“Prevalence of cognitive impairment in first ever stroke patients”

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

Dr Manish Gupta

DM Neurology Resident

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Department of Neurology

SREE CHITRATIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

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INTRODUCTION

Stroke is a major cause of morbidity in the industrialized world. It often results not only in physical disability, but also in significant cognitive impairment or dementia. Between 10 and 40% of patients with a recent stroke develop dementia.\textsuperscript{1-4} Although stroke was already recognized as an important cause of dementia more than one hundred years ago, research on determinants of poststroke dementia and the cognitive profile of dementia after a stroke has strongly intensified during the last decade. The diagnosis of dementia after a stroke is complex and poses clinicians for several problems. Poststroke dementia is a clinical entity with very heterogeneous cognitive disturbances, that may be characterized as cortical or subcortical, or a combination of the two. Furthermore, cognitive functioning may be hampered by the somatic symptoms that often accompany a stroke.

The incidence and prevalence of stroke have been steadily rising in India.\textsuperscript{5} Post-stroke cognitive impairment, recently reported to have a prevalence of 20.4%,\textsuperscript{6} is associated with many short and long-term poorer outcomes. Increasing stroke prevalence and incidence has led to the expectation that stroke dementia will be higher in India. Recently, a prospective community study from East India\textsuperscript{7} documented PR of post-stroke dementia at 13.88% (95% CI: 9.91-18.90%). The prevalence was higher than the rate calculated from a meta-analysis of the studies on stroke dementia worldwide (overall rate 7.4%; 95% CI: 4.8-10.0%).\textsuperscript{8} Higher rate in the above study may be due to inclusion of pre-stroke dementia subjects. In a clinic-based study from South India, the pattern of vascular damage and underlying vascular risk factors were documented among subjects with vascular dementia (VaD).\textsuperscript{9} Out of the different patterns, subcortical, cortical–subcortical, strategic infarcts, and cortical dementia were documented in 52.4%, 26.2%, 14.3%, and 7.1% of cases, respectively. There exists lack of agreement regarding its clinical diagnostic criteria and determinants.\textsuperscript{10} Data on post-stroke cognitive impairment in India is sparse & no data in patient with first ever stroke.
REVIEW OF LITERATURE

Definition of a stroke

According to the definition of The World Health Organisation (WHO) a stroke can be defined as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”  

Stroke epidemiology

Stroke is the third major cause of death and the leading cause of functional disability in Western countries. An ischaemic stroke or cerebral infarct occurs in 80% of all strokes, and is caused by an occlusion of a blood vessel in the neck or in the brain. The other less common type of stroke is a haemorrhagic stroke (20%), which is caused by rupture of a blood vessel resulting in the infiltration of blood into the surrounding tissue, either inside the brain tissue (intracerebral haemorrhage: 15%) or in the subarachnoid space surrounding the brain (subarachnoid haemorrhage: 5%). Most stroke trials, only report on patients with ischaemic infarction and intracerebral haemorrhage.

Risk factors

Numerous risk factors are associated with stroke, such as increasing age, male sex, black or Hispanic race/ethnicity, family history of stroke, hypertension, ischaemic heart disease, diabetes mellitus, hyperlipidaemia, atrial fibrillation, drug abuse, smoking, excessive alcohol consumption, physical inactivity, obesity, and hyperhomocysteinemia  

Stroke types and how to define them

Stroke is a heterogeneous disease group, which can be classified in two main groups according to the cause, ischemic and haemorrhagic. The distinction is critical as the medical and surgical therapies differ between them. An ischemic stroke is caused by a
physical blockage of blood flow to an area of the brain, usually due to a local thrombosis or an embolus. A haemorrhagic stroke is caused by a rupture of a blood vessel in the brain, allowing blood to leak out and accumulate inside or around the brain tissue.

The symptoms a stroke patient presents can vary depending on the topographical location and size of the lesion. Size and localisation have important implications for both rehabilitation planning and prognosis. The Oxfordshire Community Stroke Project Classification (OCSP15 classification), Table 1, which is widely used in both clinical settings and research, categorizes ischemic strokes into four subtypes based on clinical symptoms and signs, and has later also been applied to categorize haemorrhagic strokes.\textsuperscript{13,14,15}

\textbf{Table 1:} The Oxfordshire Community Stroke Project Classification (OCSP-classification) (Bamford et al. 1991)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Symptoms</th>
<th>Anatomical basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar Circulation Syndrome (LACS)</td>
<td>A pure motor stroke, pure sensory stroke, sensori-motor stroke, or ataxic hemiparesis</td>
<td>Lesion in the basal ganglia or the pons.</td>
</tr>
<tr>
<td>Total Anterior Circulation Syndrome (TACS)</td>
<td>The combination of new higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg.</td>
<td>Large lesion affecting both the deep and superficial territories of the middle cerebral artery (MCA)</td>
</tr>
<tr>
<td>Partial Anterior Circulation Syndrome (PACS)</td>
<td>Two of the three components of the TACI syndrome, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACS (e.g. confined to one limb, or to face and hand but not to the whole arm)</td>
<td>More restricted cortical lesion, either of the upper or the lower division of the MCA, or anterior cerebral artery (ACA) territory</td>
</tr>
<tr>
<td>Posterior Circulation Syndrome (POCS)</td>
<td>Any of the following: Ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e. ataxic hemiparesis), or isolated homonymous visual field defect</td>
<td>Brainstem, cerebellum or occipital lobes</td>
</tr>
</tbody>
</table>
Type and extent of neurological symptoms and signs are also frequently measured and quantified with validated scales like the National Institute of Health Stroke Scale (NIHSS).

