6–28.7% in urban areas). The possible obstacles for treatment are lack of awareness, poor socioeconomic conditions and limited access to health care [21]. While there are many types of antihypertensives used in practice, the most frequently used medications include calcium channel blockers (72.3%), angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers (ACE-I/ARBs) (41.4%) and thiazide diuretics (9%) and comorbidities guide use of the specific medications [22].

The incidence of diabetes is also one of the highest in Asian Indians and the rate of increase is projected to be the highest globally [23]. The prevalence rates for diabetes varied between different states in India from 4.3% in Bihar to 10.0% in Punjab, and are higher in urban (11.2%) than in rural areas (5.2%). Evidence suggests that there is a higher prevalence of diabetes in low socioeconomic groups in urban areas of more economically developed states [24, 25]. Furthermore, for any given body mass index (BMI), Indians have higher waist circumference and waist-hip ratios, more subcutaneous and visceral fat and insulin resistance in comparison to their European counterparts [26].

In the recent years, alcohol use has also been shown to be on a rise in LMICs compared to the HICs [27]. Tobacco and alcohol use are also widely prevalent in India [28,29]. However, there is wide regional disparity in prevalence of tobacco and alcohol use. About one-third of adults smoke tobacco. In one of the Northern states of India the overall prevalence of tobacco use was 39% [28]. However tobacco and alcohol use is not uniform across India. There are states in India where alcohol use is increasing especially in central India compared to the eastern states, [30] and tobacco use is highly prevalent in the north-eastern states compared to the southern states [31]. Older adults who smoked tobacco and consumed alcohol are found to have a significantly higher likelihood of cognitive impairment [32]. Other risk factors that are frequently encountered in the Indian context are hyperhomocysteinemia and anemia [33]. This is probably related to wide-spread vitamin B12 deficiency incident to vegetarianism [34].

2.2. Rising burden of stroke

The estimated adjusted prevalence rate of stroke in India is 84–262/100,000 in rural and 334–424/100,000 in urban areas and the incidence of stroke is 119–145/100,000. It is also observed that stroke occurs at an earlier age in India and is more severe, thereby accounting for a younger age at onset of dementia [8]. Ischemic stroke mortality is also higher in South Asians compared to non-South Asians in the UK [35]. The rising burden of stroke contributes to a high prevalence of dementia in India [10,11,36].

2.3. Pattern of stroke subtypes differs

The most common ischemic stroke subtypes identified in stroke cohorts in hospital-based registries in India is large artery atherosclerosis, accounting for about a third of the patients, followed by small vessel occlusion and less often cardio-embolism, while nearly one-fourth of patients had an undetermined etiology [37,38]. Based on the registries the major subtype of large artery disease was intracranial in India, consistent with reports from other Eastern and South Asian territories [39]. The risk of recurrence of stroke is higher in large artery atherosclerosis and cardioembolic strokes [40] and this could underlie the higher frequency of cognitive impairment due to multi-infarct dementia in India [41]. However, these findings need validation in population based or country-wide registries [39]. Since a main strategy for treating VCI is to accurately target the underlying mechanism of cerebrovascular injury, it is important to address the differing pattern of stroke subtypes across geographic regions, to develop effective global treatment strategies. Currently there are no published studies available regarding urban-rural differences between different stroke subtypes in the Indian context. However, there are some studies that have broadly compared urban-rural differences in stroke outcome. Haemorrhagic stroke was seen more in rural compared to urban regions. There were significant differences seen in stroke risk factors between urban and rural areas; hypertension, hyperlipidaemia. Rural patients were more likely to be younger (age < 40 years) as compared to urban patients. Compared to urban stroke patients, rural ones are less likely to be optimally investigated and treated. Further studies are required to determine differences between stroke subtypes and the effects on VCI patterns in urban and rural regions in India [42,43].

