

# Long-latency reflexes of hand muscles in idiopathic focal dystonia and their modification by botulinum toxin

Markus Naumann and Karlheinz Reiners

Department of Neurology, University of Würzburg, Germany

Correspondence to: Dr Markus Naumann, Neurologische Universitätsklinik, Josef-Schneider-Strasse 11, 97080 Würzburg, Germany

## Summary

Long-latency reflexes (LLR) in the hand muscles were elicited by electrical median nerve stimulation in 34 patients with idiopathic focal dystonia and 20 healthy control subjects. Twenty-seven patients had cervical dystonia and seven patients had upper limb dystonia. In about one-quarter of all patients the early LLR (LLR 1, occurring at ~40 ms) was abnormal with either increased amplitudes or only unilateral occurrence, mostly on the clinically affected side. Later responses (LLR 2, occurring at ~50 ms) were obtained bilaterally in all controls but were reduced or absent in some patients, mostly on the clinically affected side. In 12 dystonia patients, LLR studies were also performed after clinically effective injection of botulinum toxin. Following botulinum

toxin treatment there was a significant reduction of LLR 2 amplitudes on the clinically affected side. Our findings suggest a differential involvement of LLR generators in idiopathic dystonia with an antagonism between LLR 1 and LLR 2 on the affected sides. We propose that the reduction of the LLR 2 response may arise from overactivity of the supplementary motor area, confirming the current concept that dystonia results from cortical overflow due to disinhibited thalamocortical pathways projecting to the supplementary motor area. In addition, the dystonic motor pattern seems open to afferent modifications induced by peripheral botulinum toxin treatment.

**Keywords:** long-latency reflexes; dystonia; basal ganglia; supplementary motor area; botulinum toxin

**Abbreviations:** CBGD = cortical-basal ganglionic degeneration; CD = cervical dystonia; LLR = long-latency reflex; SMA = supplementary motor area; SR = short latency response; ULD = upper limb dystonia

## Introduction

Dystonia is a motor disorder characterized by abnormal involuntary movements and postures produced by prolonged muscle contraction that distort affected parts of the body into typical postures. While the pathophysiology of idiopathic dystonias is still uncertain, studies in symptomatic dystonias (Marsden *et al.*, 1985; Pettigrew and Jankovic, 1985; Lee and Marsden, 1994) demonstrated lesions of the lentiform nucleus, caudate nucleus and thalamus, indicating that dystonic disorders may be associated with basal ganglia dysfunction. The critical mechanism appears to be an impairment of striato-pallido-thalamic pathways with disinhibition of excitatory thalamo-cortical neurons resulting in cortical overflow and dystonic postures (Hallett, 1993). In the absence of consistent pathoanatomical abnormalities in idiopathic focal dystonias, electrophysiological studies are of particular value to identify

the neuronal systems involved and to explore underlying pathophysiological mechanisms.

Long-latency reflexes (LLR) have been successfully used to test afferent sensory and efferent motor pathways travelling via the cortex (Marsden *et al.*, 1973; Marsden *et al.*, 1976; Marsden *et al.*, 1983; Cheney and Fetz, 1984; Deuschl and Lücking, 1990; Hallett *et al.*, 1994). They have also proved helpful in the investigation of various movement disorders such as Parkinson's disease (Lee and Tatton, 1975; Tatton and Lee, 1975; Tatton *et al.*, 1984; Cody *et al.*, 1986; Deuschl and Lücking, 1989), Huntington's chorea (Noth *et al.*, 1983; Noth *et al.*, 1985; Deuschl *et al.*, 1989), and essential tremor (Deuschl *et al.*, 1987). Scanty reports on LLR testing in idiopathic dystonia patients have so far produced inconsistent findings. Rothwell *et al.* (1983a) found no alterations of