**Prevention & management**

The best approach to reduce the prevalence of stroke is a rapid control of those risk factors that are modifiable. Stroke is not only a preventable but also a treatable disease. Since the first licence in the USA in 1996, a growing amount of research has been devoted to the effects of thrombolytic intervention. This intervention is aimed at restoring cerebral blood flow before major ischaemic brain damage has occurred, and has been shown to exert a beneficial effect on clinical outcome (The NINDS rt-PA Stroke Study Group, 1995). However, as the treatment is only safe and licensed within the first three hours post-stroke, a revolution in neurologic services is needed with an emphasis on immediate care. Public education is essential in order to learn to recognise a stroke as such and to seek immediate care.

**Cognition in stroke**

*Definition of cognition*

The concept of cognition derives from the Latin word cognoscere, which is made up of "co-" + "gnoscere" = to come to know. According to the Webster's New World Medical Dictionary 3rd edition, cognition can be defined as the process of knowing and, more precisely, the process of being aware, knowing, thinking, learning and judging.

Cognitive functions which typically are assessed include attention, learning, memory, language, visuospatial/constructional functions, executive functions, and sensori-motor functions. These are functions which can be temporarily or permanently impaired when a person suffers a stroke. In addition, a measure of overall cognitive performance level is often given. The size and location of a brain damage are two major factors which determine type and severity of cognitive impairment. Table 2 gives an overview
of the most important cognitive functions and how they are related to brain structure and blood supply.\textsuperscript{16}

As the brain’s vascular territories are only partially congruent with its subdivision into functional neural networks and circuitries, the cognitive symptoms seen in stroke are seldom pure, but will involve several cognitive functions.

**The problem of terminology and methodology**

Although there is no disagreement that cognitive impairments are frequent after stroke, the published data on prevalence rates are highly inconsistent and vary from as low as 7% \textsuperscript{17} up to 82% \textsuperscript{18}. Differences in terminology, the characteristics of the study samples, the choice of cognitive tests, the applied cut-off score to define cognitive impairment, and the time period between stroke onset and cognitive testing all contribute to this confusing picture and make comparisons between the studies difficult \textsuperscript{19,20}

Post-stroke dementia has been extensively studied, which refers to a very serious chronic condition characterized by a loss of cognitive and intellectual abilities severe enough to interfere with the ability to cope with activities of daily living. However, by focusing entirely on dementia, one is likely to underestimate the true prevalence of post-stroke cognitive impairment. Generally, the current diagnostic criteria for dementia are heavily weighted toward memory impairment, which is a core symptom in Alzheimer’s disease (AD), but less common in stroke.\textsuperscript{21,22,23} The consequence is that stroke patients could have serious cognitive impairments, e.g. in attention or executive functions, affecting rehabilitation, quality of life and mortality, but not fulfil the diagnostic criteria of dementia. Also many stroke patients have mild cognitive impairment which do not fulfil the criteria of dementia, but still negatively affect their lives and put them at substantial risk of developing subsequent dementia. In fact, about 40-50% of the patients with mild cognitive impairments after a stroke go on to develop dementia over the next five years \textsuperscript{24,25,26}. The term post-stroke cognitive impairment no dementia (post- stroke CIND) is frequently applied to refer to this latter condition.
Presently, there is no consensus as to how post-stroke cognitive impairment should be measured. Time-consuming, sensitive neuropsychological test batteries, e.g. the Halstead-Reitan Battery, Wechsler Adult Intelligence Scale or Wechsler Memory Scale are costly to administer and not well tolerated in this patient group, due to serious capacity restraints in many of the patients (e.g. fluctuating consciousness level, dementia, aphasia, fatigue, lack of initiative/motivation). On the other hand short cognitive screening tests, like the MMSE and Clock Drawing Test have been shown to be insensitive to different cognitive symptoms frequently appearing after stroke. “Intermediate” cognitive test batteries which can be tolerated by most stroke patients exist, e.g. Addenbrooke’s Cognitive examination (ACE) Cambridge Cognitive Examination (CAMCOG), RBANS, The Neurobehavioral Cognitive Status Examination, and the Montreal Cognitive Assessment, and may be interesting alternatives.

The choice of cognitive tests, norms and the applied cut-off score to define cognitive impairment will influence on the reported prevalence rates. Cut-off scores between 2nd and 10th percentile are used to define impairment on a cognitive test. A cut-off score of 10th percentile is in accordance with the Mayo clinic's recommendation for mild cognitive impairment (MCI), while a cut-off of 2nd percentile is usually considered indicative of a severe cognitive disorder. Generally; population studies report lower prevalence rates than hospital studies, probably as a consequence of a higher proportion of patients with the mildest strokes.

