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Long Loop Reflexes in Patients with Probable Alzheimer's Disease and Frontotemporal Dementia of Behavioral Type

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Abstract

Introduction: Dementia is a leading cause of morbidity in view of increasing expectation of life all over the world. With reference to Pharmacotherapy as well as non-pharmacological treatment options to be effective, diagnosis and therapy should be initiated very early. Currently, Diagnosis is made on clinical grounds and there is gross time delay. Therefore, there is serious need for cheap, easily accessible biomarker which improves diagnostic accuracy. The two common degenerative dementia's are AD and FTD. As AD is posterior, the frontal sub cortical circuits are preserved till late stage of disease as against in FTD. Using this rationale we tried to look for differential involvement of LLR2 in the above two conditions and controls.

Objective: There is serious need for cheap, easily accessible biomarker which improves diagnostic accuracy. The two common degenerative dementias are AD and FTD. As AD is posterior, the frontal sub cortical circuits are preserved till late stage of disease as against in FTD. Using this rationale we tried to look for differential involvement of LLR2 in the above two conditions and controls.

Patients and Methods: 20 patients diagnosed as mild to moderate probable AD, FTD, underwent all mandatory dementia work up including neuropsychological work up and LLR. 20 healthy controls were also evaluated with LLR. Data analysis was done using SPSS software licensed in department of biostatistics.

Observation: LLR was preserved in 70% of AD patients, 90% in normal controls and absent in all FTD patients.

Discussion: Currently, histopathology and genetics is the only tools for the diagnosis of definite types of degenerative dementia, which involves the problems of feasibility and availability. Absent LLR will be an additional biomarker in favor of FTD and presence of LLR will favor AD in mild to moderate cases of probable AD and FTD as per consensus criteria.

Conclusion: LLR 2 confirms as an additional biomarker in very early diagnosis of FTD and AD supporting our pilot study published previously.

Keywords: Alzheimer's disease; Biomarker; Frontotemporal dementia; Long loop reflexes

Introduction

We have now started having a longer expectation of life. This has to be a resource for Nation building like the way it was several centuries ago when the knowledge and wisdom of the elder persons was the guiding light of the Nation. But now we are worried about people living longer with serious diseases the most important being Dementia. As per WHO statistics, the number of people suffering with dementia will almost double every 20 years, of which maximum burden is likely to be in India and China [1-3]. As per report of United Nations Population Division (UN 2011) percentage of elderly population in India will rise from 8% in 2010 to 19% in 2050.Early diagnosis of dementia at MCI stage is important as it allows planning methods to slow down to the process progressing to dependency stage [4,5]. There is need to develop biomarkers which are inexpensive, non-invasive and easily available to the common man. In this study we have made an attempt to use Long Loop Reflex (LLR) as an innovative new, simple, cheap and easily available biomarker for the diagnosis of early dementia of Alzheimer (AD) and Fronto-Temporal type (FTD). Although dementia can be classified definitely on basis of neuropathology during autopsy and rarely with biopsy in a living patient it is generally a clinicoradiological diagnosis who's precision can be improved by biomarkers.

Biomarkers

Biomarker act as add on evidence for *in vivo* diagnosis and pathological process confirmation to some extent and improves diagnostic sensitivity and specificity of disease. A diagnostic criterion for dementia now involves biomarkers. Early diagnosis of the exact type of dementia is important to Reverse, delay, and adapt to the mental, economic and social burden by these diseases .Criteria for establishing a good biomarker for dementia involves the fallowing. Should have role in physiological aging processes , rationale on basic pathophysiological processes of the brain, might influence pharmacological intervention, display high sensitivity and specificity for the disease as compared with

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related disorders Allow measurements repeatedly over time, Allow reproducibility in laboratories worldwide ,Should be measurable in non-invasive, easy-to-perform tests, Should not cause harm to the individuals being assessed, Tests should be inexpensive and rapid ,Changes should allow differentiation of controls and Define good cut-off values to distinguish diseases [6].

Long loop reflex

On subjecting the voluntarily contracting muscle to maximum limits, two responses can be elicited. First response is spinal stretch reflex whereas second response is of supra-spinal and transcortical origin with a long latency stretch reflex from thumb [7]. In non-human primates the presence of reflex is well established. There were initial dispute and thoughts about origin of this reflex as spinal stretch or supra-spinal transcortical. Lee and Tatton in 1975 described three components of this long loop reflex as M1, M2 and M3. Of these reflexes M1 was found to be spinal stretch reflex and M3 was very inconsistent and voluntary response mediated by cerebellum. M1 is seen at 45-60 milliseconds, M 2 at 60-90 ms and M 3 at 90-110 ms. Thus M 2 is a reflex useful to study transcortical long loop reflex [8,9]. LLR 2 afferents are Group 2 fibers. Then *via* dorsal column it reaches nucleus Cuneatus, then through leminiscal pathway to sensory cortex, from there to motor cortex and then *via* corticospinal tracts to motor neuron. After the conditioning voluntary contraction, the muscle lengthens and stretches the spindles. This increases the motor neuron excitability. The electrically evoked reflex bypasses the spindle mechanism and gives a measure of central excitability [10]. LLR 2 therefore is trans-cortically mediated and is consistent (Figure 1) [11-14].

The rationale was as AD involves medial temporal regions of the brain in mild to moderate stage it is unlikely to be affected in the early stage unlike FTD where the frontal subcortical circuits degenerate early and therefore more likely to be abnormal. If differentially affected might serve as an additional tool in the diagnostic armamentarium.

Patients and Methods

Prospective hospital based study conducted at Department of Neurology NIMHANS at Bengaluru; India This study included 20 patients each of AD, FTD and 20 controls. The study period was from December 2015 to December 2017 with total duration of 24 months. The study was approved by the Institutional Ethics Board. Informed written consent was obtained from all the participants and the information was kept confidential.

