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Long Latency Muscle Responses in Cerebellar Diseases

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Summary. Long latency reflexes were measured from the hand muscles of 27 patients suffering from different cerebellar diseases (12 diffuse cerebellar atrophies, 7 cerebellar hemispheric infarcts, 8 Friedreich's disease) and from 45 controls after electrical stimulus of the median nerve at the wrist. The M3 response (latency about 70 ms) was increased in about 50% of cerebellar atrophy cases and occasionally (10 of 12 cases) separated from the M2 response (50 ms). M3 was sometimes (3/7) increased and the M2–3 complex was prolonged ipsilaterally in cases of cerebellar infarcts. In the cases of Friedreich's ataxia M2 was always lost uni or bilaterally because of the disturbance of afferent or efferent fibres. The latencies of the spinal reflex M1 and also of M2 were not always increased strongly enough to be clearly separated from the normal values.

Key words: Long loop reflex – Cerebellar atrophy – Friedreich's ataxia – Cerebellar infarcts

Introduction

Several reflex responses can be recorded from the tonic innervated hand muscles after mechanical or electrical stimuli. The first spinal segmental response M1 (latency about 30 ms) is followed by a long latency response M2 (50 ms) and a nonconstant third component M3 (70 ms). The muscles of the hand have a wide cortical representation, and it can be assumed that their late reflex responses are generated through a transcortical loop (Claus et al. 1985; Conrad and Aschoff 1977; Marsden et al. 1976; Milner-Brown et al. 1975; Noth et al. 1984). Several authors (Lee and Tatton 1975; Marsden et al. 1978; Noth et al. 1984; Tatton and Lee 1975) concluded from reflex recordings in central nervous system diseases that M2 is influenced by the extrapyramidal motor system, and also that M3 is modulated by cerebellar influences. This idea is supported by animal experiments where the dentate nucleus has been cooled (Brooks 1984; Conrad 1978; Meyer-Lohmann et al. 1975; Miller and Brooks 1981).

The cerebellum receives information from the cortex and pyramidal tract via pontine collaterals and also receives continuing messages from the periphery (Brooks 1984; Dichgans et al. 1985; Eccles 1977; Eccles 1982; Eisen et al. 1985; Sasaki 1984). The feedback efferents pass through the nuclei interpositus and dentatus. In both of these nuclei, activity is strictly correlated to mechanical perturbations of limb position. This argues in favor of the nuclei participating in generating late reflexes (Strick 1978; Thach 1978). Therefore, it is probable that the M3 potential of hand muscles is modulated or generated through a cerebellar loop (Evarts and Vaughn 1978; Hore and Vilis 1984; Lee and Tatton 1975; Wiesendanger and Miles 1982). However, the exact reflex loop of M3 is still far from being elucidated (Dichgans et al. 1985; Lee and Tatton 1975).

Late reflex responses can also be elicited by mechanical stimulation from the lower leg muscles of patients suffering from cerebellar diseases (Dichgans et al. 1985; Diener et al. 1984a; Nasher and Grimm 1978). Typical findings have been described for paleo- and neocerebellar atrophies by these methods.

Long latency reflexes can be easily obtained from tonic innervated hand muscles after electrical stimulation of nerve trunks (Claus 1986; Claus et al. 1985; Conrad and Aschoff 1977; Eisen et al. 1985). The following paper investigates whether by using this method typical findings can be seen in the case of cerebellar diseases; and whether such findings are constant or provide additional diagnostic information to the clinical examination.

Materials and Methods

A total of 27 patients (14 female, 13 male, 22 to 76 years old, average 47 years) was investigated. A diffuse cerebellar atrophy was clearly diagnosed in 12 cases using cranial computed tomography (CCT), criteria described earlier (Claus and Aschoff 1981; Claus and Aschoff 1982). All patients of this group suffered from distinct cerebellar sysptoms (12 dysdiadochokinesia, 10 upper limb ataxia, 5 nystagmus, 11 gait ataxia). Alcoholic cerebellar atrophies and inflammatory diseases were excluded. The patients had no polyneuropathies.