2.4. A wide treatment gap

Some of the major reasons attributed to a wide treatment gap are reduced awareness and inequity in terms of access to healthcare. About 42% urban and 25% rural Indians were aware of their hypertensive status and only 38% urban and 25% rural Indians were being treated for hypertension [21]. Similarly, 43.2% of a study population had knowledge of diabetes [44] and more than half of an urban cohort were unaware of the need for the extended use of insulin [45]. Besides insulin, there other therapies especially newer oral antidiabetic medications which are available and being prescribed in India. The Indian Council of Medical Research (ICMR) guidelines on diabetes management recommend the following anti-hyperglycaemic drugs: biguanides, sulphonylureas, DPP-4 inhibitors, thiazolidinediones glucagon-like peptide 1 receptor agonist (SGLT2) inhibitors among others. Besides insulin and antihyperglycemic drugs, non-insulin injectable therapy (GLP-1 receptor agonists) are also available and prescribed. Each drug class has different clinical indications, as well as availability and cost-effectiveness, all of which influence the choice of therapy [46]. India is considered as the 'diabetes capital of the world' [47], however, the patient knowledge about prevention, treatment, risk factors and

complications of diabetes is still limited [48].

Among 265 stroke survivors in a cross-sectional community-based survey, a prior diagnosis of vascular risk factors was made only in a small proportion: hypertension in 57.4%, diabetes in 9.8%, hyperlipidemia in 0.4% and ischaemic heart disease in 1.5%. Importantly, blood pressure was uncontrolled in 46% of stroke survivors. Only 40.8% of stroke survivors were receiving antihypertensive medications and a very small proportion (10.6%) were on antiplatelet agents and statins (4.9%) [49]. In addition, recurrence of stroke has been observed to be higher in the Indian stroke cohorts. In a study conducted in northwest India, only 23% had knowledge about warning symptoms of stroke [50]. Less than half of the participants were aware about modern treatment approaches and around 10% believed in indigenous treatment [50]. Regarding the use of statins, a population based study in a region with good access to health care showed that statins were being used only by a third of patients who need it for secondary prevention, while use for primary prevention was even lower. Reasons for low statin use were lack of awareness among health care workers, poor patient compliance and high cost of statins [51]. Similarly there is a wide treatment gap for vascular dementia due to low awareness among people including health care professionals and policy makers, misconceptions and stigma associated with dementia [52].

2.5. Lack of adequate health care services

As risk factors for stroke and VCI have increased in developing countries like India, there has not been a proportionate increase in health resources to tackle the rising burden. Some of the inevitable challenges to provide adequate health-care service in the background of rapidly rising numbers include limited socioeconomic resources, limited public health prevention strategies, healthcare infrastructure and specialised centres for acute stroke management and rehabilitation facilities and a lack of social support [53,54].

2.6. Limited research evidence for effective treatment

Current strategies to treat VCI aim to reduce vascular risk, prevent ongoing vascular damage and improve neurovascular unit function by targeting the underlying pathophysiological mechanisms. This mainly relates to the central mechanisms as the cerebral blood vessels play a crucial role in brain health, not only for delivery of oxygen and nutrients, but also for trophic signaling that links inextricably the neurons and glia to that of cerebrovascular cells [55]. Cognitive enhancement and behavioural management in improving cognition are also important to reduce the clinical impact of vascular damage. However, evidence for the effectiveness of these treatment strategies comes mainly from trials conducted in developed countries and their translation and applicability to diverse countries like India remains to be established.

3. Opportunities to bridge the diagnosis, prevention and treatment gap

The large numbers of people with vascular risk factors and stroke in India stand to benefit with implementation of treatment strategies to reduce burden of VCI. Current strategies to treat VCI aim pharmacological and non-pharmacological approaches that target the underlying pathophysiological mechanisms as well as cognitive and behavioural symptoms. The implementation of these multipronged strategies in the Indian context offers a huge opportunity to reduce burden of VCI. Towards this goal, there is an urgent need to fill existing research gaps and develop evidence for these intervention strategies in the Indian context.

