Chapter 6.5

Long-latency reflexes following electrical nerve stimulation

G. Deuschl\textsuperscript{a,*} and A. Eisen\textsuperscript{b}

\textsuperscript{a}Department of Neurology, Christian-Albrechts-University Kiel, Niemannsweg 147, D-24105 Kiel (Germany)
\textsuperscript{b}Department of Neurology, University of British Columbia and Vancouver General Hospital, 855 West 12th Avenue, Vancouver, BC V5Z 1M9 (Canada)

General description of the method

Reflexes of hand and arm muscles are useful to analyze functional abnormalities of the transcortical pathway (dorsal column–medial lemniscus–thalamo-cortical–cortico-spinal). The peripheral nerve component (median nerve or superficial radial nerve) are also incorporated. These reflexes test the integrity of the transcortical pathway (absent or delayed reflexes) but can also reveal a state of hyperexcitability of the CNS. Reflexes in hand and arm muscles can be elicited with different kinds of stimuli including muscle stretch, cutaneous stimulation or electrical stimulation of various nerves. Similar reflexes can be elicited from leg muscles, but, because they are less consistent, they are seldom used compared to the hand and arm reflexes. (for review see Deuschl and Lüking 1990).

There are a variety of different reflexes that can be recorded from arm and hand muscles most likely conducted along different pathways. The present review will focus only on reflexes of hand muscles for which sufficient data are available in health and diseases.

* Correspondence to: Prof. Dr. G. Deuschl, Department of Neurology, Christian-Albrechts-Universität, Niemannsweg 147, D-24105 Kiel (Germany).

The physiology of hand muscle reflexes

The reflex pattern in hand muscles depends on the mode of stimulation. Following muscle stretch the pattern consists of the so-called M1 response and the M2 response (Rothwell 1990). Occasionally, an M3 response is discernible with a variable latency. The M1 response is equivalent to the monosynaptic reflex response elicited by Ia-afferents. The long-latency response M2 is most likely due to the activation of low-threshold muscle and cutaneous afferents (Noth et al. 1985). The central reflex pathway of the M2 is a transcortical one and equivalent to the reflex pathways of those following cutaneous stimulation. The reflexes of proximal arm muscles (m. biceps and m. brachioradialis) differ in this respect. Although the short-latency M1 response is also transmitted through the Ia-monosynaptic reflex pathway, the M2 response in arm muscles is rather mediated by group 2 afferents. The reflex pattern following adequate, pure cutaneous stimulation of finger nerves has been assessed in hand muscles only and is characterized by an early excitation (E1), an early inhibition (I1) and a later excitation (E2) comparable to the pattern after electric stimulation of finger nerves (Jenner and Stephens 1982).

The pattern of hand muscle reflexes following electric stimulation depends on the nerve which is
stimulated. When *mixed nerves* are used the pattern consists of the M-wave due to direct excitation of the motor axons at about 3–10 ms depending on the locus of stimulation. The reflex pattern consists of the Hoffmann reflex (HR), a monosynaptic reflex mediated through Ia afferents and up to three subsequent long latency reflexes (LLRs) which are termed as LLR I, II and III. These reflexes have been assessed in thenar muscles following median nerve stimulation at the wrist or the first dorsal interosseus following ulnar nerve stimulation at the wrist (Eisen and Deuschl 1994). The reflex pattern after stimulation of pure cutaneous nerves has been described after stimulation of finger nerves or of the radial superficial nerve (Friedli and Deuschl 1994) and consists of an early excitatory component (E1, cLLR I) and a second excitatory component (E2, cLLR II). Between the excitatory periods there is an inhibitory component (I1) which is regularly seen after stimulation of the second digit and recording of the first dorsal interosseus but only rarely after radial superficial nerve stimulation and thenar muscle recording.

The reflex pathway for the HR which is conducted along the Ia-afferents of the stimulated nerve and transmitted monosynaptically to the motoneuron is easy to elicit in all normal subjects. In some elderly subjects it may be difficult in to elicit without a significant amount of M-wave component and then the reflex response may be misinterpreted as an F wave. LLR II is also readily elicited in all normal subjects. This longer latency reflex response is mediated through fast conducting cutaneous and Ia afferents, and is subsequently transmitted within the dorsal column to the nucleus cuneatus and along the lemniscal pathway to the cortex. It is assumed that the excitation passes from the sensory to the motor cortex and from there along the corticospinal tract back to the motoneuron. The evidence for this has been derived from animal experiments and from clinical studies in normal subjects and patients with strategically located lesions (Deuschl and Lüking 1990).

The pathways for the LLR I and the LLR III which are less consistently elicited are not completely worked out. There is evidence that the LLR I is also a transcortical reflex, mainly because of the observation, that the so-called C-reflex, which is seen in many patients with cortical myoclonus including giant SEPs (Shibasaki 1995) has mostly the same latency as the LLR I and thus could correspond to an enhanced LLR I. Some patients have reflex myoclonic jerks after electrical stimulation of the median nerve at the latency of the LLR III, indicating that this could also be a transcortical reflex. However, a more complicated pathway for this reflex is usually assumed and there is some evidence that a transcerebellar loop is involved.

Even for the hand muscles it should not be assumed that the reflexes following stretch, cutaneous or electric nerve stimulation can be equated. Most likely, M1 is equivalent to the HR. M2 is equivalent to the LLR II and E2 (see below). However, E1, I1, LLR I and LLR III and M3 are difficult to compare and do not seem to have equivalents across the different modalities of stimulation.

**Methods**

The short and longer latency reflexes are easily recorded using routine EMG-equipment. The subject has to be seated comfortably with the arms supported. The abductor pollicis brevis, from which responses are recorded, is activated voluntarily with a constant force of roughly 40% of maximum. The reflex responses cannot be recorded in the absence of muscle contraction. Percutaneous stimulation and recording is used as for routine motor conduction studies. We recommend median nerve stimulation at the wrist at an intensity that is threshold for motor fibers (square-wave pulse, 200 μs, 3 Hz repetition rate). When the stimulus strength is correctly adjusted, averaging will elicit a small M-wave (about 50–100 μV). The EMG of the thenar muscles is filtered (5–3000 Hz), full-wave rectified and averaged (256–512 sweeps). Some commercially available EMG-machines have specially implemented filters (integrators) for the rectified EMG which sometimes can alter the shape of the reflex pattern. They should therefore be turned off. If a pure cutaneous nerve needs to be stimulated, we choose the superficial
radial nerve at the wrist. Stimulus intensity should be 2.5–4 times sensory threshold (below pain threshold). Otherwise the recording procedure is the same as for the median mixed nerve LLR.

Onset latencies are measured. Sometimes the onset of a reflex is questionable if there is an inhibitory component preceding the positive reflex. In this case we use the baseline of the EMG response as the reference. The amplitudes of the reflexes depend on the amount of baseline activation and thus the number and size of subliminal fringe motorneurons. However, the rectified baseline EMG and the reflex size are roughly linearly related. Therefore, the reflex size is defined as the fraction of baseline EMG. The duration of the reflexes is simply defined as the difference between its onset and termination.

The normal and pathologic reflex pattern of thenar reflexes

The first reflex is the Hoffmann-reflex (HR) at 25–34 ms in the thenar muscle followed by up to three long-latency reflexes (LLR I–III). The latency range of the LLR I–III is height dependent. For adults between values are 35–46 ms (LLR I), 45–58 ms (LLR II) and (68 ms (LLR III) (see Table 1). Because latencies incorporate a peripheral component, they will vary with arm length and the peripheral conduction velocity. For example, in a peripheral neuropathy, the reflex latencies will be prolonged because of the peripheral not central component. There are two ways to reduce the variance induced by these factors. The first is to use the difference between the LLR and the HR latency as a measure of central conduction (for normal values see Table 1). The second is to express the LLR-latencies as a function of the HR-latency according to the formulas:

LLR II latency = 19.3 + 1.07 HR latency

LLR I latency = 12.6 + 0.981 HR latency

By using either of these approaches it is possible to assess the reflex latency even in patients with peripheral neuropathies.

The normal pattern after median nerve stimulation consists of the HR and the LLR II. Absence of either is considered abnormal. In about 30% of the normal subjects a small LLR I response is present and in another 20% a later reflex response, the LLR III, can be found. The reflex pattern after radial superficial nerve stimulation shows the cutaneous LLR II (cLLR II) as the only constant reflex in all the normal subjects. The cLLR I corresponds to the E1 after finger nerve stimulation and is present in only 35% of the controls.

The amplitudes of the reflexes (HR, LLR II, cLLR II) show a negative correlation with age. This decrease is small and does not need to be taken into consideration for clinical purposes. The maturation of the pattern of cutaneous reflexes has been studied in detail for the reflexes following index finger stimulation. Up to the age of 8 years, the E1 can be larger than the E2. Later in life, the E2 is larger in healthy subjects.

Abnormal patterns in neurologic disease

Four abnormal patterns of the thenar reflex pattern following median nerve or radial superficial nerve stimulation can be identified: an enlarged or an absent HR, an absent LLR II, a delayed LLR II and an enlarged LLR I (see Table 2).

Spasticity

The typical reflex pattern in disorders associated with spasticity is the enhanced HR with relative amplitudes (multiples of baseline amplitude) of more than 4.5 and an absent or reduced LLR II. It is almost impossible to diagnose a reduced LLR II amplitude because the statistically defined lower limit for its amplitude is near zero (Table 1). We assume an LLR II to be present (and normal), if its latency is within the normal range (see Table 1) and if it has a discernible amplitude. When the HR is very large, the amplitude of the LLR II following stimulation of the median nerve can be indiscernible because the motoneurons might be refractory. In this case it is especially helpful to additionally test for the cutaneous LLR following radial superficial nerve stimulation.
TABLE 1

NORMAL VALUES FOR THENAR HAND MUSCLE REFLEXES FOLLOWING MEDIAN NERVE STIMULATION (HR and LLR) OR RADIAL SUPERFICIAL NERVE STIMULATION (cLLR)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
<th>Count</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean + 2.5 SD</th>
<th>Mean - 2.5 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR latency</td>
<td>28.9</td>
<td>2.4</td>
<td>0.2</td>
<td>102</td>
<td>24.1</td>
<td>35.4</td>
<td>34.804</td>
<td>22.924</td>
</tr>
<tr>
<td>LLR I latency</td>
<td>40.6</td>
<td>2.5</td>
<td>0.5</td>
<td>26</td>
<td>36.8</td>
<td>47.2</td>
<td>46.6815</td>
<td>34.4265</td>
</tr>
<tr>
<td>LLR II latency</td>
<td>50.3</td>
<td>3.2</td>
<td>0.3</td>
<td>102</td>
<td>43.1</td>
<td>59.3</td>
<td>58.173</td>
<td>42.413</td>
</tr>
<tr>
<td>LLR III latency</td>
<td>76.0</td>
<td>4.6</td>
<td>1.0</td>
<td>20</td>
<td>70.3</td>
<td>92.1</td>
<td>87.4525</td>
<td>64.4575</td>
</tr>
<tr>
<td>cLLR I latency</td>
<td>37.6</td>
<td>2.6</td>
<td>1.0</td>
<td>7</td>
<td>35.0</td>
<td>43.0</td>
<td>44.1635</td>
<td>30.9785</td>
</tr>
<tr>
<td>cLLR II latency</td>
<td>50.2</td>
<td>3.0</td>
<td>0.3</td>
<td>100</td>
<td>43.0</td>
<td>60.0</td>
<td>57.665</td>
<td>42.795</td>
</tr>
<tr>
<td>cLLR III latency</td>
<td>75.9</td>
<td>3.6</td>
<td>0.7</td>
<td>31</td>
<td>70.0</td>
<td>82.0</td>
<td>84.926</td>
<td>66.816</td>
</tr>
<tr>
<td>HR-amplitude</td>
<td>1.9</td>
<td>1.1</td>
<td>0.1</td>
<td>102</td>
<td>0.3</td>
<td>4.8</td>
<td>4.674</td>
<td>–</td>
</tr>
<tr>
<td>LLR I-amplitude</td>
<td>0.4</td>
<td>0.1</td>
<td>0.0</td>
<td>25</td>
<td>0.2</td>
<td>0.8</td>
<td>0.7325</td>
<td>–</td>
</tr>
<tr>
<td>LLR II-amplitude</td>
<td>1.2</td>
<td>0.6</td>
<td>0.1</td>
<td>102</td>
<td>0.3</td>
<td>3.0</td>
<td>2.6595</td>
<td>–</td>
</tr>
<tr>
<td>LLR III-amplitude</td>
<td>0.8</td>
<td>0.5</td>
<td>0.1</td>
<td>20</td>
<td>0.3</td>
<td>2.3</td>
<td>1.945</td>
<td>–</td>
</tr>
<tr>
<td>cLLR I-amplitude</td>
<td>0.4</td>
<td>0.2</td>
<td>0.1</td>
<td>7</td>
<td>0.1</td>
<td>0.6</td>
<td>0.787</td>
<td>–</td>
</tr>
<tr>
<td>cLLR II-amplitude</td>
<td>1.2</td>
<td>0.5</td>
<td>0.0</td>
<td>100</td>
<td>0.3</td>
<td>2.5</td>
<td>2.4355</td>
<td>–</td>
</tr>
<tr>
<td>cLLR III-amplitude</td>
<td>0.8</td>
<td>0.5</td>
<td>0.1</td>
<td>31</td>
<td>0.3</td>
<td>2.4</td>
<td>2.089</td>
<td>–</td>
</tr>
<tr>
<td>HR-duration</td>
<td>10.4</td>
<td>2.5</td>
<td>0.2</td>
<td>102</td>
<td>6.0</td>
<td>17.0</td>
<td>16.5755</td>
<td>4.1505</td>
</tr>
<tr>
<td>LLR I-duration</td>
<td>8.9</td>
<td>7.8</td>
<td>1.5</td>
<td>26</td>
<td>3.0</td>
<td>46.0</td>
<td>28.46</td>
<td>–</td>
</tr>
<tr>
<td>LLR II-duration</td>
<td>22.3</td>
<td>5.4</td>
<td>0.5</td>
<td>101</td>
<td>12.0</td>
<td>40.0</td>
<td>35.7445</td>
<td>8.9095</td>
</tr>
<tr>
<td>LLR III-duration</td>
<td>27.6</td>
<td>8.7</td>
<td>2.0</td>
<td>20</td>
<td>9.0</td>
<td>44.0</td>
<td>49.445</td>
<td>5.755</td>
</tr>
<tr>
<td>cLLR I-duration</td>
<td>10.0</td>
<td>3.7</td>
<td>1.4</td>
<td>7</td>
<td>7.0</td>
<td>17.0</td>
<td>19.1275</td>
<td>–</td>
</tr>
<tr>
<td>cLLR II-duration</td>
<td>24.0</td>
<td>6.6</td>
<td>0.7</td>
<td>100</td>
<td>9.0</td>
<td>50.0</td>
<td>40.395</td>
<td>7.605</td>
</tr>
<tr>
<td>cLLR III-duration</td>
<td>27.7</td>
<td>6.2</td>
<td>1.1</td>
<td>31</td>
<td>15.0</td>
<td>40.0</td>
<td>43.242</td>
<td>12.112</td>
</tr>
<tr>
<td>LLR I minus HR latency</td>
<td>12.1</td>
<td>1.4</td>
<td>0.3</td>
<td>26</td>
<td>9.9</td>
<td>14.4</td>
<td>15.533</td>
<td>8.613</td>
</tr>
<tr>
<td>cLLR I minus HR latency</td>
<td>10.4</td>
<td>2.9</td>
<td>1.1</td>
<td>7</td>
<td>7.9</td>
<td>16.6</td>
<td>17.7</td>
<td>3.1</td>
</tr>
<tr>
<td>LLR II minus HR latency</td>
<td>21.4</td>
<td>1.8</td>
<td>0.2</td>
<td>102</td>
<td>17.9</td>
<td>26</td>
<td>25.9225</td>
<td>16.8975</td>
</tr>
<tr>
<td>cLLR II minus HR latency</td>
<td>21.4</td>
<td>2.0</td>
<td>0.2</td>
<td>100</td>
<td>16.9</td>
<td>25.9</td>
<td>26.2505</td>
<td>16.4955</td>
</tr>
<tr>
<td>LLR III minus HR latency</td>
<td>46.5</td>
<td>5.1</td>
<td>1.1</td>
<td>20</td>
<td>40.4</td>
<td>63.2</td>
<td>59.3275</td>
<td>33.7225</td>
</tr>
<tr>
<td>cLLR III minus HR latency</td>
<td>46.5</td>
<td>3.2</td>
<td>0.6</td>
<td>31</td>
<td>39.6</td>
<td>53.9</td>
<td>54.6025</td>
<td>38.4675</td>
</tr>
</tbody>
</table>

Multiple sclerosis

Depending on the type of the central lesion, almost all the abnormal reflex patterns can be found in multiple sclerosis. Enlarged HR and absent LLR II are the most common findings. The most specific finding, however, is the delay of the LLR II. This can be found in up to 50% of patients with MS. Compared with SEP-testing it seems the investigation of the LLR seems to yield more often abnormal findings. Compared with SEP and tran-}

cranial magnetic stimulation the LLR-testing may provide additional diagnostic information (Michels et al. 1993).

Focal lesions of various origin

Focal lesions within the reflex pathway for the LLR II can lead to abnormal reflex patterns. Especially, reduced or absent LLR II are found in lesions affecting the afferent pathway to the motor cortex.
(dorsal columns, lemniscus medialis, thalamus thalamo-cortical pathway). Affection of the cortico-spinal tract is always likely to be present when the HR is enhanced – mostly together with absent LLR II.

**Movement disorders**

*Huntington’s disease*

In Huntington’s disease the LLR II amplitude is reduced or the LLR II (and cLLR II) is absent. These abnormalities are seen in about 50% of asymptomatic relatives of patients with the Huntington gene. The HR amplitude is only slightly increased in Huntington’s disease. Choreatic hyperkinesias can occur in a large variety of different other conditions other than Huntington’s disease which are commonly labeled as symptomatic chorea. Available information suggests that the absence of LLR II is unique for Huntington’s disease and does not occur in symptomatic chorea.

*Parkinson’s disease and parkinsonian syndromes*

The cutaneous inhibitory period (I1) following digital nerve stimulation was found to be reduced in Parkinson’s disease, probably indicating reduced inhibition related to parkinsonian rigidity. The LLR following median nerve stimulation often show an enhanced LLR I. The relation of this finding to the symptoms of Parkinson’s disease is not yet clear. A correlation with rigidity was not found but some correlation was found with the occurrence of an action tremor. It is interesting to mention that the cutaneous reflexes do not always show this enhanced LLR I component.

The enhanced LLR I in parkinsonian syndromes with reflex myoclonus, e.g. corticobasal degeneration (CBD) is usually much larger than in idiopathic Parkinson’s disease and is always accompanied by increased cutaneous LLR I (radial superficial or finger nerve stimulation). In this condition the combination of an akinetic-rigid syndrome with apraxia or alien limb syndrome and reflex myoclonus is already suggestive for CBD. But the routine LLR-testing may uncover a subclinical enhancement of the LLR as a further important diagnostic tool for this condition. Thus we consider this an important test for the diagnosis of CBD. Reflex myoclonus and especially enhanced LLR are almost always found in CBD, but in the very early stage of the condition it may still be normal. The question if the abnormal LLR I is found only in CBD or if it may also occur in other non-idiopathic parkinsonian syndromes is still open.

*Cerebellar disease and Friedreich’s disease*

In Friedreich’s disease the majority of patients has no longer HR and LLR because of the reduced conduction in peripheral nerves. Those which still have reflexes exhibit a delay of the LLR II-latency with respect to the HR-latency (Alfonsi et al. 1992). This is compatible with a delayed conduction within the dorsal column which is known to be affected in Friedreich’s disease. The LLR III response was found to be enhanced in various cerebellar degeneration’s suggesting a major role of the cerebellum in the generation of the LLR III.

*Essential tremor*

In patients with essential tremor, enhanced LLR I does occur in about 40% of the patients. This is usually only an enhanced reflex following median nerve but not radial superficial nerve stimulation. A statistical association between reciprocal alternating activity in antagonistic muscles of the tremor bursts has been found, but the pathophysiological significance remains unknown in this condition.

*Dystonia*

Stretch reflexes of the wrist muscles have shown to be increased (M2/3-component). More recent investigations (Naumann and Reiners 1997) of the electrically elicited hand muscle reflexes have shown an increased incidence of abnormally enlarged LLR I and reduced amplitudes of the LLR II. Botulinum toxin injections led to even smaller LLR II.

*Myoclonus*

One of the most important applications of hand-muscle testing is the diagnosis and classification of myoclonus. The different forms of myoclonus can be separated by means of clinical and electrophysiological criteria (Shibasaki 1995). The electrophysiological criteria include the LLR-testing, the
measurement of the cortical SEP following median nerve stimulation and back-averaging of the ongoing EEG by means of spontaneous myoclonic jerks (back-averaging). All forms of reflex myoclonus have abnormal LLR, no matter if their origin is cortical or subcortical (Deuschl and Lüucking 1990). The most common form is the enhanced LLR I. It can occur together or without giant-SEP and or a spike preceding the spontaneous myoclonic jerks by about 15–25 ms. This is mostly interpreted as indicating enhanced excitability of the primary sensory cortex when the SEP is enlarged or of the primary motor cortex when the back-averaging is positive. In some patients the LLR III instead of the LLR I is enhanced which often is associated with an enlargement of later components of the SEP (N2–P2–N3). In rare instances the LLR II can also be enlarged (Shibasaki 1995).

It is important to mention that some forms of myoclonus are difficult to separate from tremors. These cases have been labeled as cortical myoclonic tremor. Most of them have enhanced LLR.

Thus, for myoclonic disorders or patients suspected for myoclonus, hand muscle reflexes are a useful electrophysiological investigation.

---

**References**


