CLINICAL STUDY

Dementia-associated Dyslipidemia Study

VIKAS DHIKAV*, AK SINGHAL†, ITISHREE PANDEY‡, KULJEET SINGH ANAND#

ABSTRACT

Introduction: As age advances, the risk of several noncommunicable diseases (NCDs) like diabetes, hypertension, heart disease, dyslipidemia, etc increases. Dementia is among the most common diseases of older adults and accounts for significant disease burden globally. Dyslipidemia is especially common in older adults with diabetes. In the current study, the aim was to assess if patients with dementia have dyslipidemia and if so, whether the frequency was different in age-matched control group. **Material and methods:** A total of 836 subjects over the age of 60 years were screened and of these, 536 (67.12 ± 4.5 years) subjects who met the diagnostic criteria for diagnosis of dementia (Diagnostic and Statistical Manual-IV) were enrolled for the study. A total of 32 cognitively normal subjects above the age of 60 years, but without cardiovascular risk factors (65.12 ± 3.5 years) were selected as controls. Selected patients underwent lipid profile assessment apart from detailed neuropsychological, neurological, and radiological examination. The frequency of dyslipidemia among cases and control was compared. **Results:** Total serum cholesterol, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL) in patients with dementia were 234.56 ± 22.5 mg/dL, 136.58 ± 11.3 mg/dL, 35.5 ± 3.5 mg/dL, respectively, while high-density lipoprotein (HDL) was 28.7 ± 7.8 mg/dL. Corresponding values in the healthy controls were: Total cholesterol (TC) = 156.36 ± 12.5 mg/dL, LDL = 86.15 ± 12.3 mg/dL, VLDL = 25.5 ± 3.5 mg/dL, HDL = 37.7 ± 1.8 mg/dL. Comparison of means using paired *t*-test showed all biochemical values (TC, LDL, VLDL, HDL) differed from controls ($p < 0.0001$). Out of 536 cases with dementia, 157 (29%) had deranged lipid profile. Patients of Alzheimer's disease (AD) with comorbid diabetes and hypertension were more likely to have dyslipidemia compared to AD patients without these two comorbidities ($p < 0.05$). **Conclusion:** The current study indicates that patients with dementia have a high frequency of dyslipidemia, and the frequency is higher compared to healthy controls ($p \leq 0.05$).

Keywords: Alzheimer's disease, dyslipidemia, lipid levels, dementias

Dementia describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. Alzheimer's disease (AD) is most common type of dementia followed by vascular dementia[1]. Dyslipidemia is characterized by elevation of blood cholesterol, triglycerides (TGs), or both, or high low-density lipoprotein (LDL) with a low high-density lipoprotein (HDL) levels that contribute to the development of atherosclerosis.

Causes of dyslipidemia may be primary or secondary. It is diagnosed by measuring plasma levels of total cholesterol (TC), TGs, and individual lipoproteins. Dyslipidemia is a known vascular risk and its association with dementia has been controversial for long[1,2]. It has been said that it is appropriate and logical to treat patients with vascular risk factors that meet criteria for lipid-lowering therapy for prevention of cardiovascular events in accordance with current guidelines; hence, it is important to know the burden of the dementia-associated dyslipidemia. It is noteworthy that dyslipidemia in dementia opens up a tantalizing possibility of modifying the disease using statins, especially in the early or clinical phase.

In the current study, the aim was to assess the burden of dyslipidemia, and to evaluate if patients with dementia have a higher frequency of dyslipidemia compared to controls. The study also aimed to determine if the frequency of dyslipidemia was different in the various types of dementias.

MATERIAL AND METHODS

A total of 836 subjects coming to the Dept. of Neurology of a tertiary care hospital with subjective memory complaints were screened and 536 subjects who met the

*Senior Research Officer, Dept. of Neurology, Dr Ram Manohar Lohia Hospital, New Delhi, India
†Associate Professor, Dept. of Biochemistry, Amrita School of Medicine, Faridabad, Haryana, India
‡Senior Resident, Dept. of Biochemistry, ESIC Medical College, Faridabad, Haryana, India
#Professor, Dept. of Neurology, Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India
Address for correspondence
Dr Vikas Dhikav
Paradise Apartment, Flat 280, Rohini, Sector-13, New Delhi - 110 085, India
E-mail: vikasdhikav@hotmail.com

diagnostic criteria for diagnosis of dementia (Diagnostic and Statistical Manual [DSM]-IV) were enrolled for the current study. Thirty-two cognitively normal subjects above the age of 60 years were selected as controls for comparison.

