

Long Loop Reflex 2 in Patients with Cortical Dementias: A Pilot Study

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ABSTRACT

Introduction: Dementia is a major public health problem and it appears to be a global epidemic. The prevalence is doubling every 5 years and it is expected that 70% of persons above 60 years will live in developing countries by 2020 and 15% of them are likely to suffer from dementia. Disease modifying treatments work only if initiated very early; however, diagnostic tools are not always able to clearly differentiate the different types in very early stage. Therefore, inexpensive and easily available biomarkers are needed to know if collectively they will improve the sensitivity of specific diagnosis. Therefore, in this pilot study, we have tried to analyze if long loop reflex (LLR2) is differentially affected in these two conditions early in the course of Alzheimer's dementia (AD) and frontotemporal dementia (FTD) based on hypothesis taking into account the anatomical substrates involved. **Patients and Methods:** Mild cases of clinically probable AD and FTD after appropriate inclusion criteria were subjected for LLR testing in the upper limb at median nerve. The presence or absence of LLR was assessed and also the latency, amplitude, and duration assessed. **Results and Conclusion:** LLR 2 is differentially affected in both these conditions. Absence of LLR2 was consistently seen in FTD which can be explained by early break down of frontal subcortical circuits in this condition as against AD. This is likely to serve as a very cheap and very early biomarker to differentiate the two common types of cortical dementias.

Key words: *Alzheimer's disease, early biomarker, frontotemporal dementia, long loop reflexes*

INTRODUCTION

Sherrington in 1906 distinguished short spinal reflexes which are muscular responses within the same locality from long spinal reflexes evoked at a distance.^[1] When a voluntarily contracting muscle is stretched, the contracting muscle produces responses at varying

latencies.^[2] The response latency is the time delay after the stretch. Three responses are described by Lee and Tatton.^[3] The first response is called M1. It represents the short latency involuntary monosynaptic spinal stretch reflex involving primary afferents. The second

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response is called M2, it is delayed and probably has a transcortical pathway. The last one is called M3 and represents a voluntary component mediated by cerebellum. M1 is seen approximately at 45–60 ms after perturbation, M2 is seen at 60–90 ms, and M3 is seen at 90–110 ms. Any response with more than 110 ms is a voluntary response and therefore is not a reflex, and also M1 is demonstrated as monosynaptic reflex.^[4] Therefore, the reflex which is likely to be useful in studying transcortical circuits is M2.^[5,6] This was postulated in 1955 by Hammond *et al.* They all expressed the view that long loop reflex (LLR) may have voluntary input. They provide a pathway to the motor cortex to initiate a closed loop feedback control to agonist and antagonist.^[6,7] They fit both voluntary and reflex criteria as there is ambiguity and as it goes through motor cortex, it is voluntarily inflexible. M2 occurs without any conscious awareness of the movement and it occurs below the time threshold for voluntary and so it is called a reflex. Therefore, there is still controversy regarding the exact origin of these reflexes. The LLR gets abolished by lesions in pathways to and from the motor cortex.^[8] In isometric holding task, when asked to let go the voluntary contraction, there was 95% reduction in electromyographic (EMG) activity as against the reports of Rothwell *et al.*^[9] However, there is still debate and exact pathways are not defined. These reflexes are important for effective control of motor skills. Any error in the estimated muscle strength for a motor activity activates the muscle spindles receptors which activates the corrective LLRs. This brings about appropriate changes in the signals from motor cortex via long loop reflexes and the needed corrections are made. Therefore, they are of great importance in effective motor control which is both automatic and unconscious. They give flexibility to human stretch reflex and thus allow adaptation over a wide range of tasks. Stretch reflex modulations that require changes in limb stability are mediated by

motor pathways and helps in activities based on how the subject is instructed to modulate activities for anticipatory postural responses.