stretch-evoked LLRs on the clinically affected side of 16 dystonia patients, but observed an overflow of the reflex response to distant muscles not normally activated in the task. Tatton *et al.* (1984) studied LLR in response to imposed wrist displacements in 12 patients with idiopathic dystonia: a disturbance of the normal temporal mechanisms was described which resulted in a constant duration of the M1 (short latency response) and M2–3 responses (corresponding to LLR 2 at ~50 ms) with imposed force step loads. Most investigations were only performed on the affected side, and the more variable earliest LLR component (LLR 1, occurring at ~40 ms) was often neglected, while others (Deuschl and Lücking, 1990) disclosed that LLR 1 is frequently abnormal in various extrapyramidal disorders. The heterogeneous findings from LLR testing in dystonia patients, however, may also be due, at least in part, to differences in stimulation methods. While stretch-evoked LLRs had been studied previously, this is the first comprehensive study with electrically evoked LLRs. It is presently not known exactly in which way different methods of stimulation may influence LLR responses. In the special condition of stimulating hand muscles, stretch evoked and electrically evoked LLRs both excite Ia afferent fibres, but the central pathways of the LLR remain uncertain and may differ with different stimulation techniques (Deuschl and Lücking, 1990).

We set out to assess LLRs on both the affected and non-affected side in a large group of idiopathic focal-dystonia patients. Special attention was paid to LLR1 abnormalities. Additionally, LLR follow-up studies were performed in 12 patients, after successful treatment with botulinum toxin to evaluate its influence on the LLR pattern.

## Patients and methods

### *Clinical data of dystonia patients*

We investigated 34 patients with idiopathic focal dystonia including 27 patients with cervical dystonia (CD) and seven patients with upper limb dystonia (ULD) (17 females and 17 males; mean age 41.5 years; range 22–75 years). Sixteen patients had torticollis or laterocollis with head rotation or tilting to the left side, while nine patients had torticollis or laterocollis to the right side. Retrocollis was present in two patients. One torticollis patient had associated head tremor (7 Hz). The ULD group included five patients with simple writer's cramp and two patients with dystonic writer's cramp according to the definition of Marsden and Sheehy (1990). There was no patient with both cervical and upper limb dystonia. Dystonic symptoms were confined to the right hand in six subjects and were observed bilaterally in a single patient. One ULD patient had bilateral postural 9 Hz hand tremor in addition. The diagnosis of idiopathic dystonia was based on clinical presentation with focal dystonia without other neurological symptoms, normal cranial CT or MRI scans, and normal laboratory test of serum ceruloplasmin levels, urine copper excretion, tri-iodothyronine (T3),

thyroxine (T4), thyroid-stimulating hormone (TSH), anti-nuclear antibodies and red blood cells. The severity of cervical dystonia was classified according to Jankovic *et al.* (1990) on a scale of 0 to 4 (0 = no spasm; 1 = mild, barely noticeable; 2 = mild, without functional impairment; 3 = moderate spasm, moderate functional impairment; 4 = severe, incapacitating spasm). Eight patients had grade 4, 13 patients grade 3, and six had grade 2 dystonia. The mean duration of dystonia was 9.5 years (range 1–30 years). Throughout the text, the side showing the dystonic posture will be referred to as the 'affected side'. Conversely, the 'non-affected side' denotes the side contralateral to the clinically symptomatic side. In cervical dystonia, the side of the head turn was regarded as the 'affected side'. Twelve dystonia patients (11 CD, one ULD) were investigated before and 4–6 weeks after effective treatment with botulinum toxin.

Twenty healthy volunteers (eight females and 12 males; mean age 38.2 years; range 26–68 years) served as controls.

### *Electrophysiology*

All investigations were done with informed written consent of the subjects, patients and controls.

Electrophysiological tests were performed on a Multiliner EMG machine (Toennies, Hoechberg, Germany). Short-latency reflex (SR at ~30 ms) and LLR muscle responses were elicited by median nerve stimulation and recorded from thenar muscles on the affected and non-affected side using surface electrodes. The patient was asked to contract thenar muscles by opposing the thumb to the fifth finger so that a full EMG interference pattern could be seen on the screen. During electrical stimulation muscle contraction was maintained at ~20% of maximum force. The median nerve was stimulated (pulse duration 0.5 ms) at the wrist at a rate of 3 Hz. Stimulus strength was gradually increased to near motor threshold (1–5 mA) until a small compound muscle action potential could be recorded. The signal was filtered (1–3000 Hz bandpass) and averaged up to 500 times. Usually, peaks were more consistent on non-rectified recordings which were repeated at least twice to ensure reproducible readings of amplitudes. Amplitudes of all reflex components were measured peak to peak on non-rectified traces. In contrast, latencies were more precisely readable from rectified traces that were obtained in additional double recordings. Latencies of the brief response at ~30 ms (corresponding to the H-reflex), LLR 1 at ~40 ms, LLR 2 at ~50 ms, and LLR 3 at ~75 ms were measured. Absolute latencies and amplitudes of all components were compared intra-individually (affected side versus non-affected side) and were also compared with control subjects. In addition, amplitude ratios of SR and LLR 1–3 were calculated and compared on both sides.