Selected patients underwent lipid profile assessment, apart from detailed neuropsychological, neurological, and radiological examination. Comparison of frequency of dyslipidemia among cases and control was done.

RESULTS

A total of 836 subjects over the age of 60 years, with subjective memory complaints reporting to the Dept. of Neurology of a Tertiary Care Hospital were screened and 536 subjects (67.12 ± 4.5 years) were enrolled. A total of 32 cognitively normal subjects above the age of 60 years (65.12 ± 3.5 years) were selected for comparison. Stratification of cases was done and there were 356 patients with AD (n = 285) and vascular dementia (n = 71).

Other dementias were: Dementia with Lewy bodies (n = 55), B12 deficiency (n = 65), thyroid dementia (n = 35), frontotemporal dementia (n = 19), Creutzfeldt-Jakob disease (n = 2), human immunodeficiency virus (HIV)-associated dementia (n = 2), and corticobasal degeneration (n = 2).

Out of rest of the 180 patients with dementia, a total of 36 (20%) cases had dyslipidemia (TC 224.13 ± 12.5 mg, LDL was 126.58 ± 11.3 mg, VLDL was 33.5 ± 7.5 mg, HDL was 29.7 ± 3.8 mg). Chi-square test did not show a significant difference between the two groups ($p \geq 0.05$).

Table 1 details lipid profiles of patients with all kind of dementias including AD and controls and comparison of means using paired *t*-test. It shows all biochemical values to be different in cases and controls ($p < 0.0001$).

Table 2 details the frequency of diabetes among those with vascular dementia and AD, which differed from each other ($p = 0.01$). Likewise, the comparison of frequency of hypertension in those with vascular dementia and AD showed a significant difference (51/76 vs. 40/180) using Chi-squared test of comparison of proportion ($p = 0.04$). Dyslipidemia was seen in 36 out of 76 (45%) patients with vascular dementia compared to 45 out of 180 in those with AD (25%; $p = 0.001$).

Cases with dementia were more likely to have dyslipidemia compared to controls ($p < 0.05$). Out of 536 cases with dementia, 157 (29%) had deranged lipid profile; compared to none in the cognitively normal older adults group.

Those with a diagnosis of vascular dementia were less likely to have dyslipidemia compared to those with AD dementia. Patients of AD with a diagnosis of diabetes and hypertension were more likely to have dyslipidemia compared to AD patients without these two comorbidities ($p < 0.05$).

Analysis of proportions of dyslipidemia frequency showed that there was no significant difference between AD and other dementias ($p = 0.07$). Comparison of the same with vascular dementia showed a highly significant difference ($p = 0.0001$).

Table 1. Comparison of Lipid Profile of Cases and Control

Lipid group	Lipid profile of patients with dementia (n = 536) (mean ± SD)	Cognitively normal (n = 32) (mean ± SD)
TC	234.56 ± 22.5 mg/dL	156.36 ± 12.5 mg
LDL	136.58 ± 11.3 mg/dL	86.15 ± 12.3 mg
VLDL	35.5 ± 3.5 mg/dL	25.5 ± 3.5 mg
HDL	28.7 ± 7.8 mg/dL	37.7 ± 1.8 mg

Table 2. Frequency of Cardiovascular Risk Factors among those with Vascular Dementia and Alzheimer's Disease

	Vascular dementia		Alzheimer's disease	
Cardiovascular risk factor	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Diabetes	35/76	46.05	51/180	28.33
Hypertension	51/76	67.10	40/180	22.22
Dyslipidemia	36/76	47.36	45/180	25

DISCUSSION

Cholesterol play an important role in the maintenance of brain health and functioning. Human brain is composed of around 25% of cholesterol, most of which is present in the myelin sheaths and plasma membrane of astrocytes and neurons[3]. Structural development and functioning of the brain also depends on the sufficient availability of the cholesterol, especially during the developmental period[4]. Cholesterol also plays a significant role in regeneration following a nerve injury; however, its association with dementia is largely controversial. Due to the importance of cholesterol in brain functioning, its contents are precisely maintained[4].

