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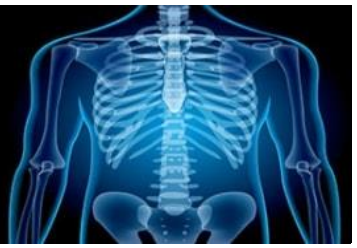

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Assessment of regional cerebral blood flow by ct perfusion in patients of Alzheimer's disease

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Abstract
Background: Alzheimer's disease is a neurodegenerative disorder and is characterized by progressive cognitive decline which starts with an impairment in the ability to recollect recent memories, but eventually affects all the intellectual functions and finally leads to a total dependence for basic functions of daily life culminating into premature death. Dementia can be defined as a clinical syndrome characterized by a cluster of symptoms and signs manifested by difficulties in memory, disturbances in language and other cognitive functions, changes in behavior, and impairments in activities of daily living. Alzheimer is an age-associated degenerative disorder. The burden of Alzheimer's disease and that of dementia *per se* is dependent on age. With increasing life expectancy, the proportion of elderly is increasing and so is the number of patients with Alzheimer's disease associated dementia.
Material and Method: This cross-sectional study was carried out for duration of 18 months at Department of Radiodiagnosis, Era's Lucknow Medical College, Lucknow with an aim to study the parameters *viz*. cerebral blood flow and cerebral blood volume and to correlate the finding of CT perfusion with the clinical score of dementia. The Patients attending adult psychiatry OPD diagnosed as a case of Alzheimer's as per DSM 4 criteria by fulfilling the inclusion criteria and giving informed consent were taken up for study. They were also evaluated for socio-demographic details and illness related variables. After obtaining an informed consent, demographic information, duration and nature of complaints was noted. All the patients were then subjected to CT Perfusion evaluation. Dementia severity was assessed using Clinical Dementia Rating Scale (CDRS).
Result: Age of patients ranged from 60 to 75 years with a mean of 66±4.03 years. Majority of cases were aged between 60 and 69 years (77.5%). There were only 9 patients aged >70 years (22.5%).Forgetfulness (40%), difficulty in thinking (27.5%) and mental confusion (27.5%) were the three most common presenting complaints followed by loneliness (22.5%), agitation (17.5%), depression and mental decline (15% each). Inability to recognize (10%) and hallucinations (7.5%) were among the least common presenting complaints. According to clinical dementia score, a total of 16 (40%) patients were categorized as mild dementia, 20 (50%) as moderate dementia and 4 (10%) as severe dementia respectively. Mean regional cerebral blood flow values for right frontal, left frontal, left temporal, right occipital, right lenticular nucleus and left lenticular nucleus were 39.46±3.82, 39.33±3.87, 45.59±4.66, 45.51±5.02, 45.59±4.76, 45.65±4.49, 42.57±4.23 and 42.87±4.81 ml/100 g/min respectively. Mean global CBF was calculated as 43.32±4.29 ml/100 g/min. Mean regional cerebral blood volume values for right frontal, left frontal, left temporal, right occipital, right lenticular nucleus and left lenticular nucleus were 2.56±0.49, 2.62±0.54, 2.97±0.50, 3.03±0.56, 2.95±0.48, 2.92±0.52, 3.13±0.55 and 3.13±0.55 ml/100 g respectively. Mean global CBF was calculated as 2.91±0.49 ml/100 g/min.
Conclusion: A total of 40 patients of Alzheimer's disease aged 60 to 75 years (Mean age 66±4.03 years; 65% males) were enrolled and subjected to clinical and CT evaluation. According to clinical dementia score, a total of 16 (40%) patients were categorized as mild dementia, 20 (50%) as moderate dementia and 4 (10%) as severe dementia respectively. Mean cerebral blood flow (CBF) ranged from 39.33±3.87 ml/100 g/min (Left frontal region) to 45.65±4.49 ml/100 g/min (Left occipital region) among different brain regions. Mean global CBF was 43.32±4.29 ml/100 g/min.

