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TRANSCRANIAL DOPPLER STUDY OF CEREBRAL HEAMODYNAMICS IN ALZHEIMERS DEMENTIA

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ABSTRACT

Objective: To evaluate the TCD blood flow hemodynamics of AD and compare with that of vascular dementia (VD) and normal control patients.

Background: Transcranial Doppler (TCD) is an inexpensive and non-invasive method for cerebral hemodynamic assessment. There are evidences of altered cerebral artery morphology in Alzheimer's dementia (AD) greater than age matched controls. We aim to evaluate this vascular status in Alzheimer's dementia aimed theories of mixed pathogenic mechanisms i.e. vasocognopathy involving both the hemodynamic and neurodegeneration .

Design/Methods: Thirty AD patients were studied and compared with 30 VD patients and 30 age matched controls at the Institute of Neurology, Madras Medical College. Two values namely Pulsatility index (PI) and mean blood flow velocity (MBFV) in the middle cerebral artery (MCA) were studied. Patients satisfying probable NINDS/AIREN and National institute of aging and Alzheimer's association criteria for VD and AD respectively were included. Patients with significant carotid artery disease ,coronary artery disease with systolic failure and acute stroke were excluded.Statistical analysis was done using SPSS statistics software (v26).

Results: The MCA MBFV in VD [37.5 ± 9.4, p< 0.05 (CI 95%)] and AD [38.3 ± 7.2, p<0.05 (CI95%)] were significantly lower than in controls (51.4 ± 10.5) but did not vary significantly between AD and VD. Similarly, PI in VD [1.3 ± .2, p<0.05 (CI95%)] and AD [1.09 ± .2, p< 0.05 (CI 95%] were significantly higher than in controls (.8 ± .2). Although MCA PI was higher in VD than AD this was not statistically significant (p >0.5).

Conclusions: In our study, although TCD did not help to distinguish between VD and AD, it showed vascular flow and resistance changes in AD similar to VD. The significance of vascular pathology in AD needs further research and evaluation

KEYWORDS :

INTRODUCTION

Robust neurovascularsynergyis a prerequisite for adequate cognitive function. Conversely, impaired blood flow is often associated with poor cerebraloutcome. Researchintovascularpathologyof Alzheimer's disease hasunraveledevidencesofanalteredcerebralartery morphology greater than age matched controls (1,2).These findings were corroborated from many autopsied brains of patients with Alzheimer's disease showing cerebrovascular pathologies (3). In this setting, some authors have proposed this pathologic condition as a vasocognopathy entity(2).

Transcranial Doppler(TCD) introduced in 1982 is a safe, fast, non invasive, non ionizing and inexpensive method for intracranial hemodynamic assessment. This technique provides two major hemodynamic measures

Pulsatility index (PI) – It is the surrogate marker of cerebral flow resistance (or arterial stiffness) measure by subtracting End diastolic velocity (EDV) from Peak systolic velocity (PSV) and dividing it by Mean blood flow velocity (MBFV). PI is independent of angle of insonation and has no unit with an arbitrary value of more than 1.2 representing high blood flow resistance.

Mean blood flow velocity (MBFV in cm/s) - It is the surrogate marker for cerebral blood flow. It is calculated by EDV plus one third of difference of PSV and EDV. MCA has the highest velocity among all major intracranial arteries. Decreased flow velocity in dementia may suggest cerebral hypoperfusion.

This study aims to evaluate the TCD blood flow hemodynamic of Alzheimer's dementia and compare with that of vascular dementia and normal control so as to give a better understanding about the vascular status in Alzheimer's dementia. In our study we will be focusing on the middle cerebral artery (MCA) as it supplies the main cognitive areas of cerebral cortex and investigation will be done by transcranial Doppler sonography focusing on changes of cerebral blood flow velocity and pulsatility index of our participants.

AIMS AND OBJECTIVES

To Study the Mean blood flow velocity and pulsatility index between Alzheimer's dementia and compare these with age matched patients of Vascular dementia and controls.

METHODOLOGY (MATERIALS &METHODS)

This case control study was done at the Institute of Neurology Madras Medical College. Two values namely Pulsatility index(PI) and mean blood flow velocity(MBFV) in the middle cerebral artery was be studied.

Subjects

Thirty AD patients were studied and compared with 30 age matched VD patients and 30 controls at the Institute of Neurology, Madras Medical College after fulfilling inclusion and exclusion criteria. Patients were recruited from the our Dementia clinic and controls were sampled from routine patient department. Cognitive impairment was quantified using the Montreal cognitive assessment (MOCA)(4) at the time of the ultrasound investigation

Inclusion Criteria

All Patients/Control had minimum education level of up to primary grade level. Patients of Vascular dementia had to satisfy the probable criteria of NINDS/AIREN vascular cognitive impairment(5) and patients of Alzheimer's disease had to satisfy the probable criteria of National institute of aging and Alzheimer's association(6). The Controls were devoid of any history of neurological history/disease.