In pilot studies, our method of testing LLR was examined with respect to its reproducibility in normal subjects. Sequential recordings on different days showed that the individual LLR components were consistent and reproducible; the

amplitudes of all LLR components varied by 19% (average) and latencies by 8%.

The possible influence of body position was tested in two ways. First, in consecutive recordings in four normal subjects, the variability of amplitudes and latencies of LLR responses was <5% in consecutive recordings made in the supine and in the sitting position. Obviously, the head position with respect to the trunk is critical in patients with torticollis. Therefore, in a second set of experiments, the variability of LLR amplitudes and latencies was tested in four sitting patients without botulinum toxin treatment. Consecutive recordings were made with the head kept straight by external fixation, then with the head turned to the left, and finally with the head turned to the right, to the maximum extent that was possible. In each case, amplitudes and latencies varied by <12%.

In patients investigated before and after botulinum toxin treatment, special care was taken that stimulus intensities and forces of muscle contraction were comparable during the respective measurements.

The majority of data proved normally distributed, so the unpaired *t* test was used for statistical analysis. Correlations were based on a linear regression model. The paired *t* test was applied to compare LLR data before and after therapy with botulinum toxin.

## Results

### *Long-latency reflexes in controls*

A typical recording from a normal subject is shown in Fig. 1A. Details of all components of the long-latency reflex can be obtained from Table 1 (amplitudes) and Table 2 (latencies). SR and LLR 2 responses could be recorded from all 20 control subjects. LLR 1 was found in eight controls, whereas LLR 3 was observed in four. The SR and LLR responses were always bilateral. The occurrence of LLR 1 or LLR 3 did not consistently depend on the intensity of voluntary activation, sex or age. To evaluate side-to-side differences, LLR amplitude ratios (right side/left side) were calculated. The range of LLR ratios was 0.6–2.3 for both LLR 1 and LLR 2, and 0.8–1.8 for LLR 3 (means  $\pm$  SD were  $1.26 \pm 0.35$  for LLR 1,  $1.04 \pm 0.39$  for LLR 2 and  $1.27 \pm 0.50$  for LLR 3).

### *Long-latency reflexes in dystonia patients*

Results of SR and LLR measurements from the affected side and non-affected side in 34 CD and ULD patients are given in Table 1 (amplitudes) and Table 2 (latencies). Bilateral SR could be recorded in all patients. Bilateral LLR 2 were found in all patients except for two CD patients (*see below*). Bilateral LLR 3 were found in 10 of the 27 CD patients. There were no merely unilateral LLR 3 responses.

The greatest variability occurred with the LLR 1 response. LLR 1 could be elicited bilaterally in nine of 34 patients