Objectives

The objective of this study was to explore whether differential involvement of LLR2 in the Alzheimer's disease and Frontotemporal demenftfia condfiftfions and conftrofls [15,16].

Inclusion criteria was mild to moderate probable dementias of AD & FTD; age between 40-70 years with HMSE score- 20-24. Exclusion Criteria was Mixed & advanced dementia, HMSE score<20, Not amenable for neuropsychological evaluation. History of past CNS disorders (head injury, mass lesion or CVA). Incidentally detected structural lesions on imaging and Patient with neuropathy of any cause. There were 20 healthy controls age, gender matched.

Both patients and controls underwent detailed history and clinical evaluation. Age, Gender, Education, Occupation, duration of illness, chronology and progression of symptoms, Significant co-morbidities like hypertension, diabetes, IHD, dyslipidemia, thyroid illness, nutritional deficiency in past ,Family history, smoking, alcohol , details of medication used were all obtained. Body Mass Index, blood pressure, general physical and systemic examination of Nervous system and all other systems was done. Dementia mandatory investigations like Complete Hemogram, Renal Function Test, Liver Function Test, Serum Electrolytes- Sodium and potassium, Fasting Blood Glucose, Thyroid Function Test, Vitamin B 12, Serum VDRL test, HIV. Hindi Mental Status Examination (HMSE) and Neuropsychology evaluation using Addenbrook's Cognitive Examination (ACE) , Colour Trail Test – 1,Colour Trail Test – 2,Bender Gestalt Test /Complex figure Test copy and Recall trials, Spatial Span, Verbal N Back Test and Rey 's Auditory Verbal Learning Test (AVLT). Patient underwent preferably MRI imaging of Brain (CT Brain if any contraindications to MRI or non-cooperative patient).

Nihon Kohden Neuropack ENMG machine was used for LLR. Short latency reflex and long loop reflex muscle responses were elicited by median nerve stimulation and recorded from thenar muscles on the affected and non-affected side using surface electrodes. The patient was asked to contract thenar muscles by opposing the thumb to the fifth finger so that a full EMG interference pattern could be seen on the screen. During electrical stimulation muscle contraction was maintained at ~20% of maximum force. Median nerve was stimulated at 3 Hz frequency with supramaximal current for 0.2 s. 200 averages were done at room temperature. High frequency filter was set at 3–5 Hz and low at 2 Hz, EMG of thenar muscles was filtered, and responses averaged 200 times (Figure 2) [17].

Both upper limbs were tested. Upper limbs were chosen as results in lower limbs are often inconsistent. Pick up electrodes were kept at C4 or C3 based on the side being tested. Opposite thenar muscles were fixed with electrodes to pick up discharges if any which might

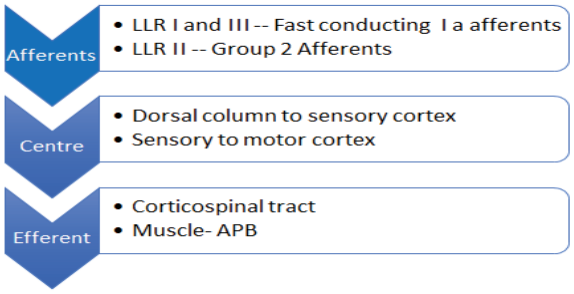

Figure 1: LLR Pathway.

METHOD

NO.	ELECTRODES	RECORDING SITE	CALIBERATION SENSITIVITY
1	C4—Fz/ C3— Fz	CORTEX	20 uV/div
2	X1—X2	BICEPS	1 milivolt/div
3	X3—X4	I/L THENAR (APB)	5 uV/div
4	X5—X6	C/L THENAR (APB)	1 milivolt/ div

Figure 2: Depicts electrode placement.

occur if there is statistically significant cortical hyper excitability. The onset latencies were measured from the baseline. The obtained graphs of LLR were evaluated for presence or absence of waveform and their association with neuropsychology, clinical and imaging data.

Statistical analysis

The data collected with above method was entered in the Microsoft Excel spreadsheet. Statistical analysis was done using SPSS software licensed in department of biostatistics. Data was expressed using descriptive statistics such as for continuous variables, mean and standard deviation and for categorical variables, frequency and percentage.

Comparison between continuous variables was done using independent student t' test or Mann Whitney test and Fisher's exact test for categorical variables. Correlation between two continuous variables was done using spearman/Pearson correlation co-efficient and between one categorical and other continuous variable by point bi serial correlation test. p value <0.05 considered statistically significant.

Observation

Demographic characteristics: patient and control

Table 1.1 shows mean age of Cases (AD and FTD) was 59.93 ± 7.83 (range 51 to 68) and in control it was 63.65 ± 5.9 (range 57 to 69). The comparison of data with t-test shows no significant difference. Thus, case and control groups are age matched.

Table 1.1 and Figure 3 shows, out of 40 cases, 24 (60%) were males and 16 (40%) were females. In control group, out of 20, 14 (70%) were males and 6 (30%) were females. The chi-square test showed no significant difference (p value 0.449).

The mean age of the patients with Alzheimer Disease was 61.8 ± 8.1 years (range 42 to 70) and that of Fronto-Temporal Dementia was 58.05 ± 7.1 years (range 40 to 69). The age was not significantly different in both groups (U value=0.071).

The Mean duration of illness in Fronto-Temporal Dementia, it was 2.5 ± 2.0 years (range 0.5 to 8 years) whereas in the Alzheimer Disease was 1.9 ± 1.42 years (range 0.25 to 5 years). The duration of illness was not different in both groups (U=0.791).

