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## Original Article

# Long Latency Reflexes in Clinical Neurology: A Systematic Review

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**ABSTRACT:** ***Background:*** Long latency reflexes (LLRs) are impaired in a wide array of clinical conditions. We aimed to illustrate the clinical applications and recent advances of LLR in various neurological disorders from a systematic review of published literature. ***Methods:*** We reviewed the literature using appropriately chosen MeSH terms on the database platforms of MEDLINE, Web of Sciences, and Google Scholar for all the articles from 1st January 1975 to 2nd February 2021 using the search terms "long loop reflex", "long latency reflex" and "C-reflex". The included articles were analyzed and reported using synthesis without meta-analysis (SWiM) guidelines. ***Results:*** Based on our selection criteria, 40 articles were selected for the systematic review. The various diseases included parkinsonian syndromes (11 studies, 217 patients), Huntington's disease (10 studies, 209 patients), myoclonus of varied etiologies (13 studies, 127 patients) including progressive myoclonic epilepsy (5 studies, 63 patients) and multiple sclerosis (6 studies, 200 patients). Patients with parkinsonian syndromes showed large amplitude LLR II response. Enlarged LLR II was also found in myoclonus of various etiologies. LLR II response was delayed or absent in Huntington's disease. Delayed LLR II response was present in multiple sclerosis. Among the other diseases, LLR response varied according to the location of cerebellar lesions while the results were equivocal in patients with essential tremor. ***Conclusions:*** Abnormal LLR is observed in many neurological disorders. However, larger systematic studies are required in many neurological disorders in order to establish its role in diagnosis and management.

**RÉSUMÉ : Les réflexes de longue latence en neurologie clinique : résultats d'une synthèse systématique.** ***Contexte :*** Les réflexes de longue latence (RLL) sont perturbés dans bon nombre d'états cliniques. L'étude visait à dégager, d'une synthèse systématique de la documentation médicale publiée, les applications cliniques de l'analyse des RLL dans divers troubles neurologiques et les progrès récents réalisés en la matière. ***Méthode :*** Il s'agit d'un examen de la documentation effectué à l'aide, tout d'abord, d'expressions MeSH bien choisies dans les bases de données MEDLINE, Web of Sciences et Google Scholar, provenant de tous les articles publiés du 1er janvier 1975 au 2 février 2021, puis des termes de recherche suivants : *long loop reflex*, *long latency reflex* et *Creflex*. Les articles retenus ont fait l'objet d'analyse et ensuite de déclaration selon les lignes directrices sur les synthèses sans méta-analyse (SWiM). ***Résultats :*** D'après les critères de sélection, 40 articles ont été retenus en vue de la synthèse systématique. Les différentes affections comprenaient les syndromes parkinsoniens (11 études; 217 patients), la chorée de Huntington (10 études; 209 patients), la myoclonie d'origine diverse (13 études; 127 patients), y compris l'épilepsie myoclonique progressive (5 études; 63 patients) et la sclérose en plaques (6 études; 200 patients). Des RLL de type II de grande amplitude ont été observés dans les syndromes parkinsoniens, de même que dans la myoclonie de différentes causes. Par contre, il y avait retard ou absence de RLL de type II dans la chorée de Huntington, et retard dans la sclérose en plaques. Parmi les autres affections, les RLL variaient selon le siège des lésions cérébelleuses, et donnaient des résultats ambigus chez les patients atteints du tremblement essentiel. ***Conclusion :*** Des RLL anormaux ont été observés dans divers troubles neurologiques. Toutefois, il faudrait réaliser des synthèses systématiques de plus grande taille portant sur de nombreuses affections neurologiques afin d'établir leur rôle dans le diagnostic et la prise en charge.

**Keywords:** Clinical neurophysiology; C-reflex; Electromyography; Long latency reflexes; Long loop reflexes; Movement disorders

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## Introduction

The origin of stretch reflex holds its roots way back to 1924 when it was first tested in the decerebrate cats after sectioning at inter-collicular level, then termed as "tonic reflex".[1] Further animal experiments attributed the origin of stretch reflex to the spinal level.[2] Three decades later, Hammond et al. demonstrated the existence of two components in response to stretch reflex during voluntary contraction of a muscle.[3,4] The early response with shorter latency, representing the mono-synaptic pathway was called M1 and the later ones were called M2 and M3 responses.[5] Although the role of transcortical pathways in mediating long latency responses was first proposed by Philips, it was Marsden, Merton, and Morton who substantiated it.[6,7,8,9] Deuschl et al. through their series of papers on long latency reflex (LLR) contributed enormously to the further understanding of the concepts.[10] They put forward the subtypes of LLR into I, II, and III that forms

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the basis of research and applications. Since then, the principles have been applied, albeit with modifications and added modalities of electrophysiology, on a plethora of clinical conditions spanning across the entire spectrum of neurological sciences and beyond.

Deuschl et al. defined LLR, as "involuntary muscle responses which succeed the short latency response and precede the voluntary response, irrespective of whether the stimulus is muscle stretch, electrical stimulation of a nerve or a more complex stimulus".[11] The wide spectrum of abnormalities exhibited by these reflexes in various clinical conditions render it as one of the promising tools in clinical neurophysiology not only as an ancillary aid in the diagnosis but also in, prognostication, following the progress of disease and depicting the neural circuitry involved in their pathophysiology. Following the detailed review article on the various clinical applications of hand muscle reflexes by Deuschl and Lucking in 1990, there has been no further consolidation on this topic even though the spectrum of applications of LLR has expanded manifold through a vast number of research papers.[11] Therefore, a systematic review encompassing the old, the new, and the emerging concepts with its applications across the fields of neuroscience was felt as the need of the hour.

## The Technical Aspects of LLR and Nomenclature

The technique to elicit LLR has been subjected to considerable modifications time and again by various authors. However, the most commonly used method in the majority of the studies testing hand muscle reflexes is in accordance with the procedure outlined by Deuschl et al.[10,11] The method involves electrical stimulation of the median nerve at the wrist, with the thumb, kept abducted at 15–20% of maximal force. Surface EMG recording is obtained from abductor pollicis brevis, filtered at 10–3000 Hz, rectified, and averaged over 64–256 sweeps. The methodology described by Conrad and Aschoff, a few years earlier was on similar lines with some minor modifications.[12] Lefaucheur et al. criticized the procedure of using 20% of the maximal force while recording LLR among patients with Huntington's disease (HD). In their study on electrophysiological assessment in HD, they instructed the patients to exert near-maximal effort, following which they could demonstrate the presence of LLR, contrary to the previous studies on HD.[13] Among the other modifications, in a study on idiopathic scoliosis, LLR was recorded intra-operatively by stimulating posterior tibial and common peroneal nerve while surface EMG was recorded from vastus medialis, tibialis anterior, gastrocnemius, and abductor hallucis.[14] LLR has also been recorded from superficial trunk muscles (rectus abdominis and erector spinae) in a study on chronic low back pain.[15] Besides, LLR of lower limbs has also been used as a part of static and dynamic posturography while testing for vestibulo-oculo-reflex using stabilometric platforms, the methodology of which has been described in various studies.[16,17]