3.1. Addressing heterogeneity is key to reducing burden of VCI in India

Risk factors, clinical patterns and outcomes of vascular cognitive impairment have significant regional heterogeneity. Conventional vascular risk factors such as hypertension, diabetes and metabolic syndrome have rural-urban, state-wise, socioeconomic and possible ethnic variability. However, there is limited evidence regarding natural history of vascular diseases in these different settings from India. Unlike in high-income countries, few longitudinal cohorts have been established. Therefore as a first step to developing effective preventive and therapeutic strategies, there is a need to establish well characterised cohorts of individuals with vascular risk factors across different regions in the country using harmonised methods. Infrastructure to implement existing policies for control of noncommunicable diseases has to be created, and that includes training of health care workers and creating awareness in society. Systematic research to evaluate outcomes of interventions has to be undertaken in the Indian context in multicentric studies. An "India-specific" approach to VCI that incorporates heterogeneity in regional, socioeconomic, cultural, lifestyle and genetic influences on VCI is crucial for effective implementation and optimization of preventive and therapeutic approaches to VCI in India.

The linguistic diversity in India poses a challenge to use of locally appropriate diagnostic tools. There is also variability in education levels and bilingualism is considered a norm in India [56]. Recognizing this need, the Indian Council of Medical Research-Neuro Cognitive Tool Box (ICMR-NCTB) consortium developed a common set of screening and diagnostic tools for diagnosis of VCI and dementia for use across several Indian languages and literacy levels [57,58]. This cognitive test battery is harmonised based on the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) VCI harmonization standards [59] and will facilitate uniform diagnosis both within India and across other countries. These tests validated in multiple languages and literacy levels can also be used to monitor response to treatment in clinical trials. Similarly, the Indian Stroke Clinical Trial Network (INSTRuCT) task force project of Indian Council of Medical Research (ICMR) set up a large multicentric pharmacological and non-pharmacological stroke clinical trials in India [60].

3.2. Vascular risk factor control

Individuals with vascular risk factors represent a "brain at risk" population for VCI and focussing on these high risk groups is crucial to prevent progression of cerebrovascular disease. Evidence is emerging that treatment of hypertension lowers the risk of cognitive decline [61–66]. Apart from hypertension, there have been very few efforts to study the effect of strategies targeting other vascular factors such as diabetes [67], obesity, hyperlipidemia, cardiac disease, smoking, and alcoholism, on the risk of developing VCI. Multidomain intervention involving dietary change, exercise, cognitive training and vascular risk monitoring is also protective against cognitive decline [68]. Together these findings emphasize the need to conduct similar research in populations with different sociocultural environment.

In the Indian context, while large scale national public health programs aim to detect and treat non-communicable diseases such as diabetes, hypertension and stroke at the community level [69,70], there have been no active efforts to investigate the effects of controlling these diseases on dementia risk. Trials demonstrating the impact of vascular risk factor control benefitting cognitive outcomes will be fundamental to influence policy change in India and develop population-based efforts to reduce burden of VCI and dementia.

3.3. Treatment of VCI

Cognitive impairment due to vascular disease can occur due to multiple mechanisms and the spectrum of VCI mainly include: post stroke dementia, multi-infarct dementia, subcortical ischemic vascular dementia and mixed dementia [71]. Mixed pathologies are very common and furthermore, there is increasing evidence that vascular disease contributes significantly to neurodegenerative disease [16]. Therefore, treatment strategies for VCI and dementia should focus on the

underlying vascular mechanism/s, and co-existing pathologies.

Secondary prevention of stroke lowers the risk of dementia and cognitive decline [72]. However, secondary prevention differs based on the underlying subtype [63,64]. Given that stroke subtypes are different in India compared to HICs, trials investigating the effect of secondary prevention of stroke on the occurrence of VCI are needed.

3.4. Management of cognitive and behavioural symptoms

Acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonists have shown improvement in cognitive performance in patients with VCI [71,72]. These drugs are approved for use in India and are widely available [73]. However, for the majority of patients who are socioeconomically disadvantaged, the long-term use of these drugs is challenging.

There is increasing awareness that nonpharmacological therapy is pivotal as a complementary approach [74]. Effective and culturally adaptable cognitive stimulation therapy (CST) programs are required for the Indian context [75]. Multidisciplinary rehabilitative services are essential to provide care for stroke patients who have both motor and cognitive impairment. There have been attempts to incorporate training of caregivers for rehabilitation of stroke in stroke units. However, this needs wider adaptation [76,77].