Friedreich's ataxia was diagnosed in 8 cases by the following criteria: slow progression of symptoms, first symptoms before the age of 25, posterior column and cerebellar signs, dysarthria, hypo- or areflexia of the legs, normo- or hypotonia of the atrophic and paretic leg muscles, and – if active dorsiflection of the toe was possible – a positive Babinski's sign (Barbeau 1976; Claus and Aschoff 1980; Geoffroy et al. 1976; Harding 1985). A clearly demarcated cerebellar infarct without edema or hemorrhagia was seen in the CCT's of 7 cases. The infarctions affected the left dorsolateral cerebellar hemispheres, which were supplied by the posterior inferior cerebellar and superior cerebellar arteries. Examinations were carried out 2 to 6 weeks after the stroke. The patients had no fur-

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ther neurological diseases (clinical symtoms see Table 1). All had suffered from cerebellar symptoms at the acute stage: nystagmus, trunk and/or limb ataxia, dysarthria. In one case the limb ataxia had disappeared by the time of neurophysiological examination. The long latency reflex was derived from the isotonically innervated first interosseus muscle of both hands consecutively using surface electrodes (20% of the maximum force controlled by a pressure gauge). The electrical impulse was applied to the median nerve at the wrist (Claus 1986; Claus et al. 1985). The signals of muscle activity were full wave rectified and averaged (timebase 20 ms/D, gain 200 to 500 μV, bandpass 20 Hz to 10 kHz, 128 sweeps, 3/s).

As controls 45 people (15–65 years, average 40 years) were examined for normal and limiting values (average + 2 SD), which were: latency M1 32.2 ms, M2 57.9 ms, difference M2–M1 31.9 ms, duration of the M2–3 complex 68 ms. M2 was judged to be diminished if the equation of the amplitudes A1/A2 exceeded 3.4. In the 45 controls a clearly separated M3 potential (Fig. 1, line 1 left) was identified 17 times on the right and 26 times on the left hand. The amplitude of M3 (A3) exceeded A2 in no single case on the right and in 5 cases on the left hand. The average height did not differ considerably between the groups.

Differences were investigated by the Mann-Whitney *U* test for a two way analysis, and for differences of frequencies by the χ^2 test with Yates correction.

Results

Of the 12 cerebellar atrophic patients 10 had a limb ataxia. M3 was increased in 7 cases, in 2 of which it was bilateral (Table 1). This was more frequent than in the control group ($\chi^2 = 10.03$; $P < 0.01$). In 3 cases with dorsal column or pyramidal symptoms (2 times Babinski's sign) M2 was lost. The latencies of late components were increased in 3 cases on the right and 1 case on the left, but the average values remained normal. The average value of the M2–3 complex duration was increased (right u = 2.16; $P = 0.03$; left u = 2.60; $P < 0.01$). However, the normal limit was exceeded in only 1 case on the right and 3 times on the left hand.

With only one exception the cerebellar infarcts led to ipsilateral limb ataxia, dysdiadochokinesia and intention tremor at the time of neurophysiological examination. But M3 was augmented ipsilaterally only in 3 cases (Table 1) – not significantly more frequently than in controls ($\chi^2 = 2.57$; $P > 0.1$). The latencies of M1 and M2 were always normal. Although, the M2–3 complex duration was never prolonged compared with normal values (right u = 0.47; $P = 0.6$; left u = 1.02; $P = 0.3$), it was significantly longer on the left than on the contralateral right hand (right average = 37.7 ms; left average = 47.4; u = 14.0; $P < 0.03$).

In 4 of the 8 Friedreich's ataxia cases Babinski's phenomenon was positive. All the patients had dorsal column symptoms (pallhypaethesia, disturbed acrognosis in the toes). Therefore, M2 was diminished or abolished at least on one side in all cases and in 6 cases bilaterally (see Table 1). Compared with A2, A3 was increased frequently in this group (6/7 right, 5/7 left; $\chi^2 = 13.2$; $P < 0.001$), despite the fact that only 4 patients suffered from limb ataxia. The latencies of M1 and M2 were prolonged (right M1 u = 2.41; $P < 0.05$; M2/; left M1 u = 2,92; $P < 0.01$; M2 u = 2.07; $P < 0.05$). The prolongation exceeded the normal limit for M1 right twice, left 4 times and