Therefore, majority of the brain cholesterol is locally synthesized. As the metabolism of the cholesterol in the brain is unique, the blood-brain barrier efficiently protects it from exchange with lipoprotein cholesterol in the circulation. Thus, to minimize the losses to the circulation, brain has a highly efficient apolipoprotein-dependent recycling of cholesterol.

Recent findings indicate that vascular risk factors and neurovascular dysfunction play integral roles in the pathogenesis of AD. In addition to aging, the most common risk factors for AD are apolipoprotein E4 (apoE4) allele, hypertension, diabetes, and hypercholesterolemia. Similar risk factors have been described for vascular disease[5].

No firm conclusions can, however, be drawn from the studies presented thus far. Even if apolipoprotein E (apoE) does not appear to be obligatory for maintenance of cholesterol homeostasis in the brain of experimental animals, the capacity of the transport function it represents seems to be critical in connection with development of neurodegenerative disorders. Studies have proposed that dyslipidemia could be an independent risk factor or it can probably increase the risk through metabolic syndrome.

Evidence of a possible link between cholesterol and neurodegeneration has accumulated in the last decade. Some of the earliest observations were the recognition of ε4 isotype of apoE as an important risk factor for late-onset.

An increased risk of developing AD is linked to the presence of apoE4 allele, which is also strongly associated with increased risk of developing atherosclerotic cardiovascular disease (ASCVD)[6,7].

There is increasing evidence linking cholesterol metabolism with the neurofibrillary pathology of AD. Cholesterol and its transport have been shown to be involved in the regulation of amyloid production and tau hyperphosphorylation in the brain, while also contributes to intracranial vascular disease and cerebral ischemia[8,9]. High blood cholesterol has been found to accelerate the beta-amyloid plaque production. Therefore, a greater risk of late-onset AD is present in people with genetic traits that increase cholesterol transport protein (apoE4) level.

Cholesterol has been shown to influence a number of processes involved in the generation of the neuritic plaques (predominantly consisting of Aβ peptides of 40 or 42 residues) and neurofibrillary tangles[6,7]. On a grosser level, atherosclerosis is a major contributor to stroke, and several drugs are available to reduce the risk.

Current evidence from epidemiological, animal, cell biology and genetic studies supports a possible involvement of cholesterol in the development of dementia and AD, suggesting dyslipidemia[9-14] as one of the modifiable risk factors to be targeted by therapeutic interventions that are already widely available[3,4,14-17]. However, the overall relationship between dementia and dyslipidemia at present appears controversial[18].

The current study found dyslipidemia to be more common in vascular dementia compared to AD, and AD patients with vascular risk factors are more likely to have dyslipidemia compared to those without them. Diabetes is an important risk factor for dyslipidemia in this population. This study is important because south Asians are more likely to have diabetes compared to non-south Asians[14]. High frequency of cardiovascular risk factors among patients with dementia, e.g., hypertension[19], diabetes, etc. as comorbidities are important risk factors for development of dementia. This association has been noted in several other studies.

The major strength of the study is that it demonstrates a high frequency of dyslipidemia among those with dementia compared to controls. Limitation is smaller number of controls (n = 32) compared to cases.

Timely management of cardiovascular risk factors[20] such as diabetes, hypertension, dyslipidemia in patients with dementias could be potentially useful either to slow down or prevent catastrophic consequences associated with dementias.

CONCLUSIONS

The current study indicates that the patients with various types of dementias have a high frequency of dyslipidemia, and the frequency is higher compared to healthy controls ($p \leq 0.05$).

Significant number of patients with dementia (29%) had derangement of lipid profile. Patients of AD with a diagnosis of diabetes and hypertension were more likely to have dyslipidemia compared to AD patients without these two comorbidities.

Findings of the current study point towards use of statins in management of dementias, which could be potentially useful in slowing down progression or reduce worsening of dementias.