LLR occur in stimulation of dorsal roots or cutaneous nerves. The pathway is as follows: LLR 1 and 3 are traveling via fast conducting 1a afferents and LLR 2 via Group 2 afferents. Then it is transmitted within dorsal column to nucleus cuneatus, then lemniscal pathway to sensory cortex and 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. The difference between the electrically and mechanically elicited response can be used as a measure of fusimotor activity.^[10] LLR 2 is the response which is believed to be transcortically mediated and consistent; therefore, our study focuses on the same. C-Reflex is the term applied to the response seen in patients with cortical myoclonus with giant somatosensory evoked potential. These are variously expressed as LLR 1 equivalent or LLR 2. There is a lack of consistency in the observations as well as the lack of agreement about the origins of the various long loop

ABNORMAL PATTERNS IN NEUROLOGIC DISEASE		
Reflex abnormality	Responsible reflex pathway	Typical lesions/diseases
Absent HR	Peripheral neuropathy	Lesion within the peripheral pathways for the reflex
Enlarged HR	Corticospinal or bulbospinal tract lesion	Various lesions along the course of the 'central motoneuron'
Absent LLR II	Demyelinating or axonal lesion within the central reflex arc of the LLR II	Lesions of the lemniscal pathways, cortex or corticospinal tracts, Huntington's disease
Delayed LLR II	Usually Demyelinating lesion within the central reflex pathway of the LLR II	Mostly Demyelinating lesions in multiple sclerosis
Enlarged LLR I	Unknown	Myoclonus of various origin (cortical, sub cortical), corticobasal degeneration, Parkinson's disease, essential tremor

Figure 1: Depicts the common conditions with changes in long loop reflex

METHOD			
NO	ELECTRODES	RECORDING SITE	STRENGTH
1	C4—Fz/ C3—Fz	CORTEX	20 milivolts
2	X1—X2	BICEPS	1 milivolt
3	X3—X4	I/L THENAR (APB)	5 μ V
4	X5—X6	C/L THENAR (APB)	500 μ V

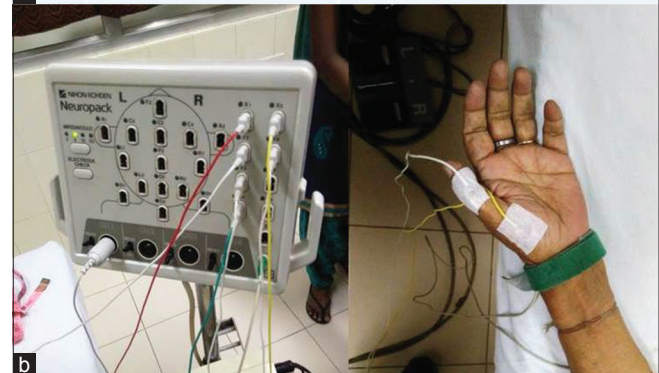


Figure 2: (a) Depicts electrode placement for our pilot study. (b) Machine with electrodes *in situ*

responses and also on terminologies used. However, in this study, we have utilized LLR 2 (C-Reflex).

Studies in various diseases

Studies in multiple sclerosis have shown 69% of patients show abnormality in M3 responses.^[11] Friedreich's ataxia shows the characteristic changes in LLR. The most specific changes seen are significant delay in stabilizing responses of anterior tibial muscles. The duration and amplitude of LLR seems to be controlled by cerebellum but latencies are not much affected.^[12]

Medium and long latency responses in Parkinsonism

Muscles studied for this purpose are triceps surae and tibialis anterior. Some authors have studied arm muscles also. The purpose of testing is based on the basic information that LLR has a role in postural stabilization, and hence may be altered in disorders associated with postural abnormalities. Patients with Parkinson's disease

showed statistically significant increase in amplitude and duration of the medium latency EMG response to muscle stretch in leg muscles but the latencies were normal. This was better expressed in standing persons. There was no definite correlation with rigidity. This could be due to the quick muscle responses which were studied, whereas the rigidity is a slowly elicited phenomena.^[13]

Alteration in LLR is also seen in Huntington's disease, Parkinsonism dementia syndromes, tremors, as well as progressive epileptic myoclonus syndromes [Figure 1].