Keywords: Cerebral, CT perfusion, dementia & clinical

Introduction
More than two and a half million people worldwide are affected by dementia with Alzheimer disease being the most common reason behind.

This number is increasing by addition of nearly 4.6 million new cases every year which translates into one new case in every 7 seconds. By this rate, it is expected that by the year 2040, there will be as many as 81.1 million cases of dementia worldwide [1]. Alzheimer's disease is a neurodegenerative disorder and is characterized by progressive cognitive decline which starts with an impairment in the ability to recollect recent memories, but eventually affects all the intellectual functions and finally leads to a total dependence for basic functions of daily life culminating into premature death. Dementia can be defined as a clinical syndrome characterized by a cluster of symptoms and signs manifested by difficulties in memory, disturbances in language and other cognitive functions, changes in behavior, and impairments in activities of daily living [2].

The patients of Alzheimer's disease as such and those having dementia as a result of Alzheimer's disease are generally elderly. In fact, Alzheimer is an age-associated degenerative disorder. The burden of Alzheimer's disease and that of dementia per se is dependent on age. With increasing life expectancy, the proportion of elderly is increasing and so is the number of patients with Alzheimer's disease associated dementia [3]. It must be kept in mind that while in the year 1990, only 26 nations had more than two million elderly citizens with age 65 years or more, however, by the year 2030, it is expected that nearly 50 countries will have more than two million elderly, thus by the year 2030, the population of elderly is expected to reach up to one billion which will be nearly one-seventh of the total population of the world [4].

As per NINCDSADRDA criteria Alzheimer's disease is defined as a "clinical disease caused by underlying brain changes". Although an ideal diagnosis could be done by direct examination and histopathological assessment only [5]. However, owing to impracticality, brain imaging comes to rescue as a "window on the brain." Undoubtedly, it is essential to understand the underlying pathology before institution of a clinical management protocol and various imaging tools play a crucial role in this direction [6].

CT and MRI scans, which reveal the anatomic structure of the brain, are used to rule out such problems as tumor, hemorrhage, stroke, and hydrocephalus, which can masquerade as Alzheimer's disease. Until the evolution of functional imaging techniques, the focus of basic structural CT and MRI examinations of the head was primarily targeted towards exclusion of organic causes of dementia and to assess the degree and location of brain atrophy. However, in the recent years, imaging has come way forward than playing just an exclusionary role. Imaging has now attained a dominant role in supporting the clinical diagnosis of AD in symptomatic individuals by identifying characteristic patterns (signatures) of structural and functional cerebral alterations [7].

Material and Method

The study was carried out at Department of Radiodiagnosis, Era's Lucknow Medical College, Lucknow for Eighteen months starting from January 2019 to June 2020.

The Patients attending adult psychiatry OPD diagnosed as a case of Alzheimer's as per DSM 4 criteria by fulfilling the inclusion criteria and giving informed consent were taken up for study and were assessed using standardized tools.

They were also evaluated for socio-demographic details and illness related variables. After obtaining an informed consent, demographic information, duration and nature of complaints was noted. All the patients were then subjected to CT Perfusion evaluation. Dementia severity was assessed using Clinical Dementia Rating Scale (CDRS).

Inclusion Criteria

- Patients of the age > 55 Years and of both sexes.
- MMSE score of <20
- Diagnosis of Major Neurocognitive disorder of Alzheimer Type (Alzheimer Dementia) as per DSM diagnostic criteria.
- Patient and/or their attendant giving consent
- Patients receiving symptomatic treatment for AD (cholinesterase inhibitor /memantine)

Exclusion Criteria

- Patients with History of head injury leading to cognitive decline
- Minimal cognitive impairment
- Dementia – major neurocognitive disorder other than Alzheimer. For eg. Vascular Dementia, Frontotemporal Dementia, Dementia of Lewy Body, Parkinson Disease Dementia.
- Those contraindicated for CT Perfusion, *viz.*
- Renal disease
- Heart pacemaker
- Patients who have history of Alcohol Abuse or Past history of Depression
- Psychiatric disorder (including a history of schizophrenia, schizoaffective disorder, bipolar disorder, major depression) insufficient visual or auditory acuity for performing cognitive tests.
- Abnormalities on MRI (WML, territorial or lacunar infarcts, cerebral lesions etc).