REFERENCES

1. Dhikav V, Anand K. Potential predictors of hippocampal atrophy in Alzheimer's disease. Drugs Aging. 2011;28(1): 1-11.
2. Dhikav V, Anand KS. Are vascular factors linked to the development of hippocampal atrophy in Alzheimer's disease? J Alzheimers Dis. 2012;32(3):711-8.
3. Smiljanic K, Loncarevic-Vasiljkovic N, Kanazir S, Djordjevic A. Cholesterol in brain health and pathologies: the role in Alzheimer's disease. In: Frontiers in Clinical Drug Research-Dementia. Vol. 1. 2020. pp. 26-77.
4. Reitz C. Dyslipidemia and dementia: current epidemiology, genetic evidence, and mechanisms behind the associations. J Alzheimers Dis. 2012;30 Suppl 2(0 2):S127-45.
5. Dhikav V, Singh P, Anand KS. Medication adherence survey of drugs useful in prevention of dementia of Alzheimer's type among Indian patients. Int Psychogeriatr. 2013;25(9):1409-13.
6. Anand KS, Dhikav V. Dhikav V, Duraisamy S, Anand KS, Garga UC. Hippocampal volumes among older Indian adults: Comparison with Alzheimer's disease and mild cognitive impairment. Ann Indian Acad Neurol. 2016; 19(2):195-200.
7. Koch M, Jensen MK. HDL-cholesterol and apolipoproteins in relation to dementia. Curr Opin Lipidol. 2016;27(1):76-87.
8. Lane-Donovan C, Philips GT, Herz J. More than cholesterol transporters: lipoprotein receptors in CNS function and neurodegeneration. Neuron. 2014;83(4):771-87.
9. Altman R, Rutledge JC. The vascular contribution to Alzheimer's disease. Clin Sci (Lond). 2010;119(10):407-21.
10. van Vliet P, Westendorp RG, van Heemst D, de Craen AJ, Oleksik AM. Cognitive decline precedes late-life longitudinal changes in vascular risk factors. J Neurol Neurosurg Psychiatry. 2010;81(9):1028-32.
11. Dickstein DL, Walsh J, Brautigam H, Stockton SD Jr, Gandy S, Hof PR. Role of vascular risk factors and vascular dysfunction in Alzheimer's disease. Mt Sinai J Med. 2010;77(1):82-102.
12. Fischer P, Zehetmayer S, Bauer K, Huber K, Jungwirth S, Tragl KH. Relation between vascular risk factors and cognition at age 75. Acta Neurol Scand. 2006;114(2):84-90.
13. Panza F, D'Introno A, Colacicco AM, Capurso C, Pichichero G, Capurso SA, et al. Lipid metabolism in cognitive decline and dementia. Brain Res Rev. 2006;51(2):275-92.
14. Chandra SR, Yadav R, Puneeth CS, Saini J, Issac TG. 'The spectrum of vascular dementia' - a retrospective study from South India. J Assoc Physicians India. 2014;62(6):498-503.
15. Taliyan R, Chandran SK, Kakoty V. Therapeutic approaches to Alzheimer's-type of dementia: a focus on FGF21 mediated neuroprotection. Curr Pharm Des. 2019;25(23): 2555-68.
16. Singh V, Dhamoon MS, Alladi S. Stroke risk and vascular dementia in South Asians. Curr Atheroscler Rep. 2018;20(9):43.
17. Hussain G, Wang J, Rasul A, Anwar H, Imran A, Qasim M. Role of cholesterol and sphingolipids in brain development and neurological diseases. Lipids Health Dis. 2019;18(1):26.
18. Dhikav V, Jadeja B, Gupta P. Community screening of probable dementia at primary care center in western India: a pilot project. J Neurosci Rural Pract. 2022;13(3):490-4.
19. Dhikav V, Jadeja B, Gupta P. Cognition and cardiovascular comorbidities among older adults in primary care in West India. J Neurosci Rural Pract. 2023;14(2):230-4.
20. Jin WS, Bu XL, Wang YR, Li L, Li WW, Liu YH, et al. Reduced cardiovascular functions in patients with Alzheimer's disease. J Alzheimers Dis. 2017;58(3):919-25.

■■■■