The total years of education in FTD and AD group was 12.6 ± 3.4 and 12.2 ± 3.1 years respectively. This shows that education was matched population in the study groups as difference was not statistically different (U value=0.404) (Figure 4).

The number of patients educated till 12th standard were 11 (57.9%) and 8 (42.1%) above 12th (graduation) in each in FTD and AD. One patient in each AD and FTD group was illiterate.

The results in Tables 1.1-1.3 shows that the study population was age, sex and education matched.

Clinical characteristics in study groups (FTD and AD)

Various clinical features in AD and FTD were noticed during study and their significance with each disease was compared (Table 2).

Apathy and low mood was found in 11 out of 20 patients (55%) of FTD and 2 out of 20 patients (10%) of AD. It was not noted in 9 patients of FTD (45%) and 18 patients of AD (90%). The Fisher t test showed significant value (p value=0.006).

Parameter		Cases (n=40) Mean ± SD	Control (n=20) Mean ± SD	Test
Age		59.93 ± 7.83	63.65 ± 5.90	0.66 (t-test)
Sex	Male	24	14	0.44 (chi-square test)
	Female	16	6	
	Female	16	6	

Table 1.1: Demographic characteristics between cases and control.

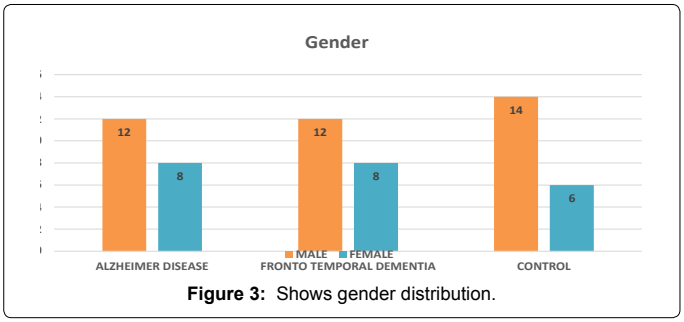

Figure 3: Shows gender distribution.

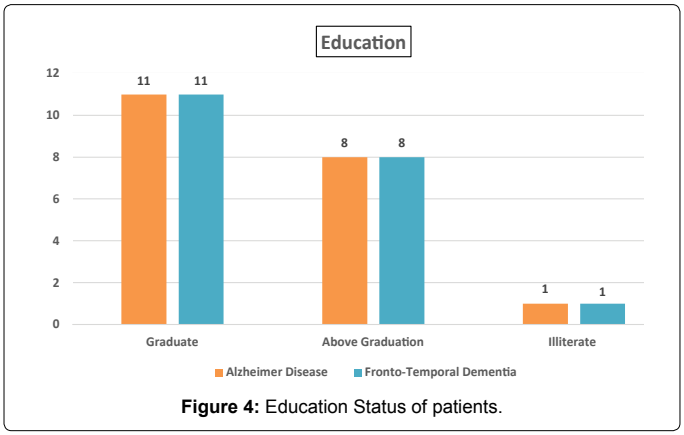

Figure 4: Education Status of patients.

Variables (Years)	Study Groups FTD (n=20) Mean ± SD Median (Range)	Study Groups AD (n=20) Mean ± SD Median (Range)	U-value#
Age	58.05 ± 7.17 58.5 (40-69)	61.80 ± 8.18 62 (42-70)	0.071
Duration of Illness	2.5 ± 2.0 1.75 (0.5-8)	1.9 ± 1.4 1.5 (0.25-5)	0.791
Years of Education	12.6 ± 3.4 12 (4-18)	12.25 ± 3.1 12 (3-16)	0.404

Mann Whitney U test

Table 1.2: Demographic characteristics between case group (FTD and AD).

Education	Study Groups FTD	Study Groups AD	p-value*
Till Graduation	11	8	1.000
Above Graduation	11	8	

*Chi-square Test

Table 1.3: Educational profile in FTD and AD.

Aggression and emotional lability was seen in 11 out of 20 patients (55%) of FTD and 3 out of 20 patients (15%) of AD. The Fisher t test showed significant value (p value=0.006).

Inattention was seen in 12 of FTD (60%) and 3 of AD (15%) patients. It was not found in 8 of FTD (40%) and 17 of AD patients (85%). The p value by chi-square was significant (p=0.003).

Executive dysfunction was noted in 7 FTD patients (35%) and

1 AD patient (5%) and absent in 13 FTD (65%) and 19 AD patients (95%).The p-value was 0.044 which suggests significant impairment in FTD group than AD.

Language impairment was seen in 9 of 20 FTD patients (45%) in the form of word retrieval difficulty and non-fluent aphasia. It was seen in 2 patients of AD (10%) as anomia. It was not found in 11 of FTD (55%) patients and 18 of AD patients (90%) (Figure 5 and Table 2).

Working memory was affected in 9 of FTD patients (45%) and 19 of AD patients (95%). This shows significant affection of working memory in Alzheimer Disease (p value=0.001).

Calculation was affected in 3 of FTD patients (15%) and 10 patients of AD patients (50%). The p value is significant (p=0.041). This shows AD patients have impairment of calculation as compared to FTD group.

Visuo-spatial dysfunction was noted in 1 patient of FTD (5%) and 10 patients of AD (50%). It was not seen in 19 patients of FTD and 10 of AD patients. The p value was significant (p=0.003) in AD as compared to FTD group (Table 2 and Figure 6).

The various other clinical features like psychosis, urinary incontinence, Semantic and recent memory, dressing apraxia were compared in both FTD and AD group and found to be insignificantly impaired.

Risk factors: fronto-temporal dementia and alzheimer disease

Table 3 shows the common risk factor for dementia and comparison among AD and FTD for the same.