Fig 1: Siemens "SOMATOM-force (384 slice) CT machine

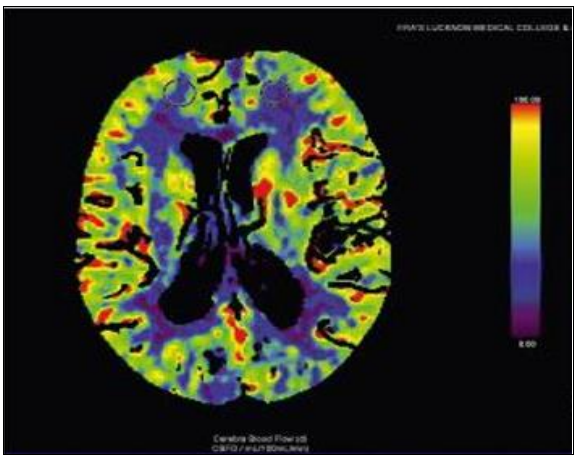


Fig 2a: Frontal cortex

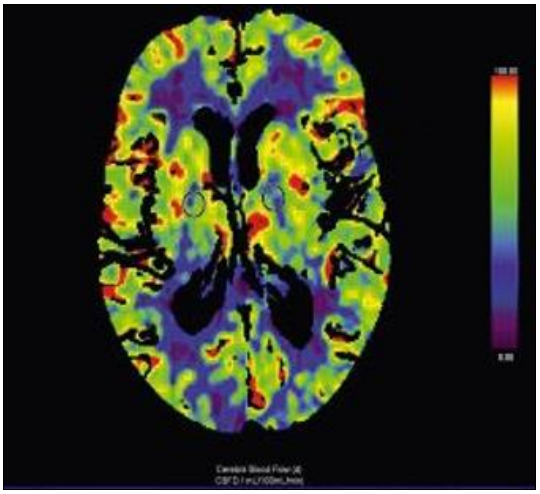


Fig 2b: Lentiform nucleus

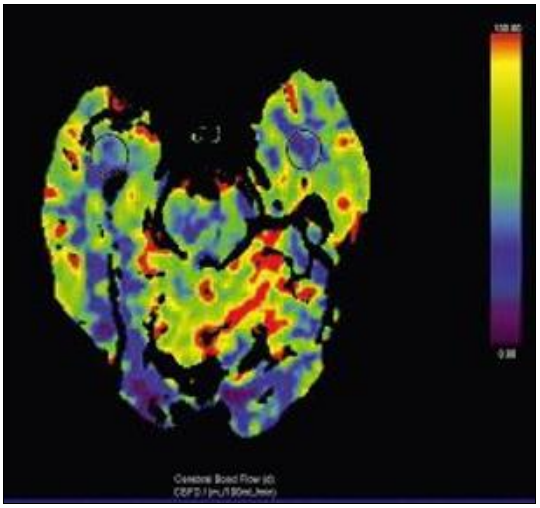


Fig 2c: Temporal cortex

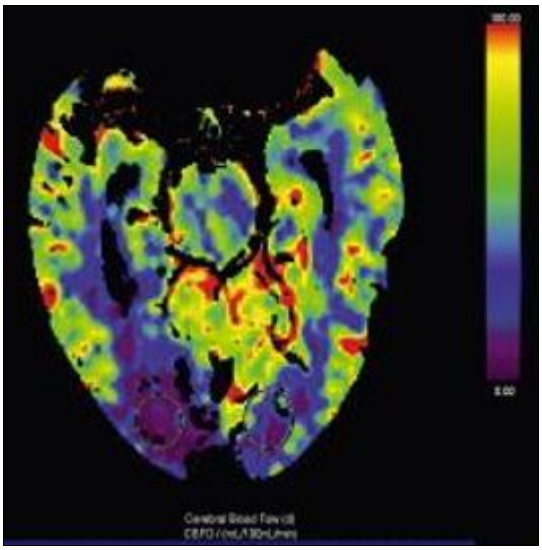


Fig 2d: Occipital cortex

A 65 year old man who presented with memory loss and confusion with diagnosis of Alzheimer's Diease. CT perfusion of the Head images showing cerebral blood volume (CBV) in the brain. Circular ROIs have been placed in the frontal cortex, lentiform nucleus, temporal cortex and occipital cortex.