## Pattern of Reflexes and Terminologies

*Reflexes on muscle stretch*: The reflex patterns and terminologies depend on the method of stimulation. In response to muscle stretch, the first response is referred to as M1, which represents monosynaptic transmission by group IA afferents. This is followed by M2 response, mediated by trans-cortical pathways.[11] The M2 response from proximal upper limb is conducted by group II afferents and involves the spinal pathways.[11] The M3 response, which follows M2, represents a modulation of reflex pathways by cerebellum, the details of which are still not well delineated.[11] In the lower limbs, the reflexes are less well defined compared to that of hand reflexes. A distinct medium latency reflex (MLR) has been reported in 50% of normal subjects, occurring at 110–120 ms from stimulation, generated by the stretched agonist muscle and has been thought to be mediated by transcortical pathways.[16] The generation of LLR in the lower limbs is related to stabilization of posture when the body is subjected to sudden displacement. It is the antagonist of a stretched muscle which generates LLR and thereby aids in stabilization of posture. Such a response is absent when the muscle is stretched in supine or sitting position.[16]

*Reflexes on Electrical Stimulation:* On electrical stimulation of a mixed nerve in the hand, the first reflex obtained at a mean latency of 29 ms is called short latency reflex (SLR), which represents stimulation of group IA afferents mediating a monosynaptic reflex.[12,11] The nomenclature of the LLR stands as LLR I, LLR II, and LLR III occurring at mean latencies of 40, 50, and 75 ms, respectively.[11] In this system, LLR I represent the early excitatory component, while LLR II, the most consistent one, is mediated by transcortical loop akin to the M2 response on stretch reflex. Finally, LLR III, representing the late excitatory response, is inconsistently seen among healthy subjects.

The cutaneous stimulation of digital nerves or superficial radial nerve leads to early excitatory (E1) also referred to cLLR I (cutaneous long latency reflex), early inhibitory (I1), and late excitatory (E2), also known as cLLR II responses.[20] Comparing the various modes of stimulation, it is most likely that HR and SLR represents M1, LLR II is equivalent to E2 and M2 response, and LLR III is the equivalent of M3 response.[11,18,19] Enhanced LLR I response in the setting of cortical myoclonus is also referred to as C-reflex since its latency correlates with that of LLR I response.[19] The possible LLR transduction pathways with terminologies is depicted in Figure 1.

## Methods

### Search Strategy

We searched the database platforms of MEDLINE, Web of Sciences, and Google scholar using the Medical Subject Heading terms (MeSH) "long loop reflex", "long latency reflex", and "C-reflex", for all the articles from 1st January 1975 till 2nd February 2021. The search strategy was modified in the Google Scholar search engine using additional search terms "clinical applications", "disease", or "disorder" in order to encompass the relevant studies.

### Study Selection and Data Extraction

The studies were reviewed critically with respect to title, authors, type, and sample size by thorough screening of the abstracts. Duplicate articles were identified during the same process. Articles lacking abstracts were assessed based on the title. Subsequently, the articles were segregated based on inclusion and exclusion criteria. Studies having patient data and those based on applications of LLR on clinical entities were included for review. Exclusion criteria were applied to the studies which were 1) purely focused on physiological aspects, 2) animal-based, 3) non-English language, 4) viewpoints and perspectives, 5) lacking patient data, 7) case reports on a single patient, 8) diseases with less than four research papers on applications of LLR, and 9) review articles. A manual search of the reference lists of the selected studies was performed to avoid missing key articles. Critical analyses of the included studies were performed after full-text reading. Quality assessment of the included studies was done using QUADAS-2 scale for primary diagnostic accuracy studies.[21]

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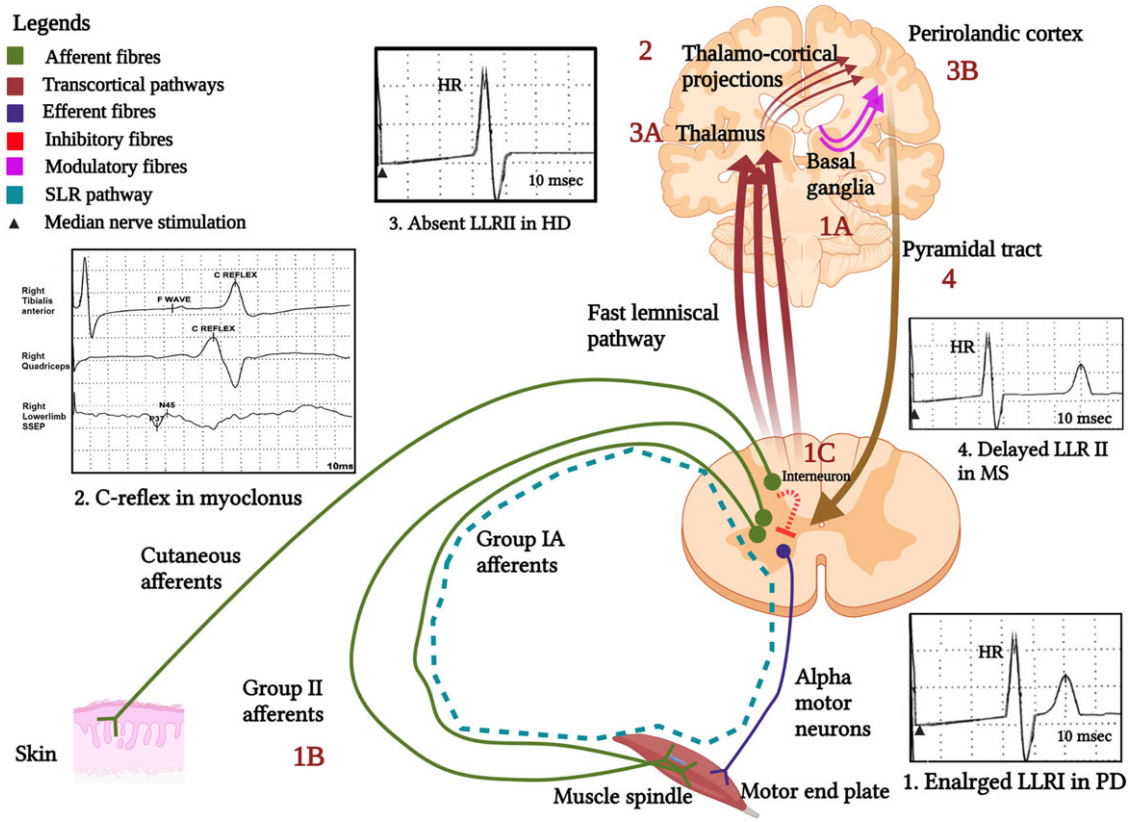


**Figure 1:** Long Latency reflex (LLR) transduction pathway and the levels involved in various clinical conditions. 1: Parkinson's disease (PD), 1A: Abnormal Basal ganglia output leading to impaired modulation of transcortical pathways, 1B: Increased transmission by Group II afferents in PD, 1C: Altered excitability of spinal interneurons, 2: Cortical excitability in myoclonus, 3: Huntington's disease (HD), reduced impulse transmission to the cortex at the thalamic or thalamocortical projection level 3A: Degeneration of neurons at Thalamus in HD, 3B: Degeneration of neurons in the cortico-cortical pathways in HD, 4: Impaired transmission of impulses along the ascending and descending fibres due to demyelinating plaques in Multiple Sclerosis. The figure was created with BioRender.com.

Subsequently, data extraction was performed from each of the articles with respect to the sample size, the disease in question, the technical details of the methodology followed, results of the studies, and the hypothesized pathophysiology. The synthesized data were reported as per the Synthesis Without Meta-analysis (SWiM) guidelines in Systematic reviews.[22]

*Quality assessment:* QUADAS-2 analyses showed all the included studies being "at risk of bias" since at least one of the items among the domains of "patient selection", "index test", "reference standard", and "flow and timings" were found to be at high risk. This was largely attributable to the lack of randomization, case-control design, and dearth of the prior knowledge of diagnosis from reference standard before the performance of the index test. With regards to the assessment of concern for applicability, all except three studies had "low concern regarding applicability" based on the domains of patient selection, index test, and reference standard.

## Results

Our search strategy yielded a total of 1828 studies, out of which, 114 duplicated articles were excluded prior to abstract screening. Inclusion and exclusion criteria were applied to the 1714 abstracts, following which 29 articles were considered eligible for full-text reading. Further 11 articles were added from the manual search of the reference lists. Subsequently, a total of 40 studies were considered for the final systematic review (Figure 2). This systematic review was not pre-registered.

### *Applications in Movement Disorders*

#### *LLR in Parkinsonian Syndromes (n = 11 Studies)*

One of the earliest diseases where LLR was studied was Parkinson's disease (PD). Of the 11 studies included on parkinsonian syndromes, the majority of the studies were on PD. The foundation was laid by Tatton and Lee in 1975, who for the first time analyzed the reflex responses to wrist flexion-extension movements in rigidity predominant parkinsonian patients.[18] They demonstrated a significant increase in response at the M2-M3 interval which was statistically significant compared to the controls. The minimally increased M1 response in the parkinsonian group was consistent with the clinical correlate of normal tendon reflex in this condition. The study by Hunter et al. on reflex pathways in parkinsonian patients revealed exaggerated LLR at a mean latency of 61.3 ± 5.1 ms suggestive of enhanced LLR II. Lack of LLR on stimulation of cutaneous afferents near fibular nerve, suggested the origin to be the fast-conducting non-cutaneous group I afferents.[23] Rothwell et al. hypothesized that the parkinsonian rigidity stems from the quantitative alterations in the long loop pathways.[24] A similar observation of enhanced LLR was also found by other researchers (Table 1).[25,26,27]

***Role of MLR, LLR in "Off state" and Other Controversies.*** Studies of stretch reflexes in lower limbs of parkinsonian patients, demonstrated exaggeration of MLR, instead of LLR.[28,29] The study by Bloem et al. stands out from the previous studies concerning the methodology as they tested reflexes among PD patients in 12 hours "off" state. Their results did not attribute any significant early

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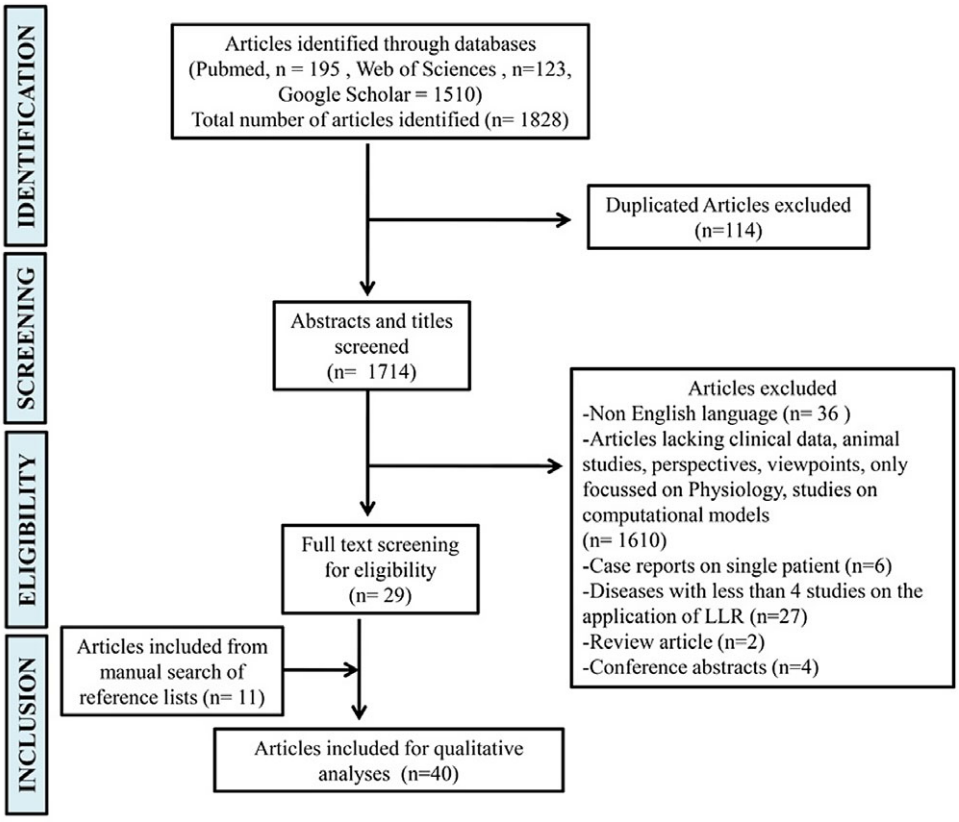


**Figure 2:** Search strategy and study selection in accordance with Systematic review without meta-analysis (SWiM) guidelines.

diagnostic value to these parameters, as altered reflex responses (MLR) was noted only among advanced long-standing PD patients.[29]

The study effectively sheds light on the supraspinal dopaminergic control of LLR, which is the pathomechanism behind low LLR response in the off state. Besides, it also showed the poor diagnostic sensitivity of LLR in detecting early PD. In another study, SLR was found to be absent to both mechanical and electrical stimuli and LLR was detected to be of normal parameters.[30] While the former was hypothesized to be a result of altered fusimotor drive in PD patients, the latter was postulated to be due to the dependence of these reflexes on the degree of muscle length perturbations applied.[30] The experimental study by Fuhr et al. revealed a less pronounced first inhibitory component (I1) of the cutaneous reflex (CR) attributed to the loss of spinal inhibition in PD patients.[31] In a single study on Ponto-pallido-nigral degeneration (PPND), Wszolek et al. showed the absence of LLR in a family of nine patients associated with chromosome 17q21-24, suggesting lack of cortical hyperexcitability.[32]

### *LLR in Myoclonus (n = 13 Studies)*

Myoclonus has been subjected to numerous levels of classifications based on clinical aspects, anatomical location, electrophysiological patterns, including transcranial magnetic stimulation (TMS), somatosensory evoked potentials (SEP), and LLR.[33,34,35] Enhanced LLR I is most commonly observed followed by LLR III and rarely LLR II.[36] One of the earliest studies on detailed electrophysiology in a patient of focal reflex myoclonus was carried out by Sutton and Mayer, where they demonstrated exaggerated LLR at a mean latency of 51 ms suggestive of LLR II, generated by the sensorimotor cortex, also called C-reflex (cortical reflex).[37] Based on etiology, myoclonus may be physiological, essential with or without dystonia, epileptic, and symptomatic or secondary.[34] Of the 13 included studies on myoclonus, 5 were on symptomatic myoclonus, where myoclonus was a part of another disease, 3 on essential myoclonus comprising the hereditary etiologies, and 5 were on progressive myoclonic epilepsy syndromes (Table 2).

### *Symptomatic Myoclonus*

***Myoclonus in Corticobasal Degeneration (CBD):*** Monza et al. evaluated 10 patients with CBD, out of which 6 had myoclonus.[38] All of them had enhanced LLR with a lower SLR/LLR amplitude ratio compared to the controls. The mean latencies of these enhanced LLR corresponds to LLR I subtype. Similar results were obtained by Carella et al. in a study on 5 CBD patients with myoclonus, probably a reflection of enhanced cortical excitability.[39] Thus, neurophysiological studies can serve as ancillary tests in the diagnosis of CBD with myoclonus.

***Multiple System Atrophy (MSA) with Myoclonus***: Okuma et al. studied consecutive patients with MSA, which included both the subtypes, of which 12 MSA-P (parkinsonian type) and 3 MSA-C (cerebellar type) had myoclonus. An enlarged LLR I (C-reflex) with a mean latency of 40 ms was observed in 7 patients, of which 6 were MSA-P variant.[40]

***Myoclonus in PD***: Caviness et al. performed electrophysiological analyses of the wrist and finger myoclonus in two patients with levodopa responsive PD. They did not observe any exaggerated LLR or giant SEP suggesting that they are unlikely to be cortical reflex myoclonus.[41] It was concluded that the origin of myoclonus was a byproduct of cortical pathology in PD manifesting as cortical myoclonus.[42]

***Orthostatic Myoclonus:*** This represents a variant, characterized by myoclonic jerks occurring predominantly on assuming upright

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**Table 1:** Studies of LLR in Parkinsonian disorders

| Study | Sample size | Type of stimulation | Method | Reflexes elicited | SLR properties | LLR properties | LLR Subtype | Interpretations and comments |
|---|---|---|---|---|---|---|---|---|
| Tatton et al.[18] | 7 patients (5 rigidity predominant, 2 tremor predominant PD) and 12 normal subjects | Stretch | Wrist flexion and extension movements- both passive and active | M1, M2 responses were present in all study and control subjects. M3 response was present in 40% of normal subjects | Minimally increased M1 response during passive and active movements compared to the controls | -Larger M2 (LLR) response<br>-No difference of LLR response between active and passive tasks in the patient group<br>-Increased responses in the M2-M3 interval in passive and active task by factors of 9 and 4.3 respectively compared to the control group | LLR II | LLR plays a significant role in generation of rigidity in parkinsonian syndromes |
| Hunter et al.[23] | 13 PD and 12 controls | Electric | Peroneal nerve stimulation | 8/13 patient group vs 2/12 in control group exhibited LLR | 32.7 ms | Mean: 61.3 ± 5.1 ms<br>Exaggerated LLR amplitude | LLR II | No LLR on stimulation of cutaneous afferents |
| Rothwell et al.[24] | 47 PD and 12 controls | Stretch | Stepwise torque disturbances exerted on Flexor pollicis longus (FPL) and Triceps brachii (TB) | SLR, LLR | 25–50 ms | Latency range:<br>FPL: 45–96 ms, TB: 45–90 ms<br>Up to a velocity of 300°/s, the size of the long-latency stretch reflex was proportional to the log velocity of stretch. | LLR II | LLR magnitude and duration correlated with the hypertonia.<br>They hypothesized Group II afferents mediated mechanism<br>LLR is one of the contributors to rigidity |
| Mortimer et al.[25] | 16 PD and 12 controls | Stretch | Sudden application of torque on biceps and lateral triceps | E1 and E2 | Mean latency:<br>22–50 ms | Mean latency: 50–75 ms.<br>Increased E2 response (LLR) during sudden passive stretch | LLR II | Magnitude of LLR correlates with rigidity among patients with PD |
| Berardelli et al.[26] | 17 PD | Stretch | Dorsiflexion stretches on triceps surae and tibilais anterior | 12/16 patients exhibited LLR | 50–80 ms | Latency Range:<br>84–122 ms | MLR and LLR II | LLR duration and amplitude correlated with rigidity in PD; Group II fibres mediated increased tone |
| Cody et al.[27] | 32 PD and 14 controls | Electric | Forcible stretch of flexor ccarpi radialis at 20% of maximal contraction | SLR, LLR | Latency range: 40–50 ms | Mean latency: 80 ms | LLR II | Enhanced LLR due to increased firing of Group II afferent neurons |
| Scholz et al.[28] | 33 PD | Stretch | EMG recording from triceps surae and tibialis anterior | SLR, MLR, LLR | SLR Mean latency:<br>47.5 ± 6.7ms<br>Duration: 23.5 ± 6.2 ms | LLR Mean latency:<br>138.5 ± 22.1 ms<br>Duration: 42.5 ± 14.9 ms.<br>MLR latency: 89.2 ± 23.9 ms<br>Duration: 42.5 ± 14.9 ms | MLR | Integrals of MLR duration in the stretched tricpes surae was increased which suggests modulation by basal ganglia. MLR could be polysynaptic reflex mediated by additional contributions from group II afferents. |
| Bloem et al.[29] | 23 patients with PD and 24 controls | Stretch | Stretched gastrocnemius for MLR and, stretched tibialis anterior for LLR | MLR, LLR | – | Enhanced MLR or reduced LLR in at least one leg was present in 15/23 patients | MLR | -Patients were tested in the off state for more than 12 hours.<br>-LLR and MLR are altered in advanced PD |
| Noth et al.[30] | 10 PD | Stretch and electric | Stretch evoked response EMG from first dorsal interossei (FDI) | SLR, LLR | Reduced SLR amplitude or absence | Normal LLR | — | Change in fusimotor control of muscle spindles is responsible for reduced SLR |
| Fuhr et al.[31] | 10 PD and 10 controls | Electric | Median nerve stimulation and recording from FDI during isometric contraction of 20% of maximal | Cutaneous reflex (CR) with 2 excitatory components (E1, E2) and one inhibitory component (I1) | E1 (corresponds to HR)<br>Amplitude: 10.4 ± 4μV | E2 (corresponds to LLR II)<br>Amplitude: 20.9 ± 14.8 μ | LLR II | -Amplitude of E1 and E2 didn't differ between patient and control group.<br>-Amplitude of I1 component was lower compared to control group ($p = 0.0041$). I1 component improved on treatment with Levodopa |
| Wszolek et al.[32] | 9 patients with PPND | Electric | Details not mentioned | LLR | – | Absent | — | Absence of LLR suggesting lack of cortical hyperexcitability |

FPL: Flexor pollicis longus; LLR: Long latency reflex; MLR: medium latency reflex; PD: Parkinson's disease; PPND: Pallido-ponto-nigral degeneration; SLR: short latency reflex; TB: Triceps brachii.

**Table 2:** Studies of LLR in myoclonus

| Study | Sample size | Type of stimulation | Method | Reflexes elicited | SLR properties | LLR properties | LLR subtype | Interpretations and comments |
|---|---|---|---|---|---|---|---|---|
| Monza et al.[38–7] | 10 probable CBD and 10 healthy controls | Electric | Median nerve stimulation at wrist and recording at thenar muscle at rest and at 50% of maximal isometric contraction | SLR, LLR I, II, III and SLR/LLR ratio | Mean latency: 27.3 ms | Mean latency: 45.7 msec at rest, 46.9 msec on activation. All 6 patients with myoclonus had enhanced LLR amplitude at rest which increased with action. | LLR I | LLR latencies were shorter than cortical reflex myoclonus. SLR/LLR amplitude ratio was significantly lower among patients with myoclonus compared to controls. |
| Carrella et al.[39] | 5 probable CBD with myoclonus | Electric | Median nerve stimulation at wrist and recording at thenar muscles at rest and isometric contraction | SLR and LLR | Mean latency: 27.9 ms | Mean latency: 41.7 msec at rest, 40.7 msec on activation. | LLR I | Myoclonus in CBD is probably related to an enhanced long-loop reflex |
| Okuma et al.[40] | 12 MSA-P and 3 MSA-C | Electric | Abductor Pollicis Brevis on stimulation of median nerve | C-reflex | – | Mean latency: 40 msec Range: 35-42 msec | LLR I | LLR were enhanced in 7 out of 11 of the studied patients. |
| Cavinness et al.[41] | 2 PD with myoclonus | Electric | Stimulation of Median nerve at wrist and surface EMG from APB twitch and skin of index finger | SLR, LLR, SEP | Normal SLR | Normal LLR | — | Normal SEP. Suggestive of cortical rather than reflex myoclonus |
| Guerrini et al.[45] | 10 Rett Syndrome with cortical myoclonus | Electric | Median nerve stimulation of wrist and recorded over thenar muscles | C- reflex | – | Mean latency: 62 ± 4.3 ms | LLR II | Prolonged intracortical delay of LLR. |
| Gunduz et al.[44] | 7 orthostatic myoclonus | Electric | Median nerve stimulation at wrist and recording from APB | C-reflex | – | Mean latency: 47.2 msec in only one patient | LLR I | Suggestive of simultaneous presence of another neurodegenerative disorder. |
| Li et al.[46] | 6 Inherited MD | Electric | Median and digital nerve stimulation, with voluntary contraction at 20% of maximum | LLR and cutaneous LLR | Normal latency | Normal latency. No abnormal LLR or SEP | — | Suggestive of subcortical origin of myoclonus. |
| Marelli et al.[47] | 9 DYT11 Myoclonus-Dystonia Syndrome | Electric | Thenar muscles at rest and at moderate isometric contraction | SLR- LLR amplitude ratio | Normal range of latency | Normal range of latency. SLR-LLR amplitude ratio = 4.3 ± 19. Mean SLR-LLR amplitude was similar in patients and controls during contraction | — | Suggestive of sub-cortical origin of myoclonus. |
| Canafoglia et al.[48] | 8 LBD, 10 ULD and 16 controls | Electric | Median nerve stimulation at wrist and recorded from ipsilateral thenar muscle | SLR and LLR | Mean latency: ULD: 27.6 ± 3 ms LBD: 26.5 ± 1.3 ms | Mean latency: ULD: 42.5 ± 5.3 msec; LBD: 44.9 ± 5.4 msec. 6/10 ULD patients had enlarged LLR. 3/8 LBD had abnormally enlarged LLR. ULD patients had shorter LLR latency with normal SLR latency. | Single wave that is a mixture of LLR I and LLR II | SLR/LLR ratio was lesser in ULD group compared to LBD and controls. ULD patients had enhanced LLR suggestive of abnormal cortical circuitry. |
| Visani et al.[49] | 25 ULD and 20 controls | Electric | Median nerve stimulation of wrist and recorded over thenar muscles | LLR | – | Enlarged LLR amplitude | — | Facilitated LLR in 9/24 patients, and it was more common among patients with giant SEP. |
| Canafoglia et al.[50] | 3 sialidosis and 10 ULD | Electric | Median nerve stimulation at wrist | SLR, LLR | Mean latency: Sialidosis: 36.5 ± 9.2 ms. ULD: 27.1 ± 2.6 ms. | Mean latency: sialidosis: 51.5 ± 10.6 ms. ULD: 44.1 ± 2.4 ms. SLR/LLR ratio: -sialidosis: 0.5 ± 0.1 -ULD: 1.3 ± 0.8 -Single component LLR was present at rest in all sialidosis patients and 2 patients with ULD -During contraction, all ULD patients had single component LLR while all sialidosis patients had 2–3 component LLR of unusual waveform. | Complex waveforms in sialidosis LLR I/II complex in ULD | Sialidosis patients had LLR of unusual waveform and multiple waves unlike ULD suggestive of the presence of pathological reverberating circuits across motor cortex or subcortical-cerebellar nuclei. LLR can enable distinguishing sialidosis from ULD among patients presenting with myoclonic jerks. |

(*Continued*)

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**Table 2:** (*Continued*)

| Study | Sample size | Type of stimulation | Method | Reflexes elicited | SLR properties | LLR properties | LLR subtype | Interpretations and comments |
|---|---|---|---|---|---|---|---|---|
| Demura et al.[51] | 4 family members with BAFME | Electric | Adductor hallucis stimulation | C-reflex | – | Mean latency: 77 msec in 1 patient. | LLR III | C reflex present in 1/3 patients. |
| Manabe et al.[52] | 3 cases of BAFME | Electric | Thenar muscle stimulation | LLR (C-reflex) | – | Mean latency: 40 msec. | LLR I | Enhanced LLR. |

BAFME: Benign adult familial myoclonic epilepsy; CBD: cortico-basal degeneration; LBD: Lafora body disease; LLR: long latency reflex; MD: myoclonus-dystonia; MLR: medium latency reflex; SEP: somatosensory evoked potential; SLR: short latency reflex; ULD: Unverricht-Lundborg disease.

posture.[43] Gunduz et al. reported an electrophysiological profile of 7 patients with orthostatic myoclonus where they found the presence of C reflex (enhanced LLR I) in a single patient suggestive of the simultaneous presence of a degenerative condition resulting in myoclonus of cortical origin.[44]

***Cortical Myoclonus Associated with Rett Syndrome:*** Guerrini et al. studied 10 girls identified with Rett Syndrome, 9 of whom had demonstratable myoclonus. Exaggerated C-reflex with marked prolongation and the intracortical delay was detected in all of them.[45]

## Essential Myoclonus

***Inherited Myoclonus-Dystonia syndrome:*** The electrophysiological features of inherited myoclonus-dystonia were evaluated by Li et al. in 6 patients, 3 of which were caused by a mutation in ϵ-sarcoglycan gene (SGCE) on chromosome 7q21, 2 belonging to DYT-11 family and one with undetermined etiology. There was no evidence of enhanced LLR amplitude or abnormal SEP, suggesting subcortical origin of myoclonus.[46] Marelli et al., in their study on 9 patients of DYT-11 myoclonus-dystonia syndrome, found normal LLR, which corroborated with the findings of normal SEPs and TMS parameters. Thus, the results of both the studies were in clear agreement with each other.[47]

## Epileptic Myoclonus

### LLR in PME Syndromes

***Unverricht–Lundborg Disease (ULD) and Lafora Body Disease (LBD)***: Canafoglia et al. demonstrated consistently enlarged LLR in 8 ULD patients that correlated with enlarged P25 and N33 components of SEP.[48] The enlarged LLR in ULD is a single wave that is a mixture of LLR I and LLR II. LLR enlargement was less consistent in patients with LBD. However, they had enlarged mid-latency N60 component of SEP, attributable to the sustained and complex cortical circuitry. Facilitated LLR was also reported in a series of 25 patients with ULD.[49] LLR subtype couldn't be delineated in these cases due to lack of data.[49]

***Sialidosis:*** Canafoglia et al. showed multiphasic complex waveforms (2–3 components) in 3 patients with sialidosis compared to 10 ULD patients suggesting the presence of reverberating loops involving the motor cortex and subcortical-cerebellar connections.[50] The enhanced LLR corresponds to LLR II.

***Benign Adult Familial Myoclonic Epilepsy (BAFME):*** Demura et al. evaluated a single family of BAFME, of which three patients had SAMD 12 gene mutation, one of which was found to have C-reflex (correlate of LLR in myoclonus) at 77 ms latency of onset (LLR III).[51] It corroborated with giant flash visual evoked potential (VEP). The longer latency of the C-reflex obtained in these patients could be attributed to the technique used in this study. Contrary to the usual electrical test of LLR, the C-reflex was obtained using F-wave study from abductor hallucis muscle. Since the stimulation intensity used in F-wave tests is higher than that of electrical LLR test, the response might be induced from all types of afferent nerves, but not Ia/II only. Enhanced LLR I, enlarged SEP and positive spikes preceding myoclonus on jerk locked back averaging (JLBA) has been described in three patients with BAFME.[52]

### LLR in Huntington's Disease (n = 10 Studies)

Noth et al. did not observe LLR in majority of the patients with HD which corroborated with reduced early cortical components of SEP amplitude.[53] Other studies by Thompson et al., and Noth et al. on 17 and 50 HD patients demonstrated similar results.[54,55] Eisen et al. demonstrated absent R2 (equivalent to LLR) in majority of HD patients and half of at-risk subjects.[56] In 1989, a study on 23 patients of HD by Deuschl et al., provided valuable insights as it concluded loss of LLR as fairly specific in HD. They showed lack of utility of LLR in detecting carriers of HD.[57] Lefaucheur et al. studied 36 patients with adult-onset HD using various neurophysiologic measures. While the role of SEP was quite apparent as a sensitive marker of disease, LLR did not correlate with disease stage or duration.[13] Two years follow up study of 20 patients with HD, LLR correlated with an increase in unified Huntington disease rating scale (UHDRS) motor score.[58] Sebastiano et al. described three patients with HD, who had enhanced LLRs suggestive of a reverberant circuit involving motor cortex.[59] Delayed LLR latency and prolonged duration were described in 27 HD patients by Huttunen et al. (Table 3).[60]

## LLR in Other Movement Disorders

***LLR in Tremor Disorders (n = 2 Studies):*** In a study on 45 subjects with essential tremor (ET) by Deuschl G et al., two distinct subgroups were identified.[61] One group had normal LLR (tremor frequency 5.5 to 10 Hz) while the other had enhanced LLR I (tremor frequency 5.5 to 10 Hz). The response to propranolol varied among the subgroups, with better responses in the former group. Elble et al., didn't find any correlation between frequency of tremor and latencies of stretch reflex.[62] Limited by the number of studies as well as sample size, the utility of LLR in the evaluation of tremor remains to be determined.

***LLR in Hyperekplexia (n = 2 Studies)*:** Markand et al. performed electrophysiological evaluation of patients with familial startle disease and observed augmented C-reflex which suggests the role of cortical neuronal hyperexcitability as the basic pathophysiologic mechanism underlying hyperekplexia.[63] The C-reflex were recorded in the F-wave study, with a latency range of 60 to 75 ms, corroborative of LLR II/III subtype. However, Brown et al. did not observe enhanced C-reflex in eight patients with

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**Table 3:** Studies of LLR in Huntington's disease

| Study | Sample size | Type of stimulation | Method | Reflexes elicited | SLR properties | LLR properties | Interpretations and comments |
|---|---|---|---|---|---|---|---|
| Lefauchur et al.[13] | 36 HD | Electric | Median nerve stimulation at wrist and recordings were obtained from thenar muscles tested at near-maximal effort | Very short latency response, H reflex, R2 component of LLR, R3 component of LLR | – | LLR normal | LLR did not correlate with staging or disease duration. SEP abnormality was found to be a more sensitive marker of disease |
| Noth et al.[53] | 30 HD and 20 controls | Electric | Surface EMG of FDI with the muscle in isometric contraction of 10-20% of normal | SLR and LLR | Normal | Absent in 21/30 patients | Supraspinal pathways responsible |
| Thompson et al.[54] | 17 HD | Electric | Stretch reflex on wrist flexors, FPL | SLR and LLR | Size, latency normal in wrist flexors<br>Duration prolonged in chorea in the wrist flexor | LLR absent in FPL in 9/15 patients with HD. Latency was delayed among patients who had LLR ($p < 0.001$), mean duration was prolonged ($p < 0.05$)<br>LLR from wrist flexors was absent in two patients with chorea. | -Effect of LLR was greater on long flexor thumb compared to that of wrist. This is compatible with the hypothesis that transcortical loop is more functional in operating distal small joints<br>-Co-existence of bradykinesia and chorea correlates with involvement of basal ganglia involvement |
| Noth et al.[55] | 50 HD and 20 controls | Electric | Median nerve stimulation at wrist | SLR and LLR | – | LLR absent in 43/50 patients | This suggests diminished somatosensory input to the cortex due to interruption at the level of thalamus or cortical projection areas |
| Eisen et al.[56] | 9 HD and 13 first degree relatives | Electric | Median nerve stimulation at wrist with the thumb opposing towards 2nd and 3rd digit | SLR (R1), LLR (R2) | Patients: Mean latency: 27.3 ± 2.3 msec<br>First degree relatives: 26.5 ± 2.5 msec | Mean latency: 46.2 ± 3.4 msec in 2 HD patients with intact LLR; 48.2 ± 1.9 msec in 10 at risk subjects<br>R2 (corresponding to LLR II) was absent in 7/9 subjects, and 3/13 at risk subjects | - Absent LLR along with reduced cortical SEP but normal cervical spine SEP is suggestive of impairment in thalamic or cortical projections. |
| Deuschl et al.[57] | 17 HD, 17 descendants of patients and 18 choreatic disorders | Electric | Median or radial superficial nerve stimulation at wrist | HR, LLR | Increased mean amplitude and duration of HR among HD patients and off springs | 61% of HD had absent LLR response in unilaterally or bilaterally. Rest of patients had reduced mean amplitude. Normal LLR among descendants and symptomatic chorea | Choreatic hyperkinesias has no influence on LLR.<br>Absent LLR could be attributed to the degeneration of neurons along the LLR trans-cortical pathway involving VPL nucleus of Thalamus and cortico-cortical connections |
| Lefaucheur et al.[58] | 20 HD | Electric | Median nerve stimulation at wrist and recordings were obtained from thenar muscles tested at near-maximal effort | LLR | Latency: 45.8 ± 4.2 | LLR was present in 17/20 patients at the time of recruitment<br>LLR was present in 7/20 patient after 2 years | LLR disappeared with the worsening of motor scores on UHDRS over 2-year period |
| Sebastiano et al.[59] | 3 HD with myoclonus | Electric | Median nerve stimulation at wrist and recordings were obtained from thenar muscle during tonic contraction of 30-40% of maximum | LLR present at rest in 1 patient, and present in all during muscle contraction | – | SLR/LLR amplitude: 0.83. Enhanced LLR Low SLR/LLR ratio, 3 S.D. less compared to controls | This suggests impairment of cortical circuitry in childhood and juvenile onset HD. |
| Huttunen et al.[60] | 27 HD | Stretch | EMG recording from stretched lateral gastrocnemius (triceps surae) and tibialis anterior bilaterally | SL1, SL2, ML (Mid latency) reflex in 50% of patients and controls and LLR | Mean latency: 34 msec | Mean latency: 114 msec<br>MLR latency: 84 msec<br>Delayed LLR onset and prolonged duration of LLR, reduced amplitude of ML | MLR delay in lower limbs is comparable with LLR absence in upper limbs.<br>There is prolonged intracerebral processing time among patients with HD since SEP (which reflects afferent pathway) is normal and efferent pathway by magnetic cortical stimulation is normal |

HD: Huntington's disease; HR: H-reflex; LLR: Long latency reflex; MLR: medium latency reflex; SLR: short latency reflex.

hereditary and sporadic hyperekplexia despite enlarged SEP in one patient. The rostro-caudal recruitment of muscles to noise and facial taps hinted at brainstem origin of the startle response.[64] In a case report by Luiz et al, a prominent C-reflex at 78 msec (LLR III) was noted in a patient with hyperekplexia secondary to neonatal hypoxia.[65]

***LLR in Miscellaneous Movement Disorders (n = 4 Studies):*** Koster et al. observed bilateral LLR response to ipsilateral stimulation in patients with persistent mirror movements (PMM).[66] Matthews et al. reported a case of Klippel-Feil syndrome with mirror movements, in which contralateral first dorsal interossei (FDI) showed comparable M2 response on stimulation of ipsilateral FDI.[67]

Patients with writer's cramps have LLR I more frequently with enhanced amplitude compared to the controls.[68] Lee et al. demonstrated delayed LLR II response along with delayed cortical relay time (CRT) suggestive of dysfunction in the sensorimotor pathways in SCA-6 patients.[69]

***LLR Following Therapeutic Interventions:*** A study on 34 patients with idiopathic focal dystonia revealed enlarged LLR I component with diminished LLR II which is attributable to the inhibitory effect of supplementary motor area (SMA) seen in dystonic subjects. Following Botulinum toxin, there was a reduction in the amplitude of LLR II without change in waveform of the opposite side, thereby maintaining a reciprocal relationship with LLR I suggesting the toxins effect at the neuromuscular level rather than central level.[70] LLR II alterations following botulinum toxin administration suggest that central motor patterns involved in focal dystonia can be modified by peripheral inputs.[70] In a study that assessed LLR while using levetiracetam in the management of cortical myoclonus, there was no significant influence of levetiracetam on LLR I among patients with cortical myoclonus. However, 3/9 patients had a reduction in SEP following levetiracetam use.[71]

### *Applications in Multiple Sclerosis (MS) (n = 6 Studies)*

Deuschl et al. studied 47 patients with probable and definite MS. Pathological LLR was found in 79 and 61% of confirmed and probable MS which was statistically significant when compared to SSEP.[72] In a study of 23 patients with acute phase MS, there was prolongation of LLR II latency, suggestive of impairment along the LLR pathway.[73] Abnormalities either in the afferent or efferent pathway can lead to altered LLR II latency, unlike SEP which is dependent only on the afferent system, that explains more frequent abnormality of LLR compared to SEP among MS patients. Many other studies also highlighted the intracortical delay as the principal factor behind the increased LLR latency among MS patients, the sensitivity of which exceeds that of SEP (Table 4).[74,75,76,77]

### *Applications in Miscellaneous Neurological and Non-neurological Conditions*

***LLR in Cerebellar Disorders (n = 2 Studies):*** Friedman et al. evaluated stretch induced LLR response in patients with cerebellar disorders. They revealed the presence of enlarged M2/M3 complex (LLR II/III) in disorders of cerebellar hemisphere, lower vermis and anterior lobe atrophy. On the contrary, diffuse cerebellar lesions didn't reveal any conclusive findings. In the Friedreich's ataxia subgroup, patients had markedly delayed or absence of M2/M3 complex. Authors have mentioned the limitation of distinguishing M2 and M3 response separately in view of overlapping latencies. Abnormalities of M3 response points towards the role of trans-cerebellar loop in modulation of M3 component of LLR.[78] In a study of 41 subjects with cerebellar disease by Diener et al., the SLR and MLR elicited by stretching triceps surae and LLR in the antagonist muscle (tibialis anterior) were found to be normal in patients with lesions restricted to cerebellar hemispheres or vestibulocerebellum; suggesting that the exact timing of these reflexes is independent of the cerebellum. Three patients with Friedreich's ataxia had delayed MLR probably attributable to the suprasegmental pathway, and markedly delayed M3 response.[79]

***LLR in Cortical Dementia (n = 1 Study):*** In a pilot study of patients with fronto-temporal dementia (FTD), LLR II response was not observed in comparison to patients with Alzheimer's disease (AD), who had normal LLR II response.[80]

***LLR in Brain Tumor (n = 1 Study):*** Stetkarova et al. reported a case series of 3 patients with brain tumor adjoining central sulcus. All had enhanced SEP and only one had exaggerated LLR. The latencies have not been mentioned in the article. The results are attributed to the increased cortical hyperexcitability or suppression of cortical inhibitory activity.[81]

***LLR in Rasmussen Encephalitis (n = 1 Study):*** Gündüz et al. studied LLR in three patients with Rasmussen encephalitis, and found the presence of enhanced LLR in all cases. One of the patients had C- reflex at a latency of 55 ms, suggestive of LLR II response. For the rest of patients, the latencies were not mentioned in the paper. The findings were attributed to the involvement of cortical pathways in stimulus sensitive positive and negative myoclonus.[82]

***LLR in Adrenomyeloneuropathy (n = 1 Study):*** Liao et al. measured LLR and CRT in 2 patients with normal MRI and compared with 10 controls. They demonstrated delayed LLR with a latency that corresponds to LLR II.[83]

***LLR in Myotonic Dystrophy Type 1 (DM1) (n = 1 Study):*** In a study of 24 patients with DM1, abnormalities in the muscle twitch properties such as reduced H-reflex depression with less robust LLR response was observed.[84]

***LLR in Stroke (n = 3 Studies) and Neurorehabilitation (n = 1 Study):*** Results of LLR assessment among long term stroke-survivors were contradictory.[85,86,87] A more recent study by Bank C et al. showed that stroke survivors with intact LLR, have a better clinical recovery with respect to walking speed and power of ankle flexors compared to healthy controls. Patients who were LLR negative had dysfunctional modulation of stretch responses.[88] This highlights the potential role of LLR in the assessment of post-stroke recovery.

***LLR in Idiopathic Scoliosis (n = 1 Study):*** Maguire et al. studied segmental reflex regulation in 37 patients with idiopathic scoliosis and 8 patients with secondary scoliosis, and demonstrated the presence of LLR in the idiopathic and their absence in the secondary group indicating the role of aberrant reflex pathways in the development of scoliosis.[14]

***LLR in Chronic Low Back Pain (n = 1 study):*** Shenoy et al. studied surface electromyograph of erector spinae and rectus abdominis muscles in athletes with chronic non-specific low backache (n = 25) and asymptomatic athletes (n = 24). They showed that symptomatic athletes had lower amplitude and delayed onset of LLR to unexpected perturbations, which is attributable to the task-modulated training of LLR which gets impaired in symptomatic athletes.[15]

***LLR and Theophyline (n = 1 Study):*** Bartel et al. studied the neurophysiological impact of theophylline on healthy volunteers. LLR showed no definite alterations from normal and no change

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**Table 4:** Studies of LLR in Multiple sclerosis

| Study | Sample size | Type of stimulation | Method | Reflexes elicited | LLR properties with subtype | Comments |
|---|---|---|---|---|---|---|
| Deuschl et al.[72] | 47 probable or definite MS | Electric | Median and superficial radial nerve stimulation, bilaterally | M wave, HR, LLR I (occasionally) LLR II and LLR III | Mean latency: LLR I: 40.2 ± 2.4 ms<br>LLR II: 49.8 ± 2.5 ms<br>LLR III: 71 ± 4.3 ms<br>Absent LLR II with preserved HR (31%)<br>Delayed LLR II (29%)<br>Enlarged HR (6%) | Pathological LLR in 23/29 (79%) of definite MS, 11/18 (61%) of probable MS. LLR studies had greater sensitivity in detecting abnormalities related to MS than SEP studies |
| Bonfiglo et al.[73] | 23 MS | Electric | Median nerve stimulation at wrist | H Reflex, LLR II | Mean latency: 53 ms (LLR II) | Prolonged intracortical delay of LLR measured by CRT in MS patients suggestive of impairment of sensorimotor intracortical pathways |
| Ivochich et al.[74] | 36 MS and 30 healthy controls | Electric | Median nerve stimulation at wrist and recording from thenar muscle | M response, R1 and R2 response | Prolonged R2 (LLR II) latency, reduced amplitude and change in waveform. Altered LLR was found in 93% patients with assured MS, 83% probable and 55% patients with possible MS | Pathological changes occurred more frequently in LLR than SEP. SEP analyses only afferent pathway while LLR analyses both afferent and efferent pathways thus, can predict silent demyelinating lesions. |
| Michelis et al.[75] | 37 MS | Electric | Median nerve stimulation at wrist | LLR I, LLR II | LLR abnormal (delayed or absent LLR II) in 17 /37 (45.9%) patients. | LLR, MEP and SEP are conducted along the same fibres |
| Mastumoto et al.[76] | 34 MS and 25 controls | Electric | Median nerve stimulation at wrist | All patients had detectable SLR. LLR was not detected in 5/34 patients. | Mean latency: 43.9 ± 3 ms. Prolonged LLR latency (LLR I) ($p < 0.0001$). | 92% of definite MS had prolonged LLR latency (n = 13), while 54% of them had N20 abnormalities. This occurs due to interruption of LLR pathways due to the demyelinating lesion. |
| Toydemir H et al.[77] | 23 definite MS and 15 controls | Electric | Stimulation of median nerve at wrist bilaterally | HR, LLR I to III | Mean latency: 54.5 ± 4.67<br>Latency difference: 3.2 ± 3.08. Prolonged LLR II latency ($p = 0.014$). | Prolonged LLR II suggests impairment along the LLR pathways. Additionally, corpus callosal area score correlated with EDSS score but not with LLR delay. |

LLR: Long latency reflex; MLR: medium latency reflex; MS: Multiple sclerosis; SEP: somatosensory evoked potential; SLR: short latency reflex.

following B6 supplementation. F wave latencies reduced and the percentage increased, highlighting the stimulatory effect of theophylline on neuraxis.[89]

## Discussion

The drive to understand the mechanism of rigidity in parkinsonian patients led to several LLR experiments, which advanced from animal models to human subjects and extended beyond, to the computational models.[90] The degeneration of neurons in the basal ganglia, as seen in PD has been thought to impair transmission via the thalamo-cortical structures to the motor cortex. Thus, the modulatory effect of basal ganglia prior to the voluntary movements is deemed to be affected in these patients, which subsequently leads to an exaggerated LLR response.[18] In the lower limbs, exaggerated MLR can be explained by the heightened excitability of the spinal reflex center due to the facilitatory inputs from group II afferents.[27] Reduced first inhibitory component of cutaneous reflex has been accounted for by another plausible hypothesis which is based on the alteration of the excitability of spinal interneurons, that form the common converging site of cutaneous afferents and descending pyramidal fibers.[31]

The electrophysiology of HD revealed the absence of LLR as an important finding in this disorder. This, in presence of markedly diminished early cortical SEP with normal neck SEP, serves to reflect a crucial hypothesis that it is the diminished impulse transmission to the cortex at the thalamic or thalamocortical projection level, which is the most probable underlying pathophysiology.[91,92] This enables us to explain the trans-cortical loop-mediated delayed LLR II response. The behavioral alterations associated with HD could also be a manifest of the impaired transcortical loop.[93] Besides, the greater diminution of LLR in distal joints compared to the wrist comes in line with the hypothesis of the greater output of transcortical pathways in the manipulation of distal small joints.[54,94] Conflicting results came from the study by Lefaucheur et al. attributable to the differences in the technical aspects of LLR measurement.[13] A single study on the unique variant of HD also called the Westphal variant, had retained LLR.[95]

The studies on cortical myoclonus either sporadic, symptomatic, essential, or epileptic, revealed the presence of enhanced LLR, which when mediated by the sensorimotor cortex, is also called C-reflex.[33] However, LLR forms only a fraction of the armamentarium in the electrophysiological evaluation and classification of myoclonus.[35,96] The studies on PME syndromes, a form of epileptic myoclonus, have reflected on the presence of cortical hyperexcitability which gets manifested in the form of enlarged LLR. One of the studies enlightened the difference in the occurrence of LLR enhancement between patients with ULD and sialodosis with greater prevalence in the former.[48]

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The studies on MS yielded consistent results with delayed LLR II response suggestive of slowing of impulse transmission in the central part of the reflex arc. In many of the other clinical entities studies are restricted to isolated case reports and small case series as mentioned above. LLR has also been assessed among patients undergoing botulinum toxin therapy for idiopathic focal dystonia, the effect of levodopa on cortical myoclonus, and CNS effects of theophylline therapy. There have been few studies on the applications of LLR outside the field of clinical neurosciences. Balestra C studied the role of LLR in the involuntary cessation of apnea.[97] Oostveen et al. have studied LLR as a tool to detect delayed spinal cord ischemia during and after descending aorta repair.[98]

Some of the novel areas where LLR has been studied to enlighten the neurophysiologic aspects or as a diagnostic marker were based on a small sample size. Large scale studies are still lacking in many of these clinical conditions, thereby rendering it difficult to draw meaningful conclusions or subject them to robust statistical analyses. Contrasting results from different studies on the same clinical entity based on differences in the measurement technique is an important aspect to consider before decision making. Some of the areas like properties of LLR in atypical parkinsonian syndromes and controlled studies on the role of dopaminergic medications on LLR have remained unexplored to a considerable extent.

## Conclusions

Our systematic review provides valuable insights on the wide array of clinical applications of LLR particularly in the field of movement disorders. The disorders such as parkinsonian syndromes, Huntington's disease and myoclonus of varied etiologies have been studied extensively till date which have yielded consistent results. Further research is needed to extend the applications of this electrophysiological tool in other areas of neurology.

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**Authors' Roles.**

1. **Debjyoti Dhar:** Conceptualization, organization, execution, writing of first draft
2. **Nitish Kamble:** Conceptualization, organization, Manuscript review and critique
3. **Pramod Kumar Pal:** Conceptualization, supervision, organization, Manuscript review and critique

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