Exclusion Criteria:

Patients with other significant neurological disease (eg. Trauma, neuroinfection), significant Carotid artery disease, history of depression, presence of significant systemic comorbidities, poorly controlled diabetes or hypertension with target organ damage, patients with intake of alcohol of more than 21 units for male/14 units for female per week or smokers and other substance abuse were excluded from this study.

Ultrasound Investigation

A color- coded 2.5 MHz phased-array probe transcranial duplex ultrasound was used in a standard transtemporal approach to analyse mean blood flow velocity (Vmean) and pulsatility index (PI) in both

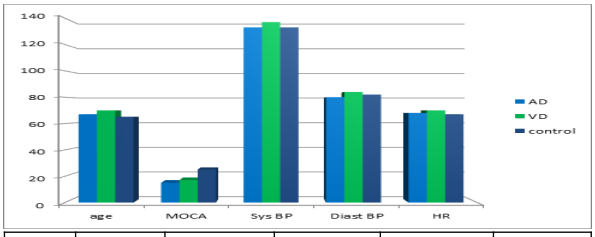
M1- segments of the middle cerebral artery (MCA) at a depth of 50 to 60 mm.

Statistic Methods

Descriptive data and results of measurements are presented as mean ± SD. Non-parametric data of differences in mean blood flow velocity (V mean) and PI were done using analysis of variance (ANOVA) and for with physiologic parameters (MOCA, age,Hr, BP) Spearman rank correlation coefficient was used. SPSS statistics software (v26) was used for all statistical analysis and a p value of less than 0.05 was considered statistically significant.

RESULTS-

Baseline characteristics



	Age	MOCA	Systolic BP	Diastolic BP	Heart rate
AD	67 ± 8	12 ±6	133 ±21	80 ± 10	68 ± 16
VD	70 ±11	15 ±9	137 ±25	84 ±13	70 ± 10
Control	65 ±10	25 ± 3	133 ±17	82 ±6	67 ±14

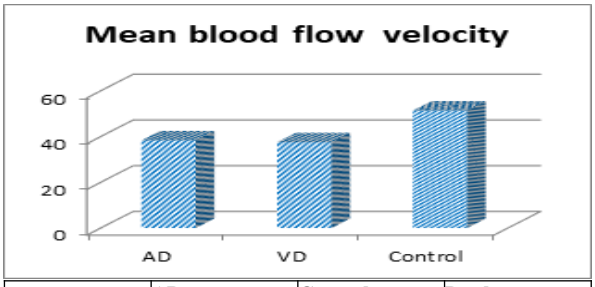
There was no statistical difference between various subgroups among their baseline characteristics.

Transcranial Ultrasound

The MCA MBFV in VD [37.5 ± 9.4, p< 0.05 (CI 95%)] and AD [38.3 ± 7.2, p<0.05 (CI95%)] were significantly lower than in controls (51.4 ± 10.5) but did not vary significantly between AD and VD.

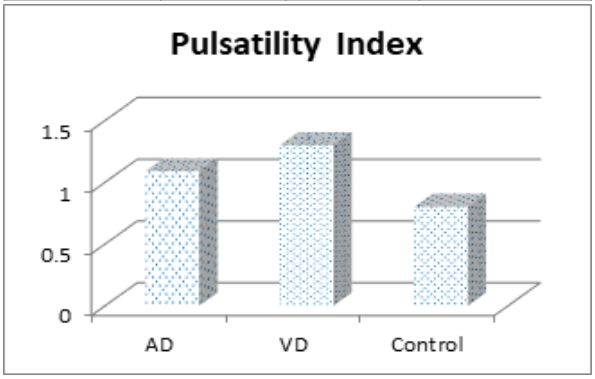
Similarly, PI in VD [1.3 ± .2, p<0.05 (CI95%)] and AD [1.09 ± .2, p< 0.05 (CI 95%] were significantly higher than in controls (.8 ± .2).

Although MCA PI was higher in VD than AD this was not statistically significant (p >0.5). None of the baseline parameters correlated with MCA -MBFV or PI.



	AD	Control	P value
MBFV	38.3	51.4	0.00026
PI	1.09	0.8	0.00049

	AD	VD	P value
MBFV	37.5	38.3	0.43
PI	1.09	1.3	0.99



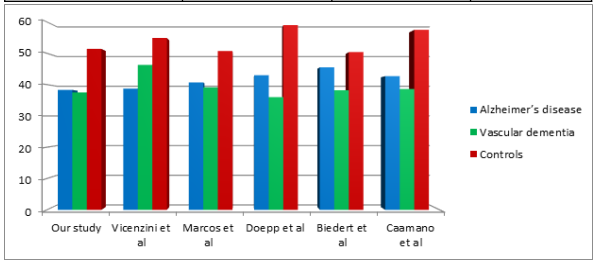
	VD	Control	P value
MBFV	37.5	51.4	0.00007
PI	1.3	0.8	0.00016

DISCUSSION

The vascular burden to Alzheimer's disease pathogenesis is an area of ongoing debate since it is considered primary a degenerative neurocognitive disorder(7). Animal models have noted presence of AD like pathology- beta-amyloid precursor protein (APP) in neighboring astrocytes areas affected by ischemia and neuronal injury (8,9). One notable hypothesis,the cerebrovascular hypothesis of dementia(2)mentions neuronal metabolic, structural and vascular changes occurring in presence of chronic brain hypoperfusion. The sequelae of such maladaptive response end in dysfunction and neuronal death with consequent cognitive disability and disease progression(1).