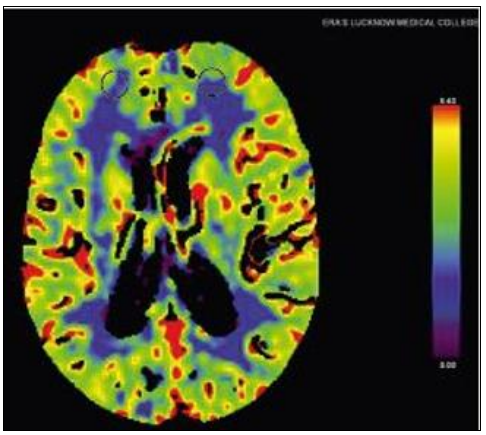


Fig 3a: Frontal cortex

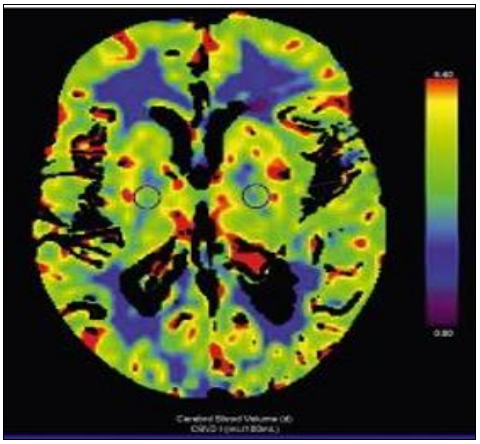


Fig 3b: Lentiform nucleus

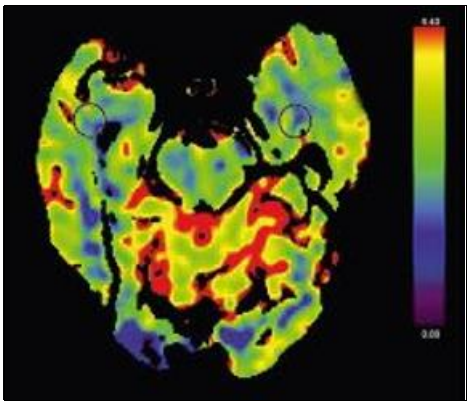
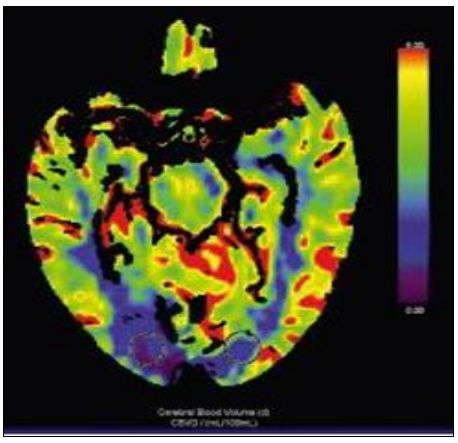


Fig 3c: Temporal cortex



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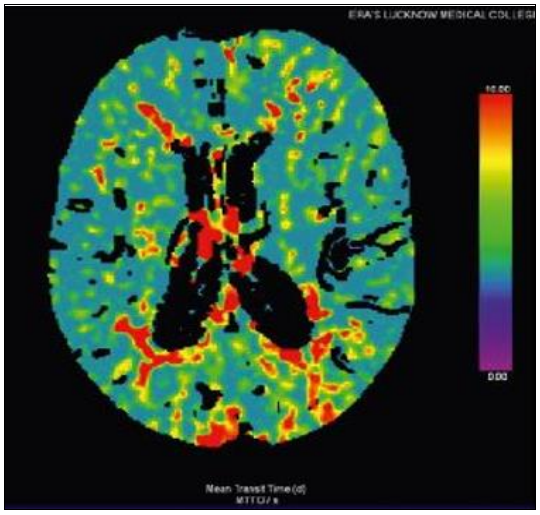