Table 1. Clinical signs (at the time of neurophysiological examination) and long loop responses of the controls and patients. M2↓ symbolizes amplitude reduced reflex response, M3 > M2 denotes amplitude of M3 higher than that of M2, for further explanations see text

		n	Age	Limb ataxia	Dorsal column symptoms	Babinski +	Spasticity	Right				Left				M2–M1 (ms)
								Latency (ms)		M2↓	M3 > M2	Latency (ms)		M2↓	M3 > M2	
								M1	M2			M1	M2			
Controls	*n* =	45		0	0	0	0			1	0			3	5	
	%	100								2.2				6.7	11.1	
	$\bar{x}$		39.4					27.0	49.5			26.6	49.3			22.8
	SD		(15–65)					2.6	4.0			2.8	4.3			4.5
Cerebellar atrophies	*n* =	12		10	4	2	2		11	2	5		11	1	4	
	%	100								16.7	41.7			8.3	33.3	
	$\bar{x}$		48					29.3	51.5			28.8	52.3			
	SD		(22–58)					4.8	7.4			3.4	5.5			
Cerebellar infarcts	*n* =	7		6 ipsilateral	0	0	0			0	1			0	3	
	$\bar{x}$		59					28.5	50.1			28.0	49.1			
	SD		(40–76)					4.5	4.5			2.9	5.2			
Friedreich's disease	*n* =	8		4	8	4	0		2	7	6		5	7	5	5
	$\bar{x}$		35					30.1*	46.8			30.8*	58.4*			26.7
	SD		(24–47)					2.8	—			2.7	9.7			6.6

* $P < 0.05$

for M2 left 3 times of the 5 values. The M2–M1 latency difference reflects the central nervous afferent-efferent volley conduction if M2 has a transcortical loop. The values of this parameter were high in the 5 left hand recordings where they could be measured (average = 26.7 ms; SD = 6.6). But these values were insufficient to prove a significant increase (u = 1.65; $P = 0.1$). The limiting value was exceeded in only 1 case. The duration of the M2-3 complex exceeded the normal limit twice on both hands. But the average values did not differ significantly (right u = 1.41; $P = 0.2$; left u = 0.50; $P = 0.6$).

Discussion

Several authors have investigated long latency reflexes in cerebellar diseases. They used mechanical stimuli of the arm (Marsden et al. 1978) and hand, and/or platformtilt for recordings of lower leg muscles (Dichgans et al. 1985). We would like to compare these results with those achieved by a more practicable method. We decided not to examine alcoholic cerebellar atrophies because of the more frequent accompanying diseases such as polyneuropathy and Wernicke's encephalopathy which may influence the results (Neundörfer and Claus 1985).

In diffuse cerebellar atrophies M3 potentials were sometimes augmented (Fig. 1, line 2) and M2–3 complexes broadened on average, compared with the controls. But the latter values became pathological only in a few cases. Since a hierarchy for the seriousness of clinical signs could not be established in the small group, it was not possible to examine the correlation of the neurophysiological results with cerebellar symptoms.

We were not able to find delayed initial components of M2 or M3 (Marsden et al. 1978) in exclusively cerebellar diseases. We found prolonged late response latencies only in connection with dorsal column symptoms. Therefore, we agree that this result is not due to a cerebellar disturbance (Dichgans et al. 1985; Diener et al. 1984a, 1984b). Despite the different methods, the frequency of augmented, split and broadened M3 answers (7 out of 12 cases on one or both sides) was comparable to the results reported by Dichgans et al. (56%; 1985). Therefore, diffuse cerebellar atrophies led to an excessive M3 answer in the upper limb as well. But M1 and M2 remained uninfluenced. This result emphasizes a cerebellar modulation of M3.