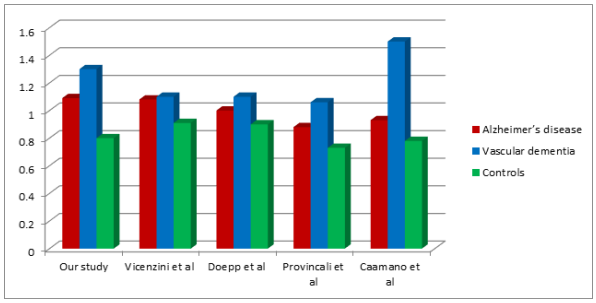
Mean Cerebral Blood Flow (other studies)

Authors (years)	Alzheimer's disease	Vascular dementia	Controls
1)Our study	38.3 ± 7.2	37.5 ± 9.4	51.4 ± 10.5
2)Vicenzini et a[10)	38.7 ± 2.9	46.3± 3.1	54.9 ± 3
3)Marcos et a[11)	40.7 ± 7.5	39.1 ± 10.2	50.7 ± 1.3
4)Doepp et a[12)	43 ± 13	36 ± 8	59 ± 13
5)Biedert et a[13)	45.5 ± 8.8	38.2 ± 9.5	50.4 ± 1.2
6)Caamano et a[14)	42.7 ± 7.2	38.6 ± 13.7	57.5 ± 8.47



Pulsatility Index (other studies)

Authors	Alzheimer's disease	Vascular dementia	Controls
1)Our study	1.09 ± 0.2	1.3 ± 0.2	0.8± 0.2
2)Vicenzini et a[10)	1.08 ± 0.05	1.1 ± 0.5	0.91 ± 0.5
3)Doepp et al(12)	1 ± 0.2	1.1 ± 0.2	0.9 ± 0.2
4)Provincali et a[15)	0.88 ± 0.14	1.06 ± 0.13	0.73 ± 0.15
5)Caamano et a[14)	0.93 ± 0.27	1.5 ± 0.22	0.78 ± 0.15



In our study, there was significant heomodynamic changes similar to previous studies mentioned in AD for both MBFV and PI when compared with healthy controls suggesting a possible vascular component.

The AD and vascular dementia group showed a trend of decreasing MBFV (p< 0.05) (marker for cerebral blood flow) compared to controls. This cerebral hypoperfusion seen in AD would be probably due to amyloid angiopathy (causing lobar and cortical infarcts). The significance of these vascular changes is not certain but some studies have linked amyloid angiopathy with ischemic infarction. In a series of 145 autopsy confirmed AD patients by Olichney et al. there was an increasing incidence of cerebral infarction correlating with the severity of amyloid angiopathy (16). This coupled with evidences for cerebral hypoperfusion early in dementia(17), a vascular insult may contribute to degenerative changes in AD(18). Our hypothesis is that amyloid angiopathy will be the main vascular pathology in

Alzheimer's dementia(19) akin to artherosclerosis (subcortical predominant micro and macro vascular infarct) being the pathogenic driver in vascular dementia .

Both VD and AD had significant increase in PI (marker of cerebrovascular stiffness).Studies have linked accumulation of Aβ in the brain over time to increased arterial stiffness causing reduced compliance with diffuse micro-vascular injury and white matter disease.(20) Furthermore,cerebral Aβ deposition levels were directly proportional to arterial stiffness(21) .This deposited Aβ induces microvascular inflammation resulting in altered coagulation cascade with associations of atherosclerosis, thrombosis, amyloid angiopathy , cerebral hypoperfusion and AD.(22)

Whether vascular lesions in AD are causal to the pathogenesis or an unrelated event to the disease is still debated. The vascular hypothesis of AD was rejected initially due to studies showing inconsistent association of dementia and artherosclesos(23). But these studies done mid-twentieth century did not use statistical analysis and relationship might not have been absolute but rather probabilistic(24). We believe that AD may not be a purely neurodegenerative disease. Many vascular risk factors like diabetes, hypertension, dyslipidemia and smoking are commonly associated with AD similar to VD(25,26). Also studies have shown higher incidence of intracranial artherosclerosis with significant narrowing in autopsied brains of AD and VD but not among other dementia disorders(21,23,24). The combination of high arterial resistance with decreased blood flow in our study also suggests a significant vascular component to both these diseases. In conclusion AD may be the result of mixed pathogenic mechanisms involving both the hemodynamic and neurodegeneration disturbances acting in concert for the development and progression of disease as there is no single unifying paradigm. Hence, primary and secondary prevention of vascular and metabolic risk factors with optimized blood pressure control may help to reduce the overall disease burden.

CONCLUSION

In our study, although TCD did not help to distinguish AD from VD and showed vascular flow and resistance changes in AD similar to VD. The significance of vascular pathology in AD needs further research and evaluation.

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