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Transcranial magnetic stimulation in pontine infarction: correlation to degree of paresis

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Abstract

Transcranial magnetic stimulation was performed in 20 patients with pontine infarction who had initially some degree of hemiparesis. Only patients with a well defined lesion on magnetic resonance imaging that was appropriate for the neurological signs were included. Recordings were made from the abductor pollicis brevis muscle (APB) bilaterally. The degree of hand paresis was estimated clinically and related to the following parameters: central motor conduction time (CMCT), interside latency difference of total latency, and amplitude ratio of affected to unaffected side. Increasing degree of paresis was associated with increasing latency parameters and decreasing amplitude ratio. In the four patients with severe paresis a low amplitude response could be evoked and CMCT was delayed by up to 10 ms. When the paresis had resolved at the time of transcranial magnetic stimulation CMCT was normal. However, amplitude ratio was less than 100% in all but one patient, with most of the values ranging between 40% and 60%, which indicates a subclinical pyramidal tract lesion. Median nerve sensory evoked potentials (SEP) and related interside latency difference to amplitude ratio N20/P25 were also recorded. In contrast to TCMS, decreased amplitude ratio of SEP was not associated with delayed latency. Clinically, the mild degree of and good recovery from paresis in ventral pontine infarction was remarkable.

Magnetic stimulation of the motor cortex (TCMS) was introduced by Barker *et al* and is set to become a routine method in clinical neurophysiology.[1] Its diagnostic value has been shown in multiple sclerosis,[2] degenerative ataxic disorders,[3] and psychogenic paresis,[4] as well as in several other conditions. Only a few studies deal with transcranial motor cortex stimulation, in patients with stroke, all of which used electrical stimulation.[5-7] As electric and magnetic motor cortex stimulation act on different cortical elements,[8] results obtained with one method cannot be directly compared with those obtained by the other mode of stimulation.[5-7] Furthermore, in the light of the D and I wave hypothesis[8-10] a given degree of paresis migh be expected from different TCMS results, depending on the location of stroke. Lesions of the cortex would affect the generation of I waves, whereas subcortical strokes would affect only the descending pathways, leaving the cortex intact as an I wave generator. In order not to confound these effects we investigated a group of patients with pure pontine infarction. Finally, subclinical lesions may affect the results of TCMS—for example, in multiple sclerosis[2]—and we were interested whether this holds also for ischaemic lesions.

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Patients and methods

We examined 20 patients with pontine ischaemic infarction that had occurred over a period of two years. All patients had branch occlusion. Patients with basilar artery occlusion were not included in this study. Their mean age was 58·2 years, ranging from 23 to 77. All patients were treated in our department immediately after their stroke so that the results of the neurological examination were available from the hospital chart for the acute state in all 20 patients. Only patients who had hemiparesis at least initially for some days or weeks were included. Patients with transient ischaemic attacks were excluded. We excluded also seven patients with pure tegmental vascular syndromes (internuclear ophthalmoplegia, gaze paresis, etc) or with pure sensory stroke due to pontine infarction who had no paresis at any time.

For the purpose of this study neurological examination, transcranial magnetic stimulation, and somatosensory evoked potentials (SEP) were performed in four patients in the acute state alone one to 10 days after the stroke and in 13 patients in the chronic state alone two to 27 months (mean 12·5 months) after the stroke in our outpatient clinic. The remaining three patients were investigated in the acute as well as in the chronic state. Neurological examination included an estimation of the

Table 1 Normative data in 43 control subjects for transcranial magnetic stimulation with recording from abductor pollicis brevis (APB) muscle. Onset latencies are expressed in ms. Upper two lines refer to cortical stimulation, lower line four magnetic stimulation over the lower cervical spine.

	Mean	*SD*	*Mean (2·5 SD)*
Cortex-APB:			
Relaxed	21·2	1·31	24·5
Active	19·5	1·04	22·1
CMCT:			
Relaxed	7·9	0·90	10·2
Active	6·0	0·97	8·4
C7-APB	13·5	1·02	16

CMCT = Central motor conduction time.