Fig 4a: Mean transit time (MTT)

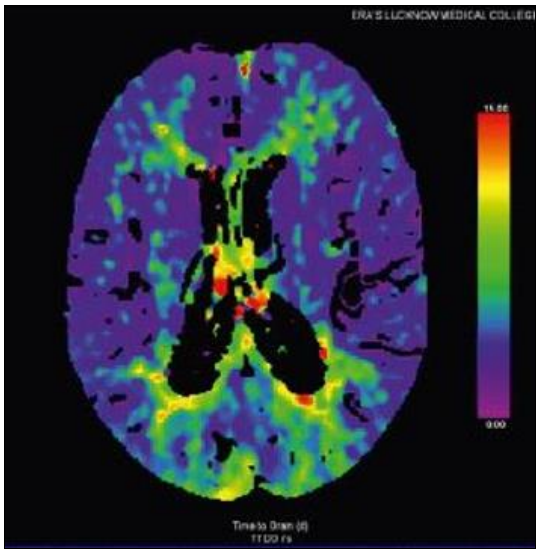

Fig 4b: Time to drain

A 65 year old man who presented with memory loss and confusion with diagnosis of Alzheimer's Diease. CT perfusion of the Head images showing Mean transit time (MTT) and time to drain (TTD) Maps of the brain.

Results

Table 1: Age wise distribution of cases

SN	Age Group	No. of cases	Percentage
1.	60-69 Years	31	77.5
2.	≥70 Years	9	22.5
Mean Age±SD (Range) in years		66±4.03 (60-75) Years	

Age of patients ranged from 60 to 75 years with a mean of 66±4.03 years. Majority of cases were aged between 60 and 69 years (77.5%). There were only 9 patients aged ≥70 years (22.5%).

Table 2: Distribution of cases according to sex

SN	Sex	No. of cases	Percentage
1.	Male	26	65.0
2.	Female	14	35.0
M:F		1.86	

Majority of patients were male (n=26; 65%). There were 14 (35%) females. Sex-ratio of study population was 1.86.

Table 3: Distribution of cases according to chief complaints*

SN	Complaint	No. of cases	Percentage
1.	Agitation	7	17.5
2.	Depression	6	15.0
3.	Difficulty thinking	11	27.5
4.	Forgetfulness	16	40.0
5.	Hallucinations	3	7.5
6.	Inability to recognize	4	10.0
7.	Loneliness	9	22.5
8.	Mental confusion	11	27.5
9.	Mental decline	6	15.0

*Multiple complaints possible

Table 4: Distribution of cases according to duration of complaints

SN	Duration	No. of cases	Percentage
1.	One year	8	20.0
2.	Two to three years	23	57.5
3.	Four to five years	9	22.5
Mean duration ±SD (Range)		2.58±1.24 (1-5)	

Duration of complaints ranged from 1 to 5 years. Majority had a history of two to three years (57.5%) followed by those having a history of four to five years (22.5%) and one year (20%) respectively. Mean duration of complaints was 2.58±1.24 years.

Table 5: Distribution of cases according to occupation

SN	Occupation	No. of cases	Percentage
1.	Farmer/Agriculture	12	30.0
2.	Skilled worker	10	25.0
3.	Housewife	6	15.0
4.	Retired	6	15.0
5.	Shopkeeper/Vendor	4	10.0
6.	Teacher	2	5.0

Table 6: Distribution of cases according to severity of dementia

SN	Severity Grade	No. of cases	Percentage
1.	Mild	16	40.0
2.	Moderate	20	50.0
3.	Severe	4	10.0

According to clinical dementia score, a total of 16 (40%) patients were categorized as mild dementia, 20 (50%) as moderate dementia and 4 (10%) as severe dementia respectively.