In the 7 cerebellar infarcts the M2 latencies were not increased (Marsden et al. 1978), either when compared with the controls, or when compared intraindividually with the unaffected side contralateral to the cerebellar lesion. Angel (1982) has described an augmented shortening reaction of the elbow joint ipsilaterally to a cerebellar infarct. Miller and Brooks (1981) saw an enlarged and broadened M3 answer in monkeys with cerebellar lesions. In our results M3 was increased more frequently (Fig. 1, line 3) and the M2–3 complex was broadened ipsilaterally to the infarcts compared with the unaffected side ($P < 0.03$). This confirms an ipsilateral neocerebellar influence on M3 (Dichgans and Diener 1984). But the variations of the late reflex responses were inconstant (Fig. 1, line 3). Despite the fact that the infarcts affected the dorsolateral left cerebellar hemisphere (posterior lobe and cerebellar nuclei) and led to limb ataxia in 6 out of 7 cases, M3 was enlarged significantly only three times (Fig. 2). This diminishes the diagnostic value of the results.

Since a gliosis of dorsal columns in Friedreich's ataxia begins in the fasciculus gracilis, the symptoms of the disease start to develop in the legs. Furthermore, Purkinje cell degenerations in the cerebellum, gliosis of the dentate nucleus, degenerations of the anterior spinocerebellar tracts, and – with

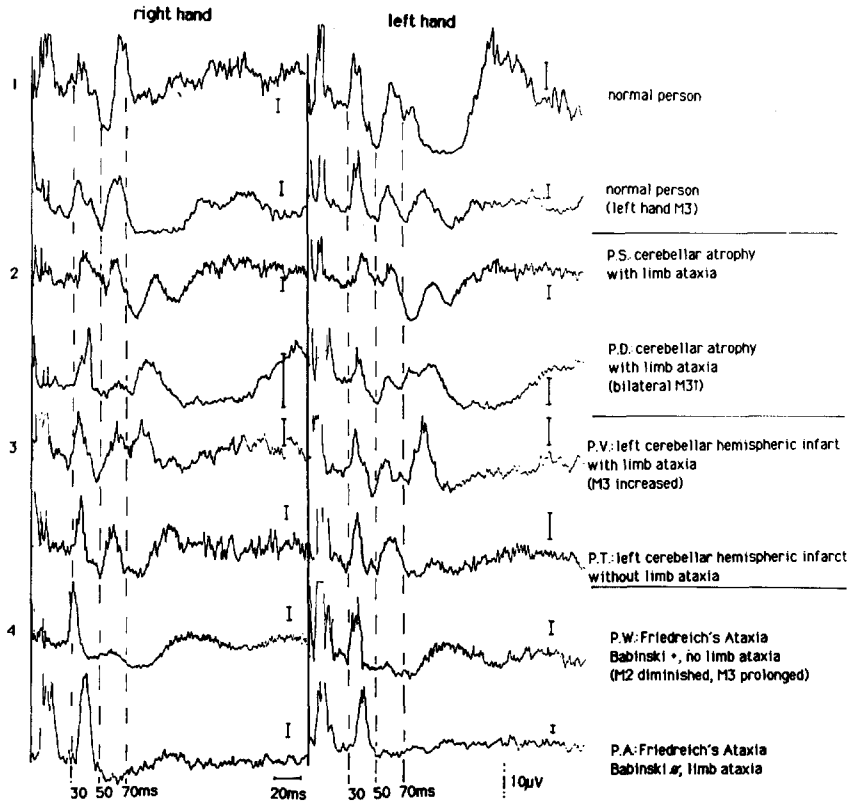

Fig. 1. Examples of different recordings. Long latency responses in 2 healthy persons *(1)*, cerebellar atrophies *(2)*, cerebellar infarcts *(3)*, Friedreich's ataxia *(4)*.