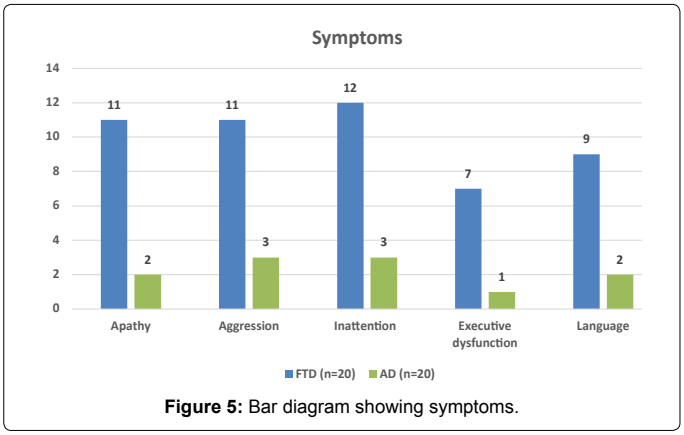

Figure 5: Bar diagram showing symptoms.

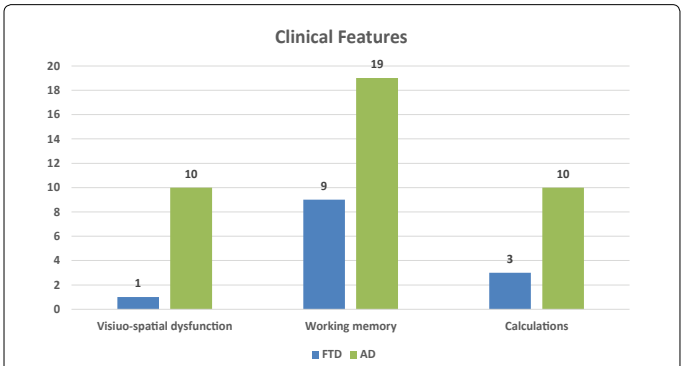

Figure 6: Bar diagram depicting clinical features.

Clinical Feature		Clinical Diagnosis		Chi-square Test
		FTD	AD	
Apathy/Low mood	Yes	11	2	0.006
	No	9	18	
Aggression/Emotion lability	Yes	11	3	0.019
	No	9	17	
Psychosis	Yes	7	2	0.127
	No	13	18	
Inattention	Yes	12	3	0.003
	No	8	17	
Urinary Incontinence	Yes	1	1	1.000
	No	19	19	
Language	Yes	9	2	0.031
	No	11	18	
Working memory	Yes	9	19	0.001
	No	11	1	
Semantic memory	Yes	1	0	1.000
	No	19	20	
Remote memory	Yes	0	3	0.231
	No	20	17	
Calculations	Yes	3	10	0.041
	No	17	10	
Dressing apraxia	Yes	0	3	0.231
	No	20	17	
Visio-spatial dysfunction	Yes	1	10	0.003
	No	19	10	
Executive dysfunction	Yes	7	1	0.044
	No	13	19	

Table 2: Clinical feature comparison in FTD and AD.

Parameter		Clinical Diagnosis		Chi-square test
		FTD	AD	
Diabetes	Yes	6	1	0.091
	No	14	19	
Hypertension	Yes	9	5	0.185
	No	11	15	
Addictions	Yes	4	1	0.342
	No	16	19	
Family History	Yes	7	8	0.744
	No	13	12	

Table 3: Risk factor in FTD and AD.

In Alzheimer disease, 6 out of 20 (30%) were found to have diabetes mellitus and rest 14 (70%) had no diabetes. In FTD, only 1 (5%) patient had diabetes mellitus and 19 (95%) patients had no diabetes. The occurrence of diabetes was not statistically significant among the two groups (p value=0.091).

Among Alzheimer disease, 5 out of 20 (25%) patients were found to have hypertension and rest 15 (75%) had no hypertension. In FTD, only 9 (45%) patients had hypertension and 11 (55%) patients had no hypertension. This difference was statistically insignificant (p value=0.185).

Addiction for smoking and alcohol was asked in case groups. 4 out of 20 (20%) FTD patients were addicted and rest 16 (80%) patients were not addicted. In Alzheimer disease, only 1 (5%) patient was addicted and 19 (95%) patients were not addicted. The difference was not statistically significant (p value=0.342).

In Alzheimer disease, 8 out of 20 (40%) had family history of illness of dementia, the other 12 patients (60%) denied family members having neurocognitive symptoms. In FTD group, 7 (35%) patient had family members with neurocognitive symptoms and rest 13 (65%) patients had no family history of neurocognitive symptoms.

The above Table shows the various common risk factors like diabetes mellitus, hypertension, addictions and family history were not significantly present in study groups.

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The above table shows the various common risk factors like diabetes mellitus, hypertension, addictions and family history were not significantly present in study groups.

Laboratory evaluation: dementia mandatory blood investigations

The laboratory tests consisting of Hemogram, Liver Function Tests (LFT), Renal Function Tests (RFT), electrolytes, fasting blood glucose, lipids, vitamin B 12, Thyroid Function Tests (TFT), VDRL and HIV ELISA (with consent) were carried. No test had statically different value for AD or FTD group (U value<0.05) (Table 4).

Hindi mental status examination (HMSE) score

The Table 5 shows comparison of HMSE scores in FTD and AD group. Mean score in both was 24 ± 3 and the difference in both groups was not statistically different (p=0.913).

Neuropsychological evaluation

The NIMHANS neuropsychological test battery was used for all patients to assess the cognitive functions. All tests were administered to the patients. Not all patients were amenable for detailed neuropsychological evaluation. Addenbrook's Cognitive Examination (ACE) –Indian version by Mathurnath et al. was conducted in all the patients.