The prevalence of post-stroke cognitive impairment and dementia

Hospital-based studies which have applied neuropsychological testing within the first three months post-stroke report prevalence rates of cognitive impairment varying from 33% to 82% in patients with first-ever stroke and free from pre-stroke dementia. A higher frequency of cognitive impairment in stroke patients compared with aging control subjects is confirmed. In Tatemichi et al.’s (1994) study, cognitive performance of 227 ischemic stroke patients free from pre-stroke dementia (mean age 70.8, SD 7.9) were examined three months post-stroke and compared with 240 stroke
free controls. A total of seventeen tests were used to assess memory, orientation, verbal skills, visuospatial ability, abstract reasoning, and attention. Cognitive impairment, defined as a failure on four tests or more (with cut-off score of 5th percentile on each test), occurred in 35.2% of the stroke patients compared to 3.8% of the controls. Reduced performance on at least one test was present in 78% of the stroke patients. Compared to the controls, the most frequently affected cognitive domains in the stroke patients were memory, orientation, language and attention.

Cognitive impairments in the stroke patients were more frequent in cases of major cortical syndromes and in patients with infarctions in the left anterior and posterior cerebral artery territories. A stroke is said to be characterized by its focal effects. This may be true for neurological symptoms, but in relation to cognition, deficits in more than one domain frequently occur. Pohjasvaara et al. (1997) examined 486 consecutively admitted ischemic stroke patients between 55 and 85 years of age (mean 71.2 years), and found that cognitive impairment of any kind was present in 61.7% of the subjects 3 months post-stroke. However, about 27% of the subjects were impaired in three or more cognitive domains. The functions most frequently affected were constructional and visuospatial abilities (37%), memory functions (23%-34%), executive functions (25%), orientation (23%), attention (22%), and aphasia (14%). Cognitive changes as assessed by neuropsychological tests are also confirmed by 50% or more of the patients and their next of kin in interviews 3-9 months post-stroke. In the study of Hochstenbach et al. (2005) the most frequent cognitive complaints were forgetfulness (60%), mental slowness (56%), poor concentration (55%), and inability to do two things simultaneously (53%).

Interestingly, the degree of agreement between patients and their next of kin tended to be low in both studies. Visser-Keitzer et al. (2002) found that while left hemisphere stroke patients agreed with their partners on the number and severity of most changes, partners of right hemisphere patients reported more frequent and more severe changes than the patients themselves. The level of observed altered behaviour, distress of the partner, distress of left sided stroke patients and hemispatial neglect of right-sided
stroke patients emerged as factors related to disagreement between the stroke patients and their partners.

Is there a specific cognitive profile of stroke patients? Albeit debated, some researchers have suggested that independent of the lesion site and size, deficits in executive functions, attention, and psychomotor speed may be the most frequent and most severely affected after a stroke, while memory functions are relatively preserved (in contrast to the early stages of Alzheimer’s Disease) \(^{41,42,43,44}\). The reason could be that both executive function and attention involve widely distributed networks of cortical, subcortical, and infratentorial areas of the brain, making these functions vulnerable to the effect of a stroke independent of site \(^{43,44,45,46}\). Such symptoms are less obvious and may therefore be overlooked or misattributed by health personnel unless formal testing is provided. They can also constitute a source of burden and confusion for the patients and their relatives. Misattributions include lack of motivation, cooperation or symptoms of depression.

With respect to frequency of post-stroke dementia, a recent systematic meta-analysis, based on twenty two hospital-based and eight population-based studies with a total of 7511 patients, concluded that 10% of the patients had dementia before their first stroke, 10% developed new dementia soon after their first stroke, and more than a third had dementia after recurrent stroke \(^{32}\). The meta-analysis illustrates well how differences in study setting (hospital based vs population based) and patient characteristics (whether persons with pre-stroke dementia and/or previous or recurrent strokes are included or not) heavily influence the reported prevalence figures of post-stroke dementia. These factors explained more than 90% of the variance between the studies. In fact, the prevalence of post-stroke dementia varied from 7% in a population-based study which excluded persons with pre-stroke dementia to 40% or more in a hospital-based study which included pre-stroke dementia and recurrent strokes. Previously, it has been reported that choice of criteria to define post-stroke dementia (e.g. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), National Institute of Neurological Disorders and
Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN)) affects the reported prevalence figure\textsuperscript{37}. However, this was not confirmed in the meta-analysis, in which diagnostic criteria only explained 2\% of the variance between the studies.

**Risk factors of post-stroke cognitive impairment and dementia**

Several risk factors have been associated with post-stroke cognitive impairment and dementia, which support the view that post-stroke cognitive performance is determined by multiple factors. These may be divided into socio-demographic variables, stroke characteristics, prestroke functioning, and vascular risk factors.