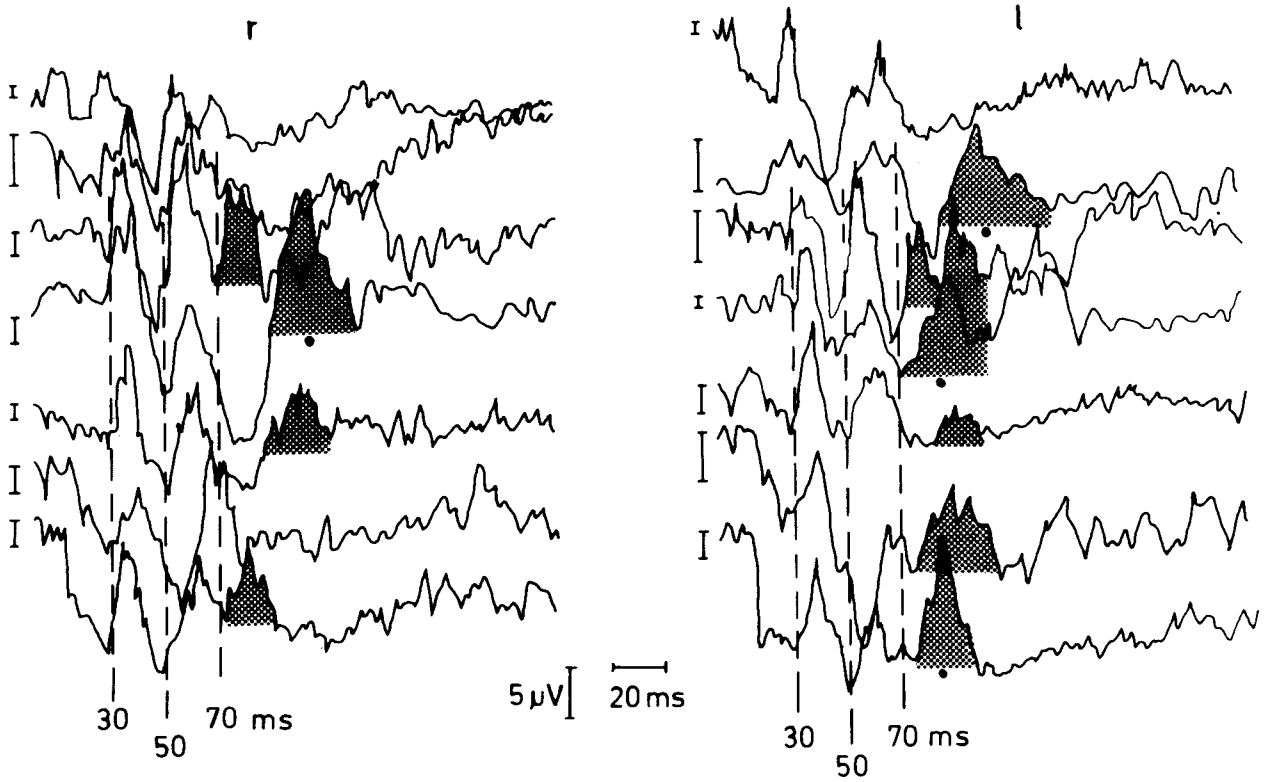

Fig. 2. Recordings of 7 patients with cerebellar infarcts. The averaged rectified muscle activity shows 2 or 3 clearly demarcated increments: M1 30 ms, M2 50 ms, and finally M3 70 ms after perturbation. The M3 responses are hatched. M3 responses with an amplitude higher than M2 are marked with a point

thoracolumbar pronounciation – degenerations of the pyramidal tracts all occur (Friedreich 1863a; Greenfield 1954; Harding 1985; Tyrer 1975). Degenerative changes of the dorsal roots and of the large axons in peripheral nerves have also been described (Friedreich 1863b; Friedreich 1877; Hughes et al. 1968). The peripheral motor conduction velocity was almost normal or only slightly diminished (Bouchard et al. 1979; Dunn 1973; Dyck and Lambert 1968; Fiaschi et al. 1978; Harding and Thomas 1980; McLeod 1971; Oh and Halsey 1973; Ouvrier et al. 1982; Peyronnard et al. 1976; Salisachs et al. 1975; Sauer 1980). The sensory nerve potentials were partly delayed (Bouchard et al. 1979; McLeod 1971; Oh and Halsey 1973; Ouvrier et al. 1982; Peyronnard et al. 1976) and amplitude reduced (Caruso et al. 1983; Fiaschi et al. 1978). It is also not surprising that somatosensory evoked potential examinations show a disturbed central volley conduction (Jones et al. 1980; Nuwer et al. 1983; Pelosi et al. 1984; Sauer 1980). These results also explain a prolonged M1 and late response latency. The fact that M1 could always be derived from the hands, while it was sometimes lost in the legs (Diener et al. 1984b), can be explained by the accentuation of symptoms in the latter. The few values of M2–M1 latency differences which could be counted were too few to determine a disturbed central nervous afferent-efferent volley conduction. M2 was decreased in all cases on at least one side, in 5 cases in both hands because of the pyramidal tract lesions in Friedreich's ataxia (Fig. 1, line 4). This result can be compared to the lack of "medium latency" responses in the lower limb (Diener et al. 1984b). The prolongation of M2 latencies ($P < 0.05$) confirmed the results of mechanically evoked late responses in the hand (Dichgans and Diener 1984). But only 3 out of the 5 M2 latencies evaluated in the left hand exceeded the borderline values.

This latency increase is a result of dorsal column lesions and may also be a consequence of pyramidal tract involvement (Dichgans and Diener 1984). It is not due to a cerebellar disturbance. The result is not so clearly separated as in examinations of the legs. Supposing that the late responses are generated in a similar way, this difference can be explained by the short intraspinal conduction distance for stimulus on the wrist, which is on the level of the C6/7 spinal segments. A constant divergence from the normal limit was not seen for the duration of M2–3 complexes either, despite the values being enlarged twice on both sides. The amplitude of M3 was often increased in comparison to the M2 amplituded (6/7 right, 5/7 left, $P < 0.001$). This result was not due to paleocerebellar influence on the M3 reflex component, but partly due to the frequently diminished M2 response. A clearly separated M3 was also seen in the antagonistic leg muscles (Dichgans et al. 1985). It reflected the cerebellar disturbance, while an increased M3 latency was due to afferent spinal disturbances.

In Friedreich's ataxia the changes of long latency response patterns were relatively specific. Sometimes the latencies of M1 were prolonged, M2 often disappeared or diminished. M3 appeared delayed, broadened, and occasionally with a higher amplitude than M2 (Fig. 1, line 4). How often these signs appear in the early stages of the disease without typical clinical signs, both in patients and in relatives of the patients, has not been investigated. This however, would be a real diagnostic aid. In typical clinically diagnosed cases this additional examination is only of limited value. The only clearly pathological and relatively constant result was the M2 attenuation – this is

in contrast to the lower limb examinations performed with platform tilt (Dienèr et al. 1984b).

In conclusion, the M2 reflex potential recorded from the first interosseus muscle of the hand after an electrical perturbation was not affected in the investigated cerebellar diseases. Therefore, there is no indication of a cerebellar modulation of M2. Occasionally, however, the late M3 response was increased and clearly separated, and the M2–3 complex was broadened. These results confirm a cerebellar influence on M3 even when derived on the hand after electrical nerve stimulation. M3 is modulated by cerebellar circuitry both in terms of amplitude and duration but not in terms of latency. However, the results were not constant, and therefore the long latency responses are not an invarying diagnostic aid for the judgement of cerebellar hemispheric diseases. Despite the existence of analogies, the results of derivations from the arm cannot easily be compared with those from the legs (Diener et al. 1984b), and it is less probable that a transcortical loop participates in generating late responses of leg muscles (Darton et al. 1985; Marsden et al. 1984).

On the other hand, a disadvantage of examinations of hand muscles is that M3 appears in the same muscle as M2 and that it is not always clearly separated. Therefore, the two late response components can be confused in pathological recordings. This cannot happen with the late antagonistic leg muscle response "LL" (Diener et al. 1984b). Furthermore, in agreement with Lee and Tatton (1975), because M3 can be seen in about 40% of healthy persons on the hand, the existence of this response cannot be evaluated as pathological. It is also important to measure the muscle force because M3 becomes higher and appears more frequently with increasing innervation. Another disadvantage of the hand derivation is the short intraspinal conduction distance. This makes the method less sensitive to spinal cord diseases than a recording from the lower limbs.

The examination of late reflex responses is of great interest for investigations dealing with the motor system organisation. However, the results of derivations from hand muscles are of only minor diagnostic value for cerebellar diseases.

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