Table 6.1 shows various components of Addenbrook's Cognitive Examination and total score comparison in both FTD and AD groups.

Orientation score in FTD was 10.55 ± 5.36 (median 12; range 0-18) and in AD score was 11.65 ± 4.4 (median 12; range 3-18). Memory score in FTD was 14.3 ± 10.25 (median 14; range 0-31) and in AD score was 9.95 ± 6.43 (median 9; range 0-25). Verbal fluency score in FTD was 3.70 ± 2.84 (median 4; range 0-9) and in AD score was 5.80 ± 3.38 (median 5; range 0-12). Language score in FTD was 16.9 ± 5.92 (median 19; range 6-25) and in AD score was 19.4 ± 6.77 (median 20; range 5-31). Visuospatial Dysfunction score in FTD was 2.5 ± 1.98 (median 2; range 0-8) and in AD score was 2.45 ± 2.23 (median 1.5; range 0-8). ACE total score in FTD was 47.95 ± 21.12 (median 52; range 12-77) and in AD score was 49.25 ± 18.38 (median 51; range 15-89). The p values were not significant for any of the score in the FTD or AD group.

Parameters	Study Groups		U- value*
	FTD (n=20)	AD (n=20)	
	Mean ± SD		
	Median (Range)		
Haemoglobin (gm/dl)	13 ± 1	13 ± 1	0.261
	13 (11-16)	13 (11-16)	
White Blood Cells (gm/dl)	7576 ± 2237	7400 ± 1997	0.914
	7450 (3400-11800)	7150 (3300-10900)	
Platelets (x 10^3 gm/dl)	253 ± 63	257 ± 84	0.745
	231 (180-450)	260 (138-428)	
Creatinine (gm/dl)	1 ± 0.3	1 ± 0.1	0.681
	1 (0.6-1.8)	1 (0.7-1.3)	
Fasting Glucose (gm/dl)	97 ± 17	102 ± 21	0.481
	100 (70-122)	105 (67-139)	
Serum Sodium (mEq/L)	137 ± 4	137 ± 4	0.849
	137 (130-146)	137 (130-145)	
Vitamin B 12 (pg/mL)	502 ± 273	550 ± 387	0.903
	438 (38-954)	410 (149-1500)	
TSH (mIU/L)	3.2 ± 3.1	3.2 ± 3.0	0.968
	2.3 (0.3-14.2)	2.6 (0.3-14.2)	

*Mann-Whitney U Test

Table 4: Dementia Mandatory Blood Investigation in FTD and AD.

Parameter HMSE	Study Groups		*U value
	FTD (n=20)	AD (n=20)	
Mean ± SD	24 ± 3	24 ± 3	0.913
Median	24	24	
Range	20-29	20-30	

Table 5: HMSE score in FTD and AD.

Components	Study Groups		U value#
	FTD (n=20)	AD (n=20)	
	Mean ± SD		
	Median (Range)		
Orientation	11 ± 5	12 ± 4	0.654
	12 (0-18)	12 (3-18)	
Memory	14 ± 10	10 ± 6	0.203
	14 (0-31)	9 (0-25)	
Verbal Fluency	4 ± 3	6 ± 3	0.056
	4 (0-9)	5 (0-12)	
Language	17 ± 6	19 ± 7	0.261
	19 (6-25)	20 (5-31)	
Visuospatial Dysfunction	3 ± 2	2 ± 2	0.794
	2 (0-8)	2 (0-8)	
Total Score	48 ± 21	49 ± 18	0.957
	52 (12-77)	51 (15-89)	

Mann Whitney U test

Table 6.1: Addenbrook's Cognitive Examination (ACE) in FTD and AD.

This is the ratio of addition of Verbal fluency (V) and Language (L) with Memory (M) and Orientation (O). This ratio was studied in various studies with variable results and was found to be sensitive to differentiate between the AD and FTD (Table 6.2).

In this study, VLMO ratio was calculated by using Addenbrook's Cognitive Examination (ACE) Indian version (65). Result showed mean VLMO ratio in FTD was 0.9 ± 0.6 and 1.2 ± 0.3 in AD. The median value of VLMO ratio was 0.7 for FTD and 1.2 for AD. The range of value of VLMO in FTD was 0-2.5 and 0.65-2.3 in AD. Mann-Whitney U test was statistically significant (p value= 0.003).

NIMHANS neuropsychology battery test

All patients of FTD and AD group were administered the NIMHANS designed neuropsychological battery for Elderly (NNB-E).

Table 6.3 shows the different numbers of patient who were amenable for detailed neuropsychological evaluation by trained neuropsychologists using NIMHANS neuropsychology Battery test.

The above Tables 6.4 and 6.5 shows different neuropsychological tests and their results as mean value with standard deviation, median value and range of results. Mann-Whitney Test was used for assessing the results. It was found to be statistically significant in AVLT trial-4 (U=0.013), rest of the tests were not significantly associated with study group (U value>0.05).

Long loop reflex and its comparison

Table 7 shows out of total 40 patient, Long Loop Reflex (LLR) was absent in 26 patient (65%) and present in 14 patients (35%). In control group, LLR was present in 18 (90%) and absent 2 (10%) healthy people. The difference between the two groups was statistically significant as p-value was 0.001. This supports the hypothesis that Long Loop Reflex (LLR) is affected in cases as compared to control population (Figure 7).

Out of 20 patients of FTD, all had absent LLR (100%), whereas in AD 6 out of 20 patients (30%) had absent LLR. In Alzheimer Disease, in 14 (70%) patients LLR was present. In control groups, out of 20, 2 (10%) healthy people had absent LLR and in rest 18 people (90%) LLR was present.