Cortical dementias generally include Alzheimer's disease (AD) and frontotemporal dementias (FTD). AD involves people above 65 years of age, females more than males and is the most common dementia with a prevalence of 60–80% of all dementias. It presents with recent memory impairment, visuospatial disorientation, apraxias, and significant impairment of occupational functioning but relatively better social functioning. In FTD, the most common type is the behavioral variant. It affects persons younger than the AD patients and males more than females. The structures involved early are frontal lobes and temporal lobes. Therefore manifests with relatively

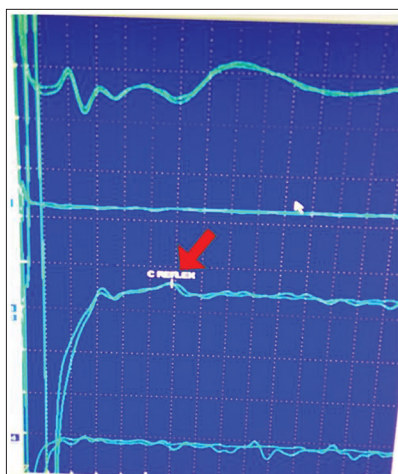


Figure 3: Long loop reflex in Alzheimer's dementia

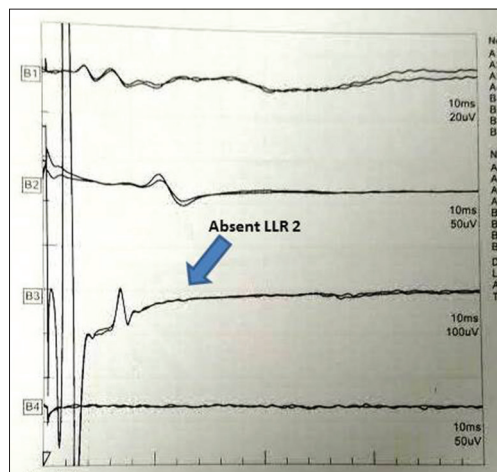


Figure 4: Long loop reflex in frontotemporal dementia

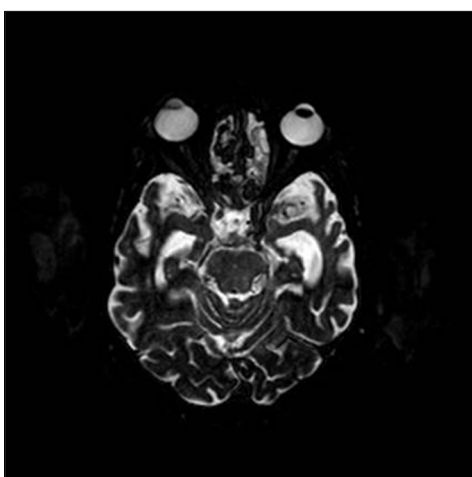


Figure 5: Magnetic resonance imaging in Alzheimer's dementia showing medial temporal atrophy

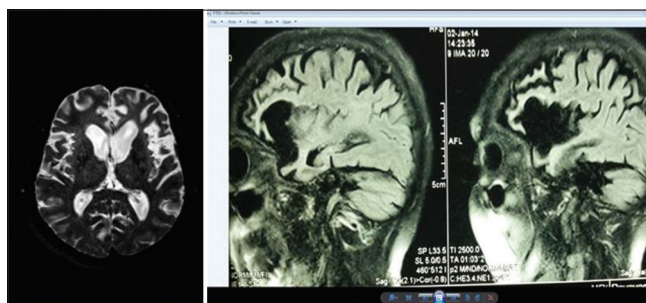


Figure 6: Magnetic resonance imaging in frontotemporal dementia showing bifrontal atrophy

Table 1: Showing Clinical, radiological and electrophysiological features in both patient groups.

AD	Affected functions	MRI	LLR 2	FTD	Affected functions	MRI	LLR2
CASE 1	Recent memory , visuspatial	Medial Temporal atrophy	Present	CASE 1	Personality change	Bifrontal atrophy	Absent
CASE 2	Recent memory, missing ways, dressing difficulty.	Medial Temporal and Parietal atrophy	Present	CASE 2	Pseudo normal, over familiar,	Bifrontal atrophy	Absent
CASE 3	Recent memory , misplacing objects	Medial Temporal and Parietal atrophy	Present	CASE 3	Aggressive , sweet craving, wandering	Bifrontal atrophy	Absent
CASE 4	Recent memory , problem in new places	Medial Temporal atrophy	Present	CASE 4	Uninhibited, aggressive	Bifrontal atrophy	Absent
CASE 5	Recent memory , apraxias	Medial Temporal atrophy	Present	CASE 5	Incontinence, wandering, aggressive	Bifrontal atrophy	Present but Very low amplitude