**Socio-demographic variables**

Of the socio-demographic variables, \textit{older age} has, with a few exceptions\textsuperscript{47}, consistently been reported to increase the risk of post-stroke cognitive impairment\textsuperscript{37}. For example, The Helsinki Stroke Aging Memory Study examined 486 consecutively admitted stroke patients between 55 and 85 years of age (mean age 71 years) three months post-stroke, of which 93\% were testable. Cognitive decline of any kind was present in 62\% of the patients, but the prevalence rates varied significantly depending on age. In the age groups 55-64 years, 65-74 years and 75-85 years, the prevalence rates of cognitive impairment were 46\%, 54\% and 74\% respectively, and for dementia (according to DSM-IV criteria) the prevalence rates were 10\%, 19\%, and 24\% in the different age-groups. \textit{Lower cognitive capacity, co-morbidity, and polypharmacy} among the elderly probably contribute to the increased risk. Fewer years of \textit{education} with post-stroke cognitive impairment in many studies, possibly as an effect of lowered constitutional capacity in combination with less efficient post-stroke coping strategies. Increased risk of post-stroke cognitive impairment in \textit{females} has been reported in few studies, but could have resulted from age-confounding\textsuperscript{32}.
Stroke characteristics

Stroke characteristics (location and size of lesion) are understood as crucial factors explaining severity of cognitive impairment and dementia. Lesions in cortical structures (TACS/PACS), especially bilaterally or in the dominant hemisphere, rather than sub cortical (LACS), in the brainstem or cerebellum (POCS) are generally considered to produce more severe cognitive impairments, although recent studies provide evidence that cognitive impairments is frequent in lacunar and cerebellar strokes.

With respect to lesion volume, earlier studies suggested that volumes larger than 50 mL of infarcted tissue might be associated with dementia and larger than 1100 mL were always associated with dementia. Later studies have demonstrated that dementia also occur inpatients with infarcted volumes of less than 20 mL (and some less than 10 mL). Other brain imaging factors significantly associated with post-stroke dementia have been leukoaraiosis, general brain atrophy, and medial temporal lobe atrophy.

Prestroke functioning

Some stroke patients diagnosed with post-stroke cognitive impairment or dementia may have had pre-existing mild cognitive impairments or dementia. In the meta-analysis of Pendlebury and Rotwell (2009) pre-stroke dementia was common with a pooled prevalence rate of 14.4% in hospital-based studies and 9.1% in population based studies. Dementia of mild degree may easily go unnoticed and affects prognosis, and is associated with medial temporal atrophy suggestive of Alzheimer-pathology in many of these patients.

Vascular risk factors

Among vascular risk factors, previous strokes, atrial fibrillation and diabetes are frequently reported to be significantly associated with both post-stroke cognitive impairment and dementia. The role of ischemic heart disease, previous TIA,
hypertension, homocysteinemia, smoking, and moderate alcohol consumption is uncertain \(^{32, 48}\).

**The long-term course of post-stroke cognitive impairment**

Longitudinal studies following the course of post-stroke cognitive performance are relatively scarce \(^{33, 36}\). Although the results of the few studies conducted are not conclusive, the general impression is that the majority of stroke patients follow a fairly stable course in overall cognitive performance over the first 1-3 years, but that some patients improve and others decline over time. In the study of del Ser et al (2005), 193 consecutive patients were tested with an extensive neuropsychological battery three months after the stroke and followed for two years. At follow up, cognitive status according to change in Clinical Dementia Rating Score had improved in 8%, was stable in 78%, and had declined in 14%.

It has been argued that the degree of early recovery is often underestimated, as most studies have waited until three months post-stroke for their baseline examination. The implication is that spontaneous cognitive recovery through self-repair mechanisms of the brain (perilesional changes, contralateral reorganisation, striatal neurogenesis) taking place in the early post-stroke phase is overlooked \(^{19}\).

Variables associated with improvement in cognitive performance over time are right-sided lesions, higher baseline MMSE-score (indicating relatively preserved cognitive functioning), and female \(^{26, 36}\).

Reported risk factors for progression include older age, pre-stroke cognitive decline, medial temporal atrophy on CT-scan, polypharmacy, hypotension during admission, expressive aphasia, impaired cognitive performance at baseline, and recurrent stroke \(^{58}\). It has been suggested that medial temporal atrophy of the brain may be of greater importance than white matter hyperintensities for subsequent post-stroke cognitive decline and increasing brain atrophy \(^{59}\), implying a link between Alzheimer-pathology and progressive cognitive decline in stroke patients. As a genetic component through the presence of the ApoE \(e4\)-allele is well-documented as a strong risk factor for late...
onset Alzheimer’s disease (AD), i.e. AD occurring after the age of 65 years 60, one interesting question arises: Is the ApoE ε4-allele also a risk factor of poststrokecognitive impairment?
AIMS AND OBJECTIVES

1. Prevalence of cognitive impairment in patients with first ever stroke over one year followup.

2. To compare the cognitive impairment in patients with cortical, subcortical, and infratentorial stroke

3. Factors associated with cognitive impairment after first ever stroke.
MATERIALS AND METHODS

Definitions:

Stroke was defined by the World Health Organization (WHO) criterion as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin.”\(^{11}\)

First-ever strokes were defined as events occurring in patients without a history of stroke. Stroke history was based on all available information from patients, hospital records, and general practitioners.