Parameters	Study Groups		Mann-Whitney U Test*
	FTD (n=20)	AD (n=20)	
Mean ± SD	0.9 ± 0.6	1.2 ± 0.38	0.003
Median	0.7	1.2	
Range	0.0-2.5	0.65-2.3	

Table 6.2: VLMO Ratio in FTD and AD.

Test	FTD (n*)	AD (n*)
Colour trail 1	16	13
Colour trail 2	16	13
CFT COPY	16	17
CFT IR	16	17
CFT DR	16	18
Spatial Span Forward (SS-F)	17	16
Spatial Span Backward (SS-B)	13	13
N Back-1	13	11
N back-2	12	11
AVLT trials (1-5), AVLT- IR and DR	14	9

n * = Number of the patients amenable for test

Table 6.3: Number of patients of FTD and AD amenable for detailed neuropsychology testing.

Tests	Study Groups		U- value#
	FTD (n=20)	AD (n=20)	
	Mean ± SD		
	Median (Range)		
Colour trail 1	154 ± 160	189 ± 133	0.324
	93 (0-600)	117 (38-420)	
Colour trail-2	166 ± 146	228 ± 193	0.451
	177 (0-420)	180 (0-659)	
Complex Figure of RAY CFT COPY	22 ± 11	18 ± 12	0.234
	20 (8-36)	18 (0-35)	
Complex Figure of RAY Immediate Recall (IR)	9 ± 8	5 ± 9	0.101
	8 (0-25)	2 (0-33)	
Complex Figure of RAY Delayed recall (DR)	8 ± 8	5 ± 8	0.126
	7 (0-25)	2 (0-33)	
Spatial Span Forward SS-F	6 ± 4	5 ± 2	0.308
	6 (2-14)	5 (3-12)	
Spatial Span Backward SS-B	4 ± 2	3 ± 2	0.222
	4 (1-7)	3 (0-6)	

U- value# --Mann-Whitney Test

Table 6.4: Neuropsychological Tests in FTD and AD.

Tests	Study Groups		U- value#
	FTD (n=20)	AD (n=20)	
	Mean ± SD		
	Median (Range)		
N Back-1	6 ± 3	7 ± 2	0.618
	7 (2-11)	8 (3-9)	
N Back -2	5 ± 3	4 ± 3	0.349
	6 (0-8)	4 (0-8)	
AVLT Test			
Trial 1	4 ± 2	4 ± 2	0.898
	4 (1-7)	4 (1-8)	
Trial 2	4 ± 2	5 ± 2	0.148
	4 (2-7)	5 (3-9)	
Trial 3	5 ± 2	5 ± 2	0.319
	5 (2-7)	5.0 (2-8)	
Trial 4	4 ± 3	7 ± 2	0.013
	4 (2-11)	7 (5-9)	
Trial 5	5 ± 3	5 ± 2	0.406
	4 (0-10)	5.0 (3-10)	
AVLT Total	22 ± 8	27 ± 7	0.115
	21 (10-34)	26 (17-40)	
Immediate Recall (IR)	4 ± 3	4 ± 3	0.774
	5 (0-7)	3 (0-9)	
Delayed recall (DR)	3 ± 3	2 ± 3	0.672
	3 (0-11)	2 (0-9)	
AVLT-LTPR	37 ± 48	41 ± 40	0.714
	13 (0-150)	50 (0-90)	

U- value# --Mann-Whitney Test

Table 6.5: Neuropsychological Tests in FTD and AD.

Parameter			Study Groups			χ^2 value*
			Case (n=40)	Control (n=20)	Total	
Long Loop Reflex (LLR)	Absent	count	26	2	28	0.001
		%	65.0%	10.0%	46.7%	
	Present	count	14	18	32	
		%	35.0%	90.0%	53.3%	
Total			40	20	60	

Table 7: Long loop reflex in cases (AD and FTD) and control (*Pearson chi square test).

Discussion

Despite extensive attempts from all levels diagnosis of dementia is based on detailed clinical evaluation and supported by imaging. The accuracy is only up to probable level as pathology and genetic testing is not feasible in most patients. Available pharmacotherapy and non-pharmacological therapy are useful only if used very early in the course of disease. Therefore it is important to have simple easily available and less time consuming biomarkers available so that diagnostic accuracy is improved (Figures 8-10.)

This study involved 20 patients each with AD, FTD and controls. Mean age of patients with FTD was 58+/_ 7, AD 61.8=/-8, and controls 63.6=/-6 years. All were matched for education, gender and age. Apathy, low mood, aggression, inattention, executive dysfunction, and language were significantly affected in FTD patients; p value <0.05. Visuospatial dysfunction, Working memory and calculation most affected in AD patients. Their mean HMSE score was 24=/-2.Total ACE score was 48=/-21 in FTD and 49=/-18 in AD. Most atrophic region was frontal lobe in 60% of FTD patients and medial temporal lobes in AD patients in 50%.VLMO ratio in FTD patients was 0.7 and AD patients 1.2.neuropsychological tests showed only AVLT Trial 4 as different in both groups. LLR was present in 70% of AD patients, 90% in normal controls and absent in all FTD patients. 30% AD patients and 10% normal controls only showed absent LLR [18].