Table 7: Perfusion CT measured blood flow in different regions (ml/100 gm/min)

SN	Region	Mean	SD	Minimum	Maximum
1.	Right frontal	39.46	3.82	30.30	44.65
2.	Left frontal	39.33	3.87	31.15	46.98
3.	Right temporal	45.59	4.66	36.33	54.06
4.	Left temporal	45.51	5.02	35.28	53.91
5.	Right occipital	45.59	4.76	35.68	52.92
6.	Left occipital	45.65	4.49	35.32	52.41
7.	Right lenticular nucleus	42.57	4.23	32.56	49.10
8.	Left lenticular nucleus	42.87	4.81	30.83	51.21
9.	Global CBF	43.32	4.29	34.1	49.4

Table 8: Perfusion CT measured blood volume in different regions (ml/100 gm)

SN	Region	Mean	SD	Minimum	Maximum
1.	Right frontal	2.56	0.49	1.68	3.65
2.	Left frontal	2.62	0.54	1.49	3.68
3.	Right temporal	2.97	0.50	2.15	4.02
4.	Left temporal	3.03	0.56	2.11	4.34
5.	Right occipital	2.95	0.48	2.17	3.89
6.	Left occipital	2.92	0.52	2	4.04
7.	Right lenticular nucleus	3.12	0.48	2.16	4.05
8.	Left lenticular nucleus	3.13	0.55	2.06	4.05
9.	Global CBF	2.91	0.47	2.1	3.7

Table 9: Distribution of cases according to Category of Brain Atrophy

SN	Category	No. of cases	Percentage
1.	Mild	18	45.0
2.	Moderate	19	47.5
3.	Severe	3	7.5

Maximum number of cases had moderate brain atrophy (n=19; 47.5%) followed by those having mild atrophy (45%). Only 3 (7.5%) had severe brain atrophy.

Table 10: Association of Severity of Dementia with different clinic-demographic parameters

SN	Parameter	Mild (n=16)	Moderate (n=20)	Severe (n=4)	Statistical significance
1.	Mean Age± SD	65.38±4.15	66.05±4.08	68.25±3.20	F=0.811; p=0.452 (ANOVA)
2.	**Sex**				
	Male	10 (62.5%)	12 (60.0%)	4 (100%)	χ^2=2.418; p=0.299 (Chi-square test)
	Female	6 (37.5%)	8 (40.0%)	0	
3.	Smoking	6 (37.5%)	9 (45.0%)	3 (75.0%)	χ^2=1.818; p=0.403
4.	Duration of disease	2.44±1.21	2.75±1.29	2.25±1.26	F=0.423; p=0.658

No significant association of age, sex, smoking status and duration of disease was observed with severity of dementia (p>0.05).

Table 11: Association of Severity of Dementia with Regional Cerebral Blood flow (ml/100 g/min)

SN	Region	Mild (n=16)		Moderate (n=20)		Severe (n=4)		Statistical significance	
		Mean	SD	Mean	SD	Mean	SD	F	p
1.	Right frontal	42.12	2.29	38.38	3.25	34.23	3.89	14.025	<0.001
2.	Left frontal	41.97	2.84	38.19	3.18	34.46	3.58	12.254	<0.001
3.	Right temporal	48.70	2.82	44.30	4.14	39.54	4.73	12.069	<0.001
4.	Left temporal	48.84	3.40	44.10	4.37	39.25	4.91	11.375	<0.001
5.	Right occipital	48.76	3.08	44.16	4.26	40.05	4.89	10.761	<0.001
6.	Left occipital	48.35	3.39	44.57	4.01	40.30	4.21	8.893	0.001
7.	Right lenticular nucleus	45.36	2.82	41.47	3.54	36.90	4.65	12.140	<0.001
8.	Left lenticular nucleus	45.81	3.39	41.80	4.04	36.49	5.69	10.358	<0.001
9.	Global CBF	46.24	2.70	42.12	3.68	37.65	4.44	12.764	<0.001