Sampling:

Consecutive first-ever strokes admitted in stroke/neurology department SCT were recruited prospectively between Dec 2011 and July 2012.

Eligibility criteria

- Patients age >18yrs.
- First ever stroke.
  1. WHO definition of stroke will be used.
  2. No history of prior stroke
- Absence of persistent moderate to severe dysphasia.
- Adequate vision & hearing

Exclusion criteria

- Case of transient ischemic attack.
- Case of subarachnoid hemorrhage/ Intracerebral hemorrhage
• Case with past history of stroke.
• Cases with primary brain lesion (tumor, trauma)
• Preexisting cognitive decline.

Assessment

The study population with first-ever symptomatic stroke admitted to a stroke unit/neurology in SCTIMST between December 2011 and July 2012. Patients were eligible for inclusion if they had an ischemic stroke provided that they had no neurological or psychiatric history. The diagnosis of stroke was based on the presence of an acute focal deficit, confirmed by an associated lesion on CT or MRI. Patients with a history of drug or alcohol abuse, pre-existent dependence in activities of daily living, pre-existent cognitive decline were excluded. This population has been reported previously interviews were performed for strokes at 3 months and 12 months. For Neuropsychological assessment stroke patients were examined using Mini mental scale examination (MMSE) and Addenbrooke’s cognitive scale- Malayalam (m-ACE) for post-stroke cognitive deficits. Subjects were defined as cognitively impaired according to predefined cut-off points (MMSE- <24 & ACE < 82). Disability assessed by the NIHSS & MRS, while other information were from a questionnaire-based history of hypertension, diabetes mellitus, hyperlipidemia, smoking, ischemic heart disease, and alcohol consumption. Clinicoradiological classification into cortical, subcortical & infratentorial stroke were performed.

Design:

Prospective observational hospital based analytical study.

Statistical Analysis:

Statistical analysis was done by standard software. The prevalence of post stroke cognitive impairment is calculated as the ratio of no. of patient with poststroke
cognitive impairment to total no. of patient. Univariate & multivariate analysis was done for different determinants to find the association with cognitive impairment.
RESULTS

A total of 172 patients with ischemic stroke between Dec 2011 and July 2012, were registered in stroke/neurology department, of whom 53 patients were eligible & but 11 lost follow up. Total 42 patients (7 Females & 35 Males) with first ever stroke were examined at 3 month & 12 month.

On the whole 8 patients (19.09%) at 3 month & 13 patients (30.09%) at 12 months demonstrated cognitive impairment. On analysis of the ACE scores after 12 months follow up, all 13 subjects were found to have Attention and Orientation score over 13/18, Memory score over 22/35 & Language score over 20/26. However, Fluency scores were poor, ranging from 3/14 to 10/14, Visuospatial function ranged from 1/5 to 3/5, especially Clock drawing.

As shown in table no 1, Cognitive impairment at 3 month was found in 3 (37.4%) of patients with a cortical stroke, in 5 (62%) of patients with subcortical stroke while at 12 months was found in 6 (46%) patients with cortical stroke & 7 (54%) patients with subcortical stroke. We did not find any cognitive impairment of patients with infratentorial stroke during 1 year follow-up.

Table no. 1

<table>
<thead>
<tr>
<th>Stroke subtypes</th>
<th>CI at 3 months</th>
<th>CI at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>37.4%</td>
<td>46%</td>
</tr>
<tr>
<td>Subcortical</td>
<td>62%</td>
<td>54%</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
To evaluate further regarding the association of different clinical & radiological determinants with cognition impairment after stroke we made three groups i.e. Cognitively intact group during 1 year follow up, cognitively impaired group at 3 months & cognitively impaired at 12 months.

**Demographic** associated with the cognitive impairment after stroke is shown in Table. 2

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Normal N- 29</th>
<th>CI – 3 months N- 8</th>
<th>CI- 12 months N-13</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age , years</td>
<td>54.68 ± 10.46</td>
<td>66.12 ± 9.87</td>
<td>63.76 ± 11.96</td>
<td>0.017</td>
</tr>
<tr>
<td>Sex ,female</td>
<td>10.3 % ( 3)</td>
<td>37% (3)</td>
<td>30.7% (4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Education, yrs</td>
<td></td>
<td></td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>&lt;10</td>
<td>34.4% (10)</td>
<td>37.5% (3)</td>
<td>38.4% (5)</td>
<td></td>
</tr>
<tr>
<td>10- 12</td>
<td>41.3% (12)</td>
<td>62.5% (5)</td>
<td>53.8% (7)</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>24.1% (7)</td>
<td>0 (0)</td>
<td>7.6%(1)</td>
<td></td>
</tr>
</tbody>
</table>
Mean age was higher in cognitive impairment group at 3 months (66.12 SD 9.87) & 12 months (63.76 SD 11.96) as compared to cognitively intact group (54.68 SD 10.46). Even though there was low number female patients, our results showed that female were more prone for poststroke cognition impairment in comparison to male patients. Regarding the education status, we found that those patients who had > 12 yrs of education were had less chances to get cognition impairment after a stroke.