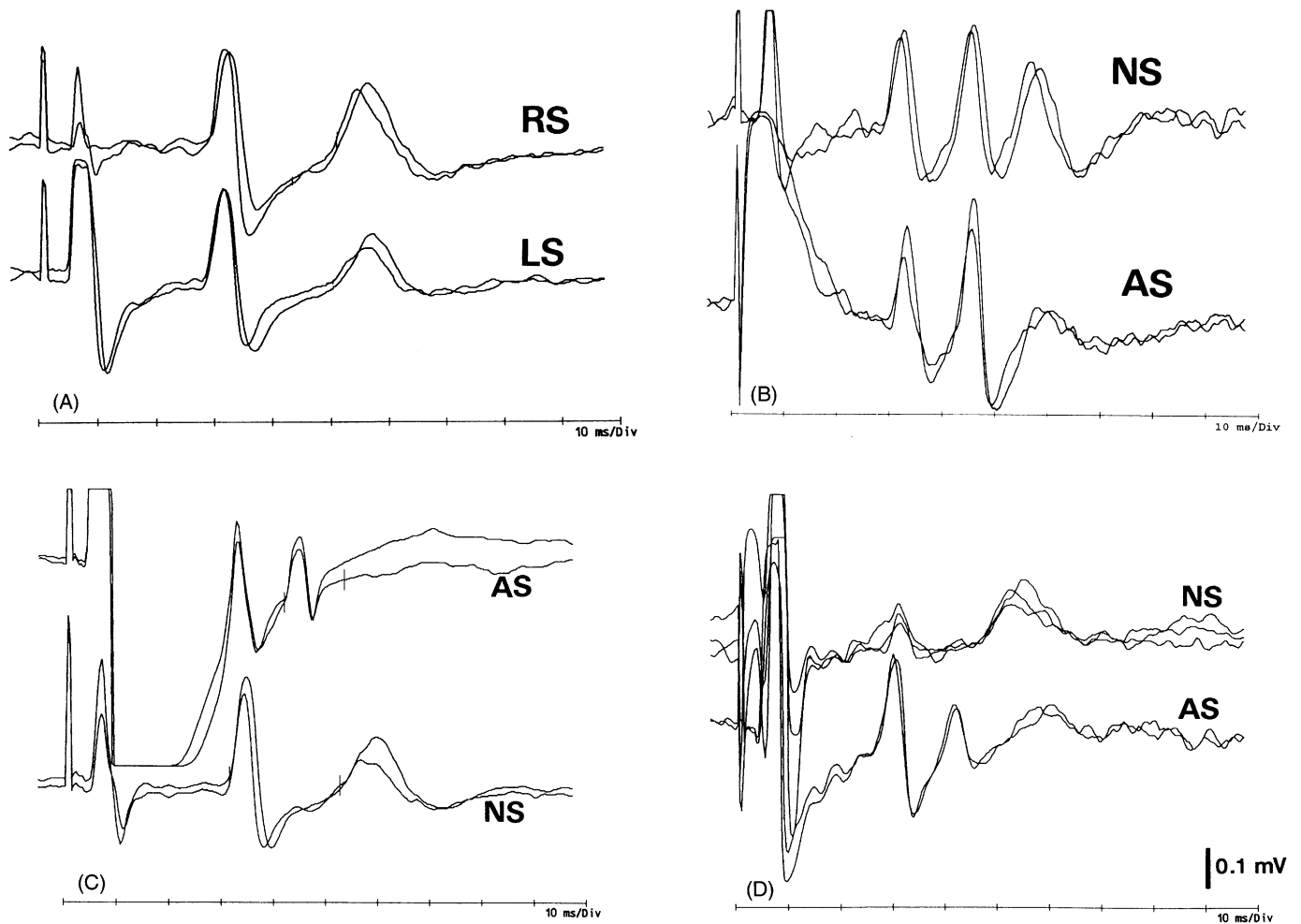
(eight CD, one ULD) among whom the LLR 1 amplitude was enhanced on both sides in one CD patient (more than twice the highest control value; *see Fig. 1B*) and enlarged only on the non-affected side in two CD patients (individual ratios of affected side/non-affected side 0.2 and 0.06). A unilateral LLR 1 response occurred in five patients (*Fig. 1C*). This LLR 1 abnormality was found on the clinically affected side in three CD patients and one ULD patient (*Fig. 1D*) and on the left side of a bilaterally affected ULD patient; amplitudes in these cases were within the control range. Thus, eight dystonic patients (six CD, two ULD) showed abnormal LLR 1 characteristics which were not observed in any control subject. The two patients with associated tremor had no LLR 1 abnormalities.

In addition, in some patients, the LLR 1 alteration was linked to LLR 2 abnormalities. In a severely affected CD patient with bilaterally enlarged LLR 1 amplitudes, the LLR 2 response was absent on the affected side and in the lower range of normal on the non-affected side (*Fig. 1B*). A ULD patient with unilateral occurrence of a normally sized LLR 1 on the affected side had no subsequent LLR 2 (*Fig. 1D*). This observation was also made in a CD patient who had abnormally increased LLR 1 on the non-affected side associated with a significant reduction of LLR 2 amplitude. Two other CD patients with unilateral but normal-sized occurrence of LLR 1 on the affected side had a moderate reduction of the following LLR 2 amplitude (within the lower range of normal). Despite the apparent negative correlation between LLR 1 and LLR 2 responses in individual patients, the group statistics within CD and ULD patients, and statistics including all dystonia patients failed to demonstrate a negative correlation of amplitudes ( $P > 0.05$ ). For pooled amplitude and latency data, significant differences could not be established between controls and dystonia patients.