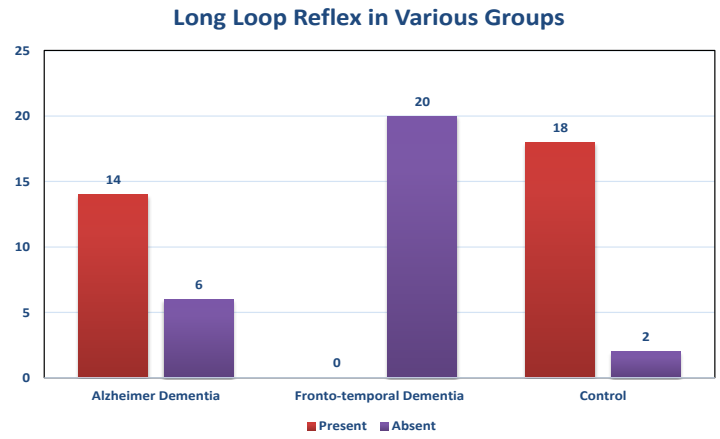

Figure 7: shows comparison of Long Loop Reflex (LLR) between AD, FTD and control groups.

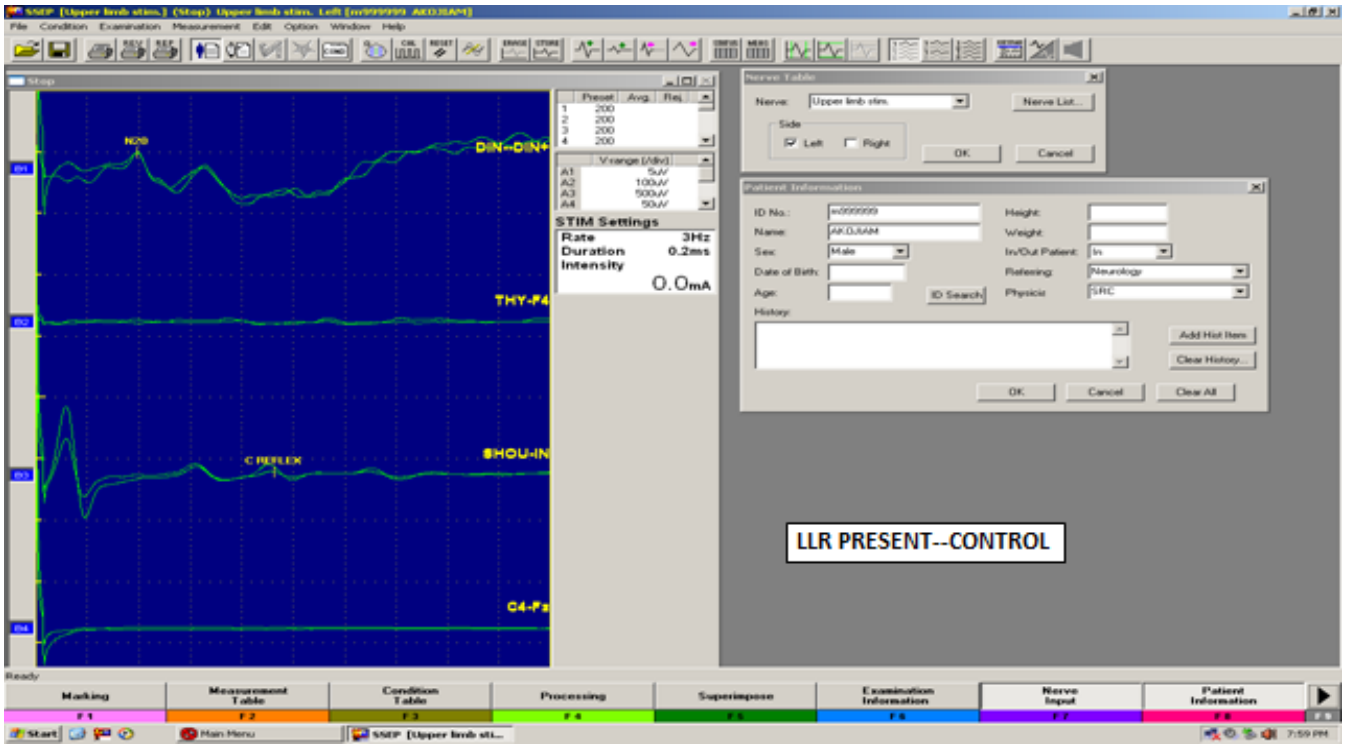

Figure 8: Normal control.

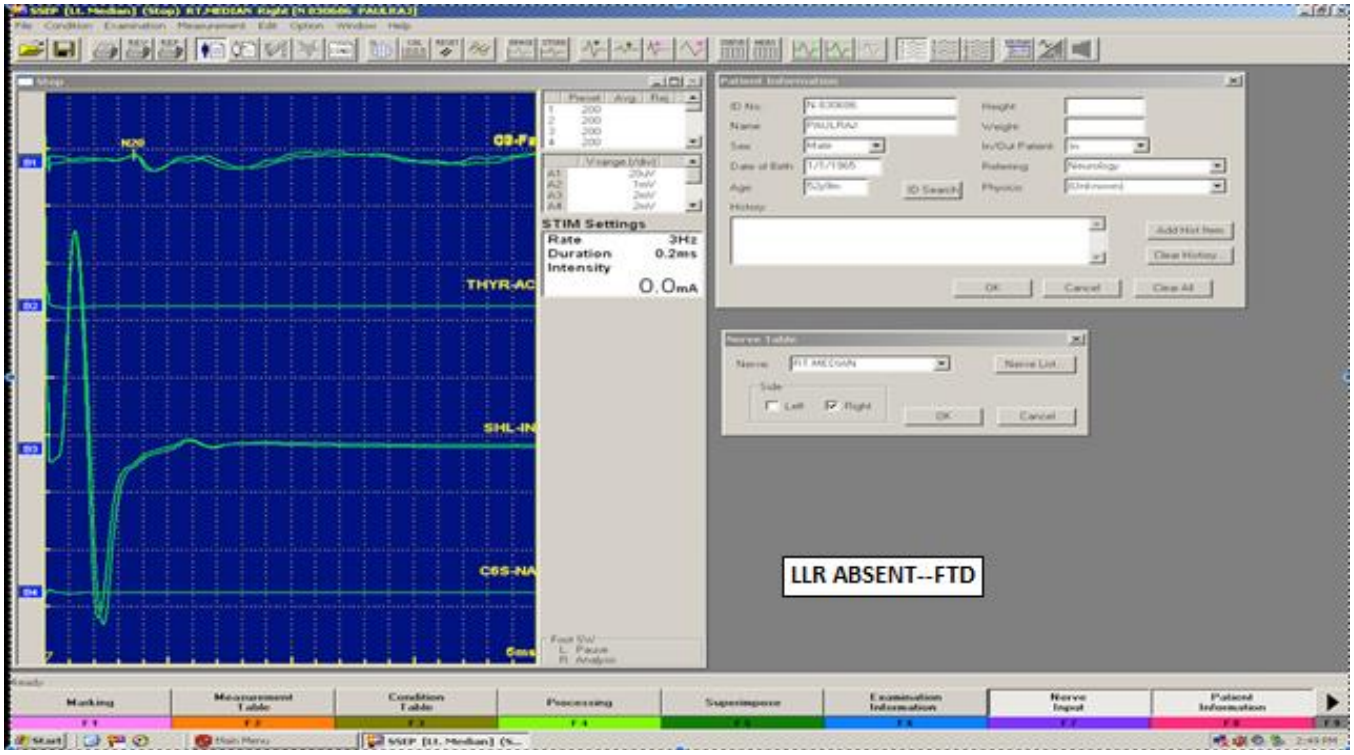

Figure 9: LLR Absent FTD.

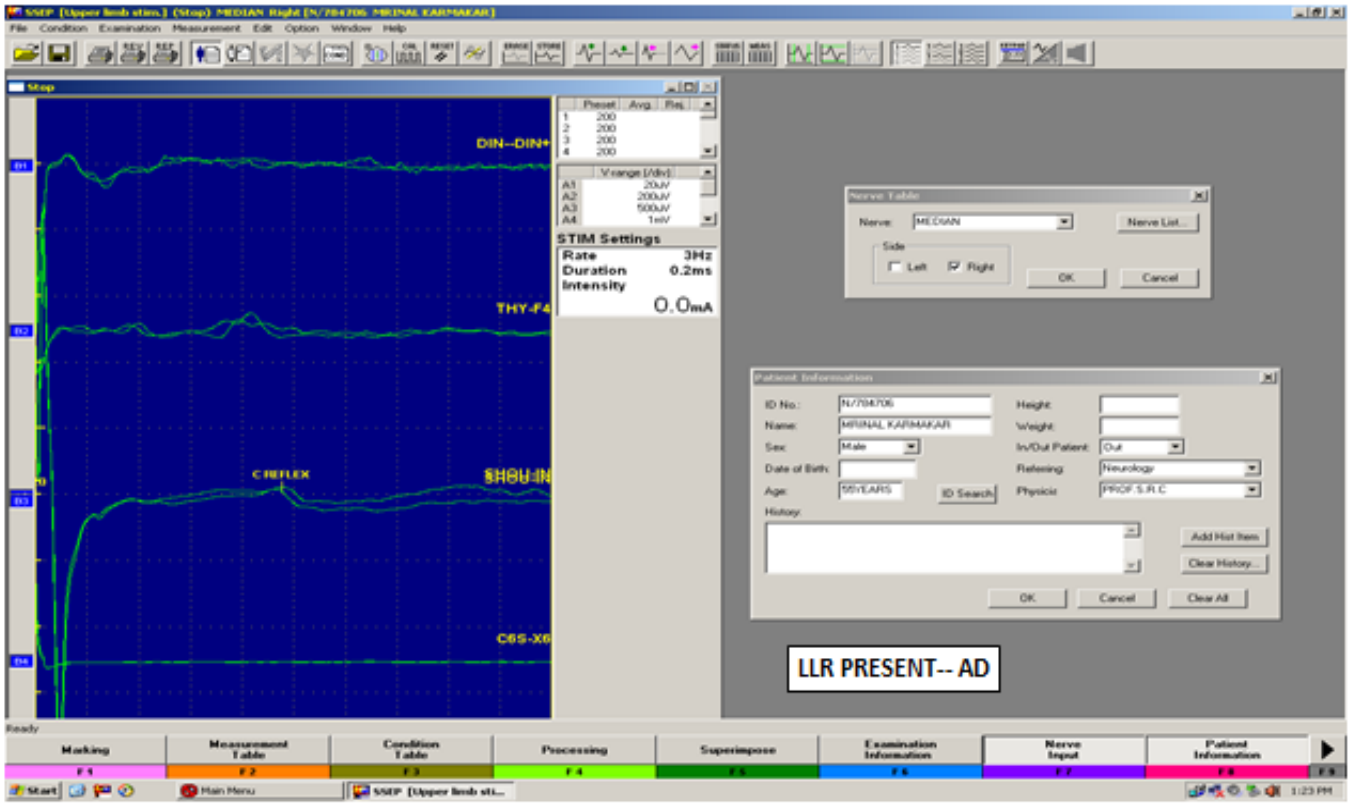

Figure 10: LLR present AD.

Conclusion

This study reveals that LLR is differentially affected in the two common cortical dementias as compared to normal persons. This needs to be studied in a larger sample and correlated with more stringent criteria including definite cases with genetics and pathology as entry criteria so that the information obtained can be more accurate for the condition considered. Then LLR will become a cost effective very cheap diagnostic tool for screening early patients in resource restricted institutions.

Limitation

The number in each category is only twenty. They were all probable cases and not definite as biopsy confirmation in live patients involves a lot of ethical problems. Follow up of the evaluation tools could not be done.

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