**Table no.3**

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Normal</th>
<th>CI-12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N-29</td>
<td>N-13</td>
</tr>
<tr>
<td>Right</td>
<td>44%(13)</td>
<td>53% (7)</td>
</tr>
<tr>
<td>Left</td>
<td>51%(15)</td>
<td>46% (6)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3.4%(1)</td>
<td>0</td>
</tr>
</tbody>
</table>

We did not found any significant association of cognitive impaired with regard to the side of the lesion.
Vascular risk factors associated with the cognitive impairment after stroke are shown in Table. 4

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Normal</th>
<th>CI – 3 months</th>
<th>CI- 12 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N- 29</td>
<td>N- 8</td>
<td>N-13</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>68.9% (20)</td>
<td>100% (8)</td>
<td>92.3% (12)</td>
<td>0.101</td>
</tr>
<tr>
<td>CAD</td>
<td>13.7% (4)</td>
<td>25% (2)</td>
<td>23.07% (3)</td>
<td>0.455</td>
</tr>
<tr>
<td>DM</td>
<td>65.5% (19)</td>
<td>75% (6)</td>
<td>76.9% (10)</td>
<td>0.460</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>44.8% (13)</td>
<td>37.5% (3)</td>
<td>30.7% (4)</td>
<td>0.391</td>
</tr>
<tr>
<td>AF</td>
<td>6.8% (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.323</td>
</tr>
<tr>
<td>Smoking</td>
<td>31.0% (9)</td>
<td>37.5% (3)</td>
<td>38.4% (5)</td>
<td>0.637</td>
</tr>
<tr>
<td>Alcohol</td>
<td>13.7% (4)</td>
<td>12.5% (1)</td>
<td>7.6% (1)</td>
<td>0.572</td>
</tr>
</tbody>
</table>
We studied various risk factors including smoking, alcoholism, hypertension, diabetes mellitus, presence of cardiac illness, atrial fibrillation & dyslipidemia & found that there is trend of DM & HTN more towards the cognitive impaired group while other risk factors did not showed any significant difference between the groups.

Association of cognitive impairment after stroke with disability at onset of stroke.  
**Table no. 5**

<table>
<thead>
<tr>
<th>Disability score</th>
<th>Normal</th>
<th>CI – 3 months</th>
<th>CI- 12 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At onset</td>
<td>N- 29</td>
<td>N- 8</td>
<td>N-13</td>
<td></td>
</tr>
</tbody>
</table>

| | | | | |
| | NIHSS (Mean±SD) | 5.103± 2.6 | 9.25± 5.57 | 7.8± 5.12 |
| | Range            | 2-11       | 5-19       | 2-19      |
| | 0-5 | 65.5% (19) | 37.5% (3) | 46.1% (6) | 0.765 |
| | 6-15 | 34.4% (10) | 50% (4) | 46.1% (6) |
| | >15 | 0 | 12.5% (1) | 7.6% (0) |

| | | | |
| | MRS (Mean±SD) | 2.96± 0.90 | 3.87± 0.83 | 3.53± 0.96 |
| | Range            | 1-4       | 3-5       | 2-5      |
| | 0-2 | 34.4% (10) | 0 (0) | 15.3% (2) | 0.891 |
| | 3 | 31% (9) | 37.5% (3) | 30.7% (4) |
| | 4-5 | 34.4% (10) | 62.5% (5) | 53.8% (7) |
In our study the mean NIHSS score at stroke onset were higher in cognitively impaired group (9.25 SD 5.57) at 3 months & (7.8 SD 5.12) 12 months in comparison to the cognitively intact group (5.10 SD 2.6). The same trend we noticed in MRS score at stroke onset also, with mean of 3.87 SD 0.83 at 3 months, 3.53 SD 0.96 at 12 months cognitively impaired group & 2.96 SD 0.90 in normal group. 3 patients underwent intravenous thrombolytic therapy at stroke onset, out of which 2 had higher NIHSS & MRS at presentation & recovered well after therapy without any impaired cognition on follow up. Our study showed that as the severity of disability at stroke onset increases the chances of impaired cognition will also increase.

MRS score at stroke onset

MRS score at 3 months
MRS score at 12 months

Sub types of stroke & association with post stroke cognitive impairment. **Table 6**

<table>
<thead>
<tr>
<th>Stroke subtypes</th>
<th>Normal</th>
<th>CI – 3 months</th>
<th>CI- 12 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA± ACA</td>
<td>41.3% (12)</td>
<td>50% (4)</td>
<td>53.8% (7)</td>
<td>0.583</td>
</tr>
<tr>
<td>PCA</td>
<td>10.3% (3)</td>
<td>12.5% (1)</td>
<td>7.6% (1)</td>
<td></td>
</tr>
<tr>
<td>VBA</td>
<td>24.3% (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>24.1% (7)</td>
<td>37.5% (3)</td>
<td>38.4% (5)</td>
<td></td>
</tr>
</tbody>
</table>
In our study maximum cases were of anterior circulation (2 cases involving both ACA & MCA) & lacunar stroke followed by posterior circulation stroke. Out of above stroke subtype, cognitive impairment was slightly predominant in anterior circulation stroke & lacunar stroke. No case of cognitive impairment documented in vertebrobasilar stroke.

Table no.7

<table>
<thead>
<tr>
<th>Aetiology of stroke</th>
<th>Normal N-29</th>
<th>CI – 3 months N-8</th>
<th>CI- 12 months N-13</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large artery Atherosclerosis</td>
<td>17.24% (5)</td>
<td>37.5% (3)</td>
<td>30.7% (4)</td>
<td>0.764</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>20.6% (6)</td>
<td>12.5% (1)</td>
<td>15.3% (2)</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>24.1% (7)</td>
<td>37.5% (3)</td>
<td>38.4% (5)</td>
<td></td>
</tr>
<tr>
<td>Dissection</td>
<td>3.4% (1)</td>
<td>12.5% (1)</td>
<td>15.3% (2)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>34.4% (10)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
</tr>
</tbody>
</table>
Patients with large artery atherosclerosis & Lacunar stroke were more in cognitively impaired group with proportion of 30.7% & 38.4% respectively over 1 year. Cardioembolic group consist mostly of old/recent myocardial ischemia associated regional wall motion abnormality, 1 case of PFO with septal aneurysm & 2 cases of AF on ECG/ECHO. Out of total 3 cases of dissection (1 vertebral artery & 2 internal carotid arteries) 1 patient developed cognitive impairment at 3 months & 1 more added on 12 months follow up.
As we described earlier the prevalence of cognitive impairment after 3 & 12 months in cortical & subcortical stroke, we did not found any correlation of cognitive impairment on location wise except for the presence of associated small vessel ischemic changes. CT or MRI with SVIC of grade I & II was found in 9 patients out of which 6 patients had cognitive impairment at 3 moths & 1 more had of 12 months follow-up.
DISCUSSION

In the present study cognition was carefully assessed by using m-ACE, which includes all domains of cognition, in patients with first ever stroke at 3 month & 12 months intervals. The prevalence of poststroke cognitive impairment was 19.09% at 3 months after stroke and 30.09% at 12 months after stroke.

In India, data regarding the poststroke cognitive impairment is sparse. One study done by Sundar et al in 2010 reported 31.1% prevalence of cognitive dysfunction after 3 months of stroke, either on MMSE or the FAB.

Worldwide published data on prevalence rates are highly inconsistent and vary from as low as 7% up to 82%.
Differences in terminology, the characteristics of the study samples, the choice of cognitive tests, the applied cut-off score to define cognitive impairment, and the time period between stroke onset and cognitive testing all contribute to this confusing picture and make comparisons between the studies difficult.\(^{19,20}\)

Hospital-based studies which have applied neuropsychological testing within the first three months post-stroke report prevalence rates of cognitive impairment varying from 33% to 82% in patients with first-ever stroke and free from pre-stroke dementia \(^{33-38}\), which is much higher in comparison to our study prevalence at 3 month.

A major observation is that there are some differences in the cognitive impairment rates among groups when stratified by sociodemography, past medical history of vascular risk factors, and stroke subtypes. These differences in prevalence of cognitive impairment by group after stroke bear witness to the heterogeneity of this condition. Age could be linked to accumulated lifetime exposures affecting cognitive function and socioeconomic status in the form of education level.

Of the socio-demographic variables, older age has consistently been reported to increase the risk of post-stroke cognitive impairment \(^{37}\). For example, The Helsinki Stroke Aging Memory Study examined 486 consecutively admitted stroke patients between 55 and 85 years of age (mean age 71 years) three months post-stroke, of which 93% were testable. Cognitive decline of any kind was present in 62% of the patients, but the prevalence rates varied significantly depending on age. In the age groups 55-64 years, 65-74 years and 75-85 years, the prevalence rates of cognitive impairment were 46%, 54% and 74% respectively.

We also found similar association with age, which was statistically significant with p value 0.017. Increased risk of post-stroke cognitive impairment in females has been reported in few studies\(^{32}\) & similarly noticed in present study, even though numbers were few, but could have resulted from age-confounding. Among vascular risk factors, diabetes & hypertension are frequently reported to be significantly associated with both post-stroke cognitive impairment and dementia\(^{32,48}\).
A study done in India by Mukhopadhyay et al 2012\textsuperscript{67} reported Severe disability by Modified Rankin Score (OR 136, 95% CI 7.51 - 2462.91, P <0.0001), and Diabetes mellitus (OR 10, 95% CI 1.39 – 71.87, P <0.05) were significantly associated with cognitive dysfunction. In our study also trend is similar but statistically insignificant.

A prevalence of cognitive impairment of almost half was found in patients having a total anterior circulation infarct stroke & almost one third in lacunar infarct stroke, which may represent vascular dementia associated with stroke. Studies have shown that the cognitive decline of these groups could be related to vascular dementia\textsuperscript{64,65} or Alzheimer disease\textsuperscript{66}.

This hospital based study has produced estimates of cognitive status in stroke survivors, but with no comparison to the nonstroke population. Because of small sample size the association of different predictors did not showed any statistically significance, except for older age group, even though the trend in many of the predictors were towards the cognitively impaired group.

The strengths of our study include its prospective design, the population-based nature of the sample & the length of follow-up. The possibility of bias because of the sampling of less severe stroke cases and loss to follow-up was the limitation in our study. Further longitudinal analyses of predictors in various sociodemographic, vascular risk factors, stroke subtype, and disability scale are thus needed to develop a useful predictive tool for patient management. Furthermore, the psychometric screening tools used in this study may underestimate the impact of cognitive impairments, particularly mild cognitive impairment & need more detailed neuropsychometric test. Although these are limitations in detecting mild cases, this study has shown high prevalence of cognitive impairment.
CONCLUSION

Prevalence rate of poststroke cognitive impairment i.e 19.09% at 3 month & 30.09% at 12 months from our study, were found to be comparable to rates from contemporary Indian studies. Prevalence rate varies in world wide studies which could be explained by subgroup differences and temporal changes after stroke. Out of all predictors, only older age was found to be statistically significant in poststroke cognitive impairment. Many of the predictors, as described in results, has shown an association with poststroke cognitive impairment (statistically not significant), but because of small sample size & sampling bias, the results can not be generalized to population & need longitudinal analyses with large sample size to find the predictors in various sociodemographic, vascular risk factors, stroke subtype, and disability scale for the poststroke cognitive impairment.
BIBLIOGRAPHY


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# ANNEXURE I

ADDELBROOKE'S COGNITIVE EXAMINATION

COMPONENTS:

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
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<tbody>
<tr>
<td>ORIENTATION</td>
<td>10</td>
</tr>
<tr>
<td>ATTENTION AND CONCENTRATION</td>
<td>8</td>
</tr>
<tr>
<td>MEMORY</td>
<td>3</td>
</tr>
<tr>
<td>ANTEROGRADE MEMORY</td>
<td>21</td>
</tr>
<tr>
<td>RETROGRADE MEMORY</td>
<td>4</td>
</tr>
<tr>
<td>VERBAL FLUENCY[LETTER-7 AND CATEGORY-7]</td>
<td>14</td>
</tr>
<tr>
<td>NAMING</td>
<td>12</td>
</tr>
<tr>
<td>COMPREHENSION ONE STAGE</td>
<td>2</td>
</tr>
<tr>
<td>READING COMPREHENSION</td>
<td>1</td>
</tr>
<tr>
<td>COMPREHENSION THREE STAGE</td>
<td>3</td>
</tr>
<tr>
<td>COMPREHENSION COMPLEX</td>
<td>2</td>
</tr>
<tr>
<td>REPETITION SINGLE WORDS</td>
<td>3</td>
</tr>
<tr>
<td>REPETITION PHRASES</td>
<td>2</td>
</tr>
<tr>
<td>READING</td>
<td>2</td>
</tr>
<tr>
<td>WRITING</td>
<td>1</td>
</tr>
<tr>
<td>Test</td>
<td>Score</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>ADDRESS RECALL-7</td>
<td>7</td>
</tr>
<tr>
<td>VISUO SPATIAL CONSTRUCTION</td>
<td></td>
</tr>
<tr>
<td>PENTAGON</td>
<td>1</td>
</tr>
<tr>
<td>CUBE</td>
<td>1</td>
</tr>
<tr>
<td>CLOCK DRAWING</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>100</td>
</tr>
</tbody>
</table>
ABBR EVIATIONS

CI at 3 months: cognitive impairment after 3 months of stroke

CI at 12 months: cognitive impairment after 12 months of stroke

DM: Diabetes Mellitus

CAD: Coronary artery disease

AF: Atrial fibrillation

HTN: Hypertension

m-RS: Modified Rankins Scale

MRI: Magnetic Resonance Imaging

MRA: MR Angiogram

NIHSS: National institute of Health Stroke Scale

TIA: Transient Ischemic Attack
DECLARATION

I, Dr. Manish Gupta, hereby declare that the projects in this book were undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram

Dr. Manish Gupta

Date:

Forwarded

The candidate, Dr. Manish Gupta, has carried out the minimum required project.

Thiruvananthapuram

Dr. Muralidharan Nair

Professor & Head,
Dept of Neurology
SCTIMST

Date:
ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to Dr. P.S. Mathuranath, Additional Professor of Neurology, SCTIMST, my guide for the study, for his expert guidance, constant review, kind help and keen interest at each and every step during the completion of the study.

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Last but not the least, I extend my gratitude’s to all my patients and their primary caregivers who participated in this study as well as my colleagues without whose help this study was not possible.
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<th>PAGE NO.</th>
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