With respect to dystonia subgroups, a significantly lower amplitude SR was found on the affected side in ULD patients (mean  $\pm$  SD;  $334 \pm 136 \mu\text{V}$ ) compared with CD patients (mean  $\pm$  SD;  $500 \pm 168 \mu\text{V}$ ) ( $P < 0.05$ ). ULD patients also had significantly greater side-to-side differences of SR latencies ( $0.96 \pm 1.8 \text{ ms}$ ) (affected side minus non-affected side) compared with CD patients ( $0.66 \pm 0.9 \text{ ms}$ ) ( $P < 0.01$ ). However, mean SR amplitudes and latencies in both CD and ULD patients were not significantly different from controls ( $P > 0.05$ ). Since LLR latencies did not show a similar difference between patient subgroups the implication of this finding remains uncertain.

### *Long-latency reflexes before and after botulinum toxin treatment*

All patients (11 CD, one ULD) treated with botulinum toxin responded well to this therapy. Detailed information on pre- and post-treatment data is given in Table 3. SR and LLR 2 responses could be recorded from all 12 patients, whereas the LLR 1 and LLR 3 could each be



**Fig. 1** (A) Normal LLR responses (SR and LLR 2) in a control subject (LS = left side, RS = right side). (B) Bilaterally increased LLR 1 responses with reduction of LLR 2 on the affected side (AS) in a cervical dystonia patient. (C) Unilateral occurrence of LLR 1 on the affected side with loss of subsequent LLR 2 in a patient with writer's cramp. (D) Unilateral occurrence of LLR 1 on the affected side with preserved subsequent LLR 2 in a cervical dystonia patient. Short responses were normal in all patients. Sweep 10 ms/division; calibration = 100  $\mu$ V.

**Table 1** Response amplitudes in CD and ULD patients, and in control subjects

	SR (AS)	SR (NS)	LLR 1 (AS)	LLR 1 (NS)	LLR 2 (AS)	LLR 2 (NS)	LLR 3 (AS)	LLR 3 (NS)
CD ( <i>n</i> = 27)	500 $\pm$ 169	443 $\pm$ 170	119 $\pm$ 134	255 $\pm$ 262	198 $\pm$ 109	170 $\pm$ 100	74 $\pm$ 63	82 $\pm$ 77
ULD ( <i>n</i> = 7)	334 $\pm$ 137	406 $\pm$ 175	130 $\pm$ 99	60 $\pm$ 42	175 $\pm$ 97	174 $\pm$ 93	–	–
CD and ULD (pooled data; <i>n</i> = 34)	464 $\pm$ 175	435 $\pm$ 168	120 $\pm$ 125	220 $\pm$ 247	191 $\pm$ 104	171 $\pm$ 97	74 $\pm$ 63	82 $\pm$ 77
Controls ( <i>n</i> = 20)*	439 $\pm$ 198(R)	445 $\pm$ 246(L)	101 $\pm$ 73(R)	96 $\pm$ 82(L)	162 $\pm$ 104(R)	164 $\pm$ 103(L)	102 $\pm$ 10(R)	83 $\pm$ 30(L)

Response amplitudes ( $\mu$ V) are given as mean  $\pm$  SD. SR = short latency response; LLR = long latency response (1 at ~40 ms, 2 at ~50 ms, 3 at ~75 ms); AS = affected side; NS = non-affected side; CD = cervical dystonia; ULD = upper limb dystonia. \*There is no 'affected side' in controls, so right/left values are given as indicated (R/L).

elicited in only three of them. Compared with pretreatment recordings, there was a significant reduction of the LLR 2 amplitude on the clinically affected side after treatment ( $P < 0.05$ ), while no alteration of the amplitudes was found on the clinically asymptomatic side ( $P > 0.05$ ). No significant changes in the SR, LLR 1 and LLR 3 amplitudes were seen on either side ( $P > 0.05$ ). Latencies of all LLR

components remained unaltered ( $P > 0.05$ ). The most obvious change of the LLR pattern was found in a torticollis patient who had head rotation to the right side. In this patient, the LLR 1 response increased after medication on the affected (right) side, and there was a loss of LLR 2 (Fig. 2A and B). No alterations were seen on the non-affected side of this patient.