Dementia care in India currently is limited to medical care in a network of health centres and hospitals. There are only around 40 day-care centers, six dementia long term care facilities, and around 100 designated memory clinics throughout the country [78]. Home based care dependant on families is the main support available for patients with VCI. Very few randomised trials in rehabilitation and lack of awareness and resources are major obstacles for scaling efforts to provide functional rehabilitation for patients with VCI in India.

3.5. Building cognitive resilience

The protective role of life course factors in building cognitive reserve and resilience in dementia and VCI is also being recognised [68]. Educational status, physical exercise and bilingualism have been associated with reduced post stroke cognitive impairment and VCI [79,80]. Improving cognitive resilience by modifying lifestyle factors are important in the context of a demographically diverse population that characterises India, however these changes will require widespread societal and policy commitment.

3.6. Need for treatment trials specific to the Indian context

Filling research gaps and developing evidence for intervention strategies for the Indian context is crucial to address the burden of VCI. Treatment trials aimed at reducing risk of VCI and preventing progression should be considered as priority. Trials that aim to incorporate modifications in diet, physical exercise, social interaction and other lifestyle measures are also important to develop cost-effective preventive strategies that are congruent with socio-cultural practices of India.

Well-designed randomised controlled trials with cognitive status as the primary outcome, a systematic derivation of the numbers needed to treat, use of validated and culturally appropriate cognitive tests, advanced MRI imaging and blood-based biomarkers and long follow-up are required. The application of a conceptual model that accounts for diversity is vital. Collaboration between stroke and dementia clinical research centres is crucial for successful implementation of trials across the country. These efforts are ongoing in India and reflect efforts towards clinical trial readiness of its population. Investment in conducting research into the basic biological mechanisms, genetic factors, novel drug development and biomarkers for VCI will also have a major impact in developing treatment strategies that address the problem of VCI and dementia in India. Research in the area of VCI has to become a high priority for the research community as well as policy makers in India.

Table 1
Challenges and opportunities for treatment of VCI in India.

Sl. No.	Challenges and opportunities for treatment of VCI in India
1	India represents 17.7% of the world's population, and around 11% of people with dementia are in India. 39% of dementia in India are due to vascular causes. Treatment trials for vascular cognitive impairment (VCI) should have adequate representation from India to ensure their global implementation.
2	"At risk" population for VCI is large in India due to the high prevalence of vascular risk factors and stroke. This group stands to benefit significantly from treatment strategies that aim to reduce burden of VCI.
3	Large numbers of people with vascular risk factors and stroke remain untreated and there is a wide treatment gap for vascular risk factor control in India. Hence, there is an urgent need and a major opportunity to develop and implement strong evidence-based strategies for VCI in this population.
4	VCI risk can be affected by a range of biological and environmental factors that vary with ethnicity and geography. Including a diverse population like India can contribute significantly to determine the role of genetics and lifestyle factors in influencing risk of VCI.
5	VCI represents a wide clinical and pathological spectrum that occur a s a result of varied vascular mechanisms and subtypes of stroke. These factors are heterogeneous across regions and need to be considered while designing clinical trials for VCI in diverse populations.
6	Educational, linguistic and sociocultural diversity pose a challenge to evaluating patients with dementia. Validated cognitive and functional test batteries are available in India across literacies and languages and these have been harmonized with international test batteries. The development of harmonized treatment outcome measures will facilitate inclusion of Indian participants in global clinical trials of VCI.
7	Advance imaging and blood biomarkers are increasingly being recommended to determine efficacy of treatment outcomes. Specialised centres in India have the infrastructural capability to conduct advanced imaging and participate in state-of-art VCI trials
8	There is currently a knowledge gap and paucity of research for VCI treatment in India due to low awareness and resources. Hence there is an opportunity to support and expand VCI therapy trials to diverse populations in India, to develop evidence to mitigate the large global burden of VCI.

4. Conclusion

While the VCI epidemic is an inevitable consequence of the ongoing demographic shift in countries like India, there is a lag in the development of effective management strategies. There is also a gap in research, especially in areas of newer pathophysiological mechanisms, prevention strategies and disease-modifying agents. Treatment trials targeting vascular risk factors and stroke will significantly reduce burden of dementia in India.

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