Table 12: Association of Severity of Dementia with Regional Cerebral Blood volume (ml/100 g)

SN	Region	Mild (n=16)		Moderate (n=20)		Severe (n=4)		Statistical significance	
		Mean	SD	Mean	SD	Mean	SD	F	P
1.	Right frontal	2.75	0.44	2.52	0.49	2.04	0.31	4.065	0.025
2.	Left frontal	2.85	0.55	2.54	0.48	2.15	0.50	3.576	0.038
3.	Right temporal	3.15	0.44	2.97	0.48	2.26	0.08	6.545	0.004
4.	Left temporal	3.26	0.45	2.98	0.57	2.33	0.39	5.473	0.008
5.	Right occipital	3.19	0.39	2.89	0.47	2.32	0.13	7.379	0.002
6.	Left occipital	3.21	0.45	2.83	0.43	2.20	0.24	9.964	<0.001
7.	Right lenticular nucleus	3.42	0.40	3.03	0.39	2.39	0.20	12.564	<0.001
8.	Left lenticular nucleus	3.47	0.47	3.01	0.42	2.31	0.26	13.130	<0.001
9.	Global CBV	3.16	0.39	2.85	0.42	2.25	0.24	9.085	0.001

Table 13: Association of Severity of Dementia with Brain Atrophy

SN	Atrophy Grade	Mild dementia (n=16)		Moderate dementia (n=20)		Severe dementia (n=4)	
		No.	%	No.	%	No.	%
1.	Mild	13	81.3	5	25.0	0	0
2.	Moderate	3	18.8	15	75.0	1	25.0
3.	Severe	0	0	0	0	3	75.0

χ^2=41.645; p<0.001

Table 14: Association of Severity of Atrophy with Regional Cerebral Blood flow (ml/100 g/min)

SN	Region	Mild atrophy (n=18)		Moderate atrophy (n=19)		Severe atrophy (n=3)		Statistical significance	
		Mean	SD	Mean	SD	Mean	SD	F	p
1.	Right frontal	41.39	2.65	38.72	3.49	32.58	2.55	11.586	<0.001
2.	Left frontal	41.21	3.07	38.54	3.46	33.02	2.61	9.252	0.001
3.	Right temporal	47.83	2.95	44.77	4.61	37.26	1.52	10.754	<0.001
4.	Left temporal	47.78	2.99	44.73	5.25	36.87	1.50	9.281	0.001
5.	Right occipital	47.83	3.14	44.67	4.80	37.93	3.02	8.705	0.001
6.	Left occipital	47.70	3.01	44.81	4.57	38.72	3.42	7.794	0.001
7.	Right lenticular nucleus	44.63	2.90	41.83	3.91	34.88	2.82	11.241	<0.001
8.	Left lenticular nucleus	45.11	3.91	42.11	3.96	34.33	4.54	10.162	<0.001
9.	Global CBF	45.43	2.86	42.52	4.08	35.70	2.60	10.907	<0.001

Table 15: Association of Severity of Brain Atrophy with Regional Cerebral Blood volume (ml/100 g)

SN	Region	Mild atrophy (n=18)		Moderate atrophy (n=19)		Severe atrophy (n=3)		Statistical significance	
		Mean	SD	Mean	SD	Mean	SD	F	P
1.	Right frontal	2.85	0.47	2.40	0.35	1.90	0.15	10.192	<0.001
2.	Left frontal	2.92	0.55	2.45	0.38	1.91	0.19	8.865	0.001
3.	Right temporal	3.25	0.51	2.83	0.33	2.23	0.08	10.031	<0.001
4.	Left temporal	3.42	0.53	2.80	0.29	2.14	0.03	18.117	<0.001
5.	Right occipital	3.24	0.47	2.78	0.32	2.26	0.07	11.583	<0.001
6.	Left occipital	3.21	0.50	2.77	0.34	2.08	0.09	12.013	<0.001
7.	Right lenticular nucleus	3.40	0.44	2.99	0.34	2.32	0.16	12.626	<0.001
8.	Left lenticular nucleus	3.39	0.47	3.02	0.46	2.23	0.25	9.093	0.001
9.	Global CBV	3.21	0.43	2.75	0.30	2.13	0.06	15.295	<0.001

Mean cerebral blood volume values were maximum in patients with mild atrophy and minimum in those with severe atrophy for all the brain regions. Global cerebral blood volume values were 3.21±0.43, 2.75±0.30 and 2.13±0.06 ml/100 mg respectively for mild, moderate and severe atrophy respectively, thereby showing a significant intergroup difference (p<0.001).

Discussion

Brain imaging plays an important role in diagnosis of Alzheimer's disease and its differential diagnosis to rule out other causes of dementia. Until recently, imaging techniques like Computed tomography and Magnetic resonance imaging were limited only to study the structural changes related with AD [8]. As far as functional changes are concerned, use of techniques like Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are preferred over the conventional imaging tools like CT and MRI. However, in the recent years, with rapid advancements in the field of computed tomography and magnetic resonance imaging not only the resolution of images produced by these modalities has changed but with the addition of newer techniques, they have become capable of assessing the functional images too [9].

Perfusion imaging is a game-changing radiological investigation that has placed the otherwise disadvantage of computed tomography and magnetic resonance imaging in their disability to carry out functional evaluation of tissue vascularity by enabling them to be able to measure the changes in tissue characteristics following administration of an intravenous contrast medium (IVCM) [10]. The technological advancements in the field of computed tomography and magnetic resonance imaging along with availability of post-processing software have helped to make perfusion imaging as the means to carry out functional imaging with the help of widely available computed tomography and magnetic resonance imaging and reducing the dependency on the otherwise less commonly available PET and SPECT investigations [11].

Perfusion CT or MRI, work by sequential acquisition of images of the desired tissue following administration of a contrast medium, Following intravenous administration, the contrast medium passes through the vascular system and reaches to the desired tissue through tissue vasculature and then returns back into the vascular system and finally is excreted out through urinary system [12]. However, during this course, changes in tissue density take place which are measured with the help of variation in signal intensity while the contrast medium moves through the tissue of interest. Perfusion CT/MRI record these semi quantitative measures of perfusion of contrast medium through the tissue and thus give an estimate of tissue vascularity and thus provide an idea about the functional vascularity of the desired region of interest (ROI) [13].

Conclusion

A total of 40 patients of Alzheimer's disease aged 60 to 75 years (Mean age 66±4.03 years; 65% males) were enrolled and subjected to clinical and CT evaluation. According to

clinical dementia score, a total of 16 (40%) patients were categorized as mild dementia, 20 (50%) as moderate dementia and 4 (10%) as severe dementia respectively. Mean cerebral blood flow (CBF) ranged from 39.33±3.87 ml/100 g/min (Left frontal region) to 45.65±4.49 ml/100 g/min (Left occipital region) among different brain regions. Mean global CBF was 43.32±4.29 ml/100 g/min. Mean cerebral blood volume (CBV) ranged from 2.56±0.49 ml/100 g (Right frontal region) to 3.13±0.55 ml/100 g (left lenticular nucleus region) among different brain regions. Mean global CBV was 2.91±0.47 ml/100 g. Mild, moderate and severe brain atrophy was seen in 18 (45%), 19 (47.5%) and 3 (7.5%) cases respectively. The findings of study showed the relationship between cognitive impairment according to the Clinical Dementia Rating and perfusion parameters. Cerebral Blood Flow and Cerebral blood Volume which cannot be acquired by conventional CT and MRI methods, can be acquired by the CT Perfusion. Cerebral hypoperfusion is associated with accelerated cognitive decline and an increased risk of dementia. CT Perfusion scan will obtain in more significant role in the early diagnosis and treatment of Alzheimer's disease.

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