**Table 2** Response latencies in cervical and upper limb dystonia patients, and in control subjects

	SR (AS)	SR (NS)	LLR 1 (AS)	LLR 1 (NS)	LLR 2 (AS)	LLR 2 (NS)	LLR 3 (AS)	LLR 3 (NS)
CD ( <i>n</i> = 27)	29.0 ± 2.7	29.7 ± 2.8	41.7 ± 2.7	42.0 ± 2.9	51.6 ± 2.8	51.8 ± 3.3	74.8 ± 4.3	74.8 ± 4.1
ULD ( <i>n</i> = 7)	30.3 ± 3.2	29.3 ± 1.9	39.8 ± 3.1	38.7 ± 0.4	50.0 ± 3.3	49.2 ± 2.6	–	–
CD and ULD (pooled data; <i>n</i> = 34)	29.3 ± 2.8	29.6 ± 2.6	41.4 ± 2.7	41.5 ± 2.9	51.3 ± 2.9	51.0 ± 3.3	74.8 ± 4.3	74.8 ± 4.1
Controls ( <i>n</i> = 20)	28.8 ± 2.6(R)	28.4 ± 2.7(L)	43.7 ± 2.8(R)	43.5 ± 2.9(L)	50.6 ± 4.3(R)	50.3 ± 4.5(L)	70.9 ± 2.2(R)	70.6 ± 2.9(L)

Latencies (ms) are given as mean ± SD. See Table 1 footnotes.

**Table 3** Response amplitudes and latencies in 12 focal dystonia patients, before and after botulinum toxin treatment

	SR		LLR 1		LLR 2		LLR 3	
	AS	NS	AS	NS	AS	NS	AS	NS
Amplitude (µV)								
Before BTX	469 ± 161	346 ± 177	112 ± 30	45 ± 7	192 ± 115*	144 ± 83	140 ± 35	107 ± 50
After BTX	395 ± 175	446 ± 162	153 ± 50	38 ± 4	156 ± 100	126 ± 85	123 ± 66	70 ± 10
Latency (ms)								
Before BTX	28.5 ± 2.4	29.0 ± 2.5	41.0 ± 0.8	41.8 ± 3.4	51.3 ± 1.9	50.6 ± 3.5	73.7 ± 2.3	73.5 ± 0.3
After BTX	28.6 ± 2.9	28.9 ± 2.8	39.4 ± 2.4	40.9 ± 3.0	52.0 ± 2.5	51.6 ± 2.4	77.3 ± 5.0	77.0 ± 4.0

The values are given as mean ± SD. BTX = botulinum toxin treatment; see footnote to Table 1 for other abbreviations. \**P* = 0.02 before/after BTX (paired *t* test).

## Discussion

This study on electrically evoked long-latency responses in 34 idiopathic focal dystonia patients indicated abnormalities of LLR 1 in 24% of patients and in addition, alterations of LLR 2 responses in single cases.

### LLR 1 abnormalities

LLR 1 components were either abnormal because of their unilaterality or because of pathologically enhanced unilateral or bilateral amplitudes. At present, the significance of such LLR 1 alterations is not clear; so far, LLR 1 abnormalities were seen mainly in patients with extrapyramidal disorders and essential tremor. In Parkinson's disease, LLR 1 was found to be enhanced unilaterally or bilaterally (Deuschl and Lüking, 1989). Similar LLR 1 abnormalities were described in about one-third of essential tremor patients (Deuschl *et al.*, 1987). Our results in dystonia patients extend these findings to other extrapyramidal disorders. It appears that LLR 1 abnormalities are more prominent in hyperkinetic movement disorders such as tremor and dystonia and, even in Parkinson's disease, increased LLR 1 amplitudes have been found predominantly in patients with resting and postural tremor (Deuschl and Lüking, 1989). If one accepts this association, LLR 1 modifications may represent disinhibited thalamocortical stimulation.