better preserved memory and functional capacity but severely impaired social functioning. Neurochemical problems are different in both conditions. Motor problems and extrapyramidal problems are seen earlier in FTD due to the extensive subcortical connections of the frontal lobe which is spared till late in AD. The available disease modifying agents are different and slow down the process only if used early in the course of the disease. Moreover, course and prognosis is different and care giver-related problems are also different in these two groups of diseases. However, early diagnosis is not always easy and needs a lot of supportive data. There is lack of literature in the alterations in LLR in cortical dementias in literature. Based on the structures involved and the clinical course of these diseases, FTD is likely to show abnormalities in LLR than AD, as the later has very little to do with motor tracts until end stage and therefore differential patterns are expected in both these conditions and might serve as an additional biomarker in differentiating these two conditions.

PATIENTS AND METHODS

Patients attending the neurology outpatient department of our tertiary level center were taken up for study after informed consent. Patients with moderate impairment with a Hindi Mental Status Examination (HMSE) score of not <20 were included to ensure cooperation for voluntary contraction. The LLR reflex responses cannot be recorded without voluntary activation of muscles. This pilot study included five patients each in AD and FTD group.

Inclusion and exclusion criteria

Patients with mild to moderate AD and FTD by Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria as well as the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria were used for AD. Consensus criteria were used for FTD. Those with past history of head injury, central nervous

system infections, surgery, vascular events, mixed dementias and those not willing were excluded. They underwent thorough clinical and neuropsychological assessment. HMSE and clinical dementia rating scale scales were applied. They also underwent all mandatory investigations such as thyroid function test, HIV, Venereal Disease Research Laboratory, B12, routine liver function, renal function, and hematology testing.

Methodology

The short and long latency responses were obtained using Nihon Kohden EMG machine. The subject was asked to comfortably lie-down in supine posture. Surface electrodes were placed as per routine median nerve stimulation. Abductor polices was voluntarily activated with approximately a force of 40% of normal [Figure 2a and b].

Electrode placement

Median nerve was stimulated at 3 Hz frequency with supramaximal current for 0.2 s. 500 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 500 times. Both sides 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 occur if there is statistically significant cortical hyperexcitability. The onset latencies were measured from the baseline. Moreover, amplitude was measured from peak to peak and duration from onset to termination. Absent or delayed LLR 2 is reported in demyelinating, axonal, or other destructive diseases affecting the leminiscal pathway, sensory, motor cortex, or corticospinal tracts.

OBSERVATIONS AND RESULTS

There were five patients in each group. All were males. All had been educated for 10 school years and

were right handed. The mean age of the AD patients was 64.60 ± 8.73 years, and the mean age of FTD was 57.28 ± 6.87 years. Their general functional features are enclosed [Table 1]. Both groups had mean HMSE score of 22. Neuroimaging showed typical features and no evidence of mixed dementia. LLR in AD [Figure 3], LLR in FTD [Figure 4], magnetic resonance imaging (MRI) in AD [Figure 5], and MRI in FTD [Figure 6] are depicted. Out of five patients with FTD four patients showed absent long loop reflex and one patient showed low amplitude delayed LLR 2. All five patients with AD showed normal LLR 2.

CONCLUSION AND DISCUSSION

LLR2 has afferent pathway through the proprioceptive tracts and efferent through the corticospinal tracts. Frontal lobe is extensively connected to subcortical structures, especially the extrapyramidal system resulting in early extrapyramidal features clinically than AD. Moreover, the frontal motor circuit, which is the first circuit in frontal lobe, involves the corticospinal pathways. This explains the consistent absence of LLR 2 in patients with FTD indicating very early breakdown of the motor circuit. In AD, the parieto-temporal areas are not directly connected to subcortical structures and therefore are unaffected. This information gives some insight into the pattern of disintegration of specific structures in these two disorders. Also the well-defined differences seen in this pilot study if consistently replicated in a larger population of patients it will serve as a very simple additional diagnostic biomarker. Hence, we have already started a larger study with larger number of patients.

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Conflicts of interest

There are no conflicts of interest.

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