This suggestion does not contradict LLR studies in cortical-basal ganglionic degeneration (CBGD), a degenerative multisystem disorder mainly involving the frontoparietal cortex and various basal ganglia structures. In this disorder, enhancement of the LLR 1 has been found which was not observed in other akinetic-rigid syndromes such as idiopathic

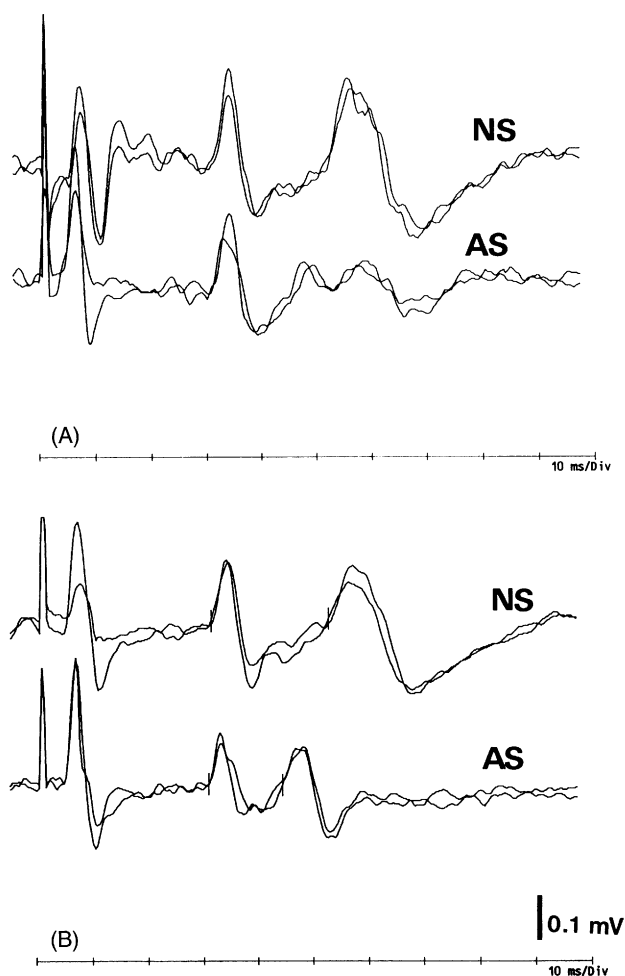
Parkinson's disease or multiple system atrophy (Chen *et al.*, 1992). The authors suggested that this LLR 1 abnormality may arise from the involvement of the frontoparietal cortex. Based on our results, and in view of the typical association between CBGD and dystonic symptoms (Riley *et al.*, 1990), we suggest an alternative to the above, that LLR 1 enhancement is characteristic of a dystonic component in a variety of motor disorders including CBGD.

In most cases, LLR 1 alterations occurred on the clinically affected side (six patients), but LLR 1 responses were also abnormal on the non-affected side in two other patients. This is in keeping with radiological and electrophysiological findings in idiopathic dystonia showing that basal ganglia may be affected bilaterally despite unilateral clinical presentation (Stoessl *et al.*, 1986; Nakashima *et al.*, 1989; Schneider *et al.*, 1994; Naumann *et al.*, 1996). A similar unilateral abnormality of long-latency reflexes has been reported in Huntington's disease (Noth *et al.*, 1985).

### LLR 2 abnormalities and LLR 3

Long-latency reflex studies in normal subjects have shown that the presence of a LLR 1 response is always associated with a well-defined LLR 2 (Deuschl *et al.*, 1987). In contrast, LLR 1 abnormalities in dystonia were combined with an absent or low LLR 2 in four of our patients (including the cases after botulinum toxin treatment). Sources for smaller or delayed LLR 2 responses are heterogeneous and include disorders of the afferent sensory or efferent motor pathways (Marsden *et al.*, 1977a, b; Claus *et al.*, 1985).

On the other hand, lesions of the supplementary motor area (SMA) may lead to increased LLR 2 responses as shown



**Fig. 2** LLR responses of a cervical dystonia patient before and after treatment with botulinum toxin. **(A)** Before treatment: unilateral occurrence of a small LLR 1 followed by a low LLR 2 response on the affected side (AS); on the non-affected side (NS) only the LLR 2 response is present. **(B)** After treatment: LLR 1 is enhanced on the affected side while the subsequent LLR 2 has disappeared; no changes were seen on the non-affected side. Short responses were normal in all patients. Sweep 10 ms/division; calibration = 100  $\mu$ V.

in the animal model (Hummelsheim *et al.*, 1986) and as observed in a patient with an SMA lesion (Dick *et al.*, 1987). It has therefore been suggested that the SMA has an inhibitory influence on afferents to, or the excitability level of, cortical motor neurons thereby affecting the gain of LLR 2. Based on these findings, absence or reduction of LLR 2, as observed in our cases, argues for a disinhibition of the SMA, a major cortical target for basal ganglia output, in dystonia patients. Recently, increased motor cortex excitability has been shown by transcranial magnetic stimulation studies in dystonia patients (Ikoma *et al.*, 1996). This supports the current pathophysiological concept of dystonia (Hallett, 1993) suggesting that reduced striato-pallido-thalamic inhibition may lead to cortical overflow and dystonic postures. PET studies in dystonia patients have shown decreased regional cerebral blood flow in the posterior SMA (Ceballos-Baumann

*et al.*, 1995; Ibanez *et al.*, 1996) that has a direct influence on LLR 2. There is, at present, no sufficient explanation for these two apparently contradictory findings, although an inverse relationship between regional brain metabolism and neuronal activity has been observed in patients with focal epilepsy (Pawlik *et al.*, 1994)

Our observation in dystonia patients is the opposite to the enhanced LLR 2 amplitudes seen in Parkinson's disease patients (Tatton and Lee, 1975; Mortimer and Webster, 1979; Rothwell *et al.*, 1983b; Cody *et al.*, 1986) where the SMA is less active due to reduced thalamocortical activation (Jenkins *et al.*, 1992; Playford *et al.*, 1992). As pointed out, these LLR abnormalities were only found in single dystonia cases (with no discriminating clinical features); in pooled data from all dystonia patients no statistically significant reduction of LLR 2 amplitudes could be established.

An alternative explanation for a reduction or loss of LLR 2 could be that a large or enhanced LLR 1 induces a partial refractoriness in the motor neuron pool and thereby reduces the LLR 2 response (Michels *et al.*, 1993). However, LLR 2 was lost in two of our patients despite a normal sized, unilateral LLR 1 on the affected side so that the loss of LLR 2 in these cases would not be explained by the refractoriness of the motor neuron pool. In addition, there was no negative correlation between the amplitudes of LLR 1 and 2 in pooled data, from either dystonia patients or controls ( $P > 0.05$ ).

Since LLR 3 is an inconstant reflex found only in up to one-third of normal subjects (Hallett *et al.*, 1994; Deuschl and Lücking, 1990) the significance of missing LLR 3 responses in our small subgroup of ULD patients remains undetermined. No LLR 3 abnormalities were seen in CD patients or controls.

### **LLR studies after treatment with botulinum toxin**

After treatment with botulinum toxin, LLR 2 amplitudes in dystonia patients were significantly reduced. The reciprocal pattern of LLR 1 and LLR 2 amplitudes was maintained. Thus, clinically effective treatment with botulinum toxin led surprisingly to an accentuation of the LLR alterations found in dystonia patients. This seems not to be caused by a direct action of botulinum toxin on the CNS because no significant effects on LLR were seen on the clinically unaffected side. As shown in controls, even active head turns did not modify amplitudes or timing of LLR responses so that posture-related influences are unlikely to account for any LLR alterations. We therefore propose that the imbalance in the motor system underlying dystonia is exaggerated by the artificial peripheral neuromuscular 'lesion' induced by botulinum toxin. This effect complies with the common notion that dystonia may spread into muscles close to a muscle group effectively treated by botulinum toxin (Gelb *et al.*, 1991). Worsening of dystonia outside the treated region or a shift of the symptomatic region may therefore not only

be due to a progression of the disease but could also be triggered by treatment-related modification of the peripheral input to the CNS. Furthermore, this positive feedback mechanism may explain why peripheral trauma in some patients uncovers previously asymptomatic dystonia or seemingly produces dystonic movements (Scherokman *et al.*, 1986; Jankovic and van der Linden, 1988; Fletcher *et al.*, 1991)

In conclusion, distinct alterations of LLR 1 and 2 were found in a substantial proportion of patients with idiopathic dystonia. These findings underscore the involvement of LLR 1 in several extrapyramidal disorders and, at least in some patients, link LLR-2 abnormalities to overactivity of the SMA. LLR-2 alterations following botulinum toxin treatment suggest that central motor patterns involved in focal dystonia can be modified by peripheral inputs. This sheds new light on cases with dystonia provoked by peripheral trauma and extends the range of factors involved in CNS plasticity.

## Acknowledgements

We wish to thank Professor Dr K.V. Toyka and Professor Dr G. Deuschl for helpful suggestions and a critical review of the manuscript.

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*Received August 20, 1996. Revised October 24, 1996.*

*Accepted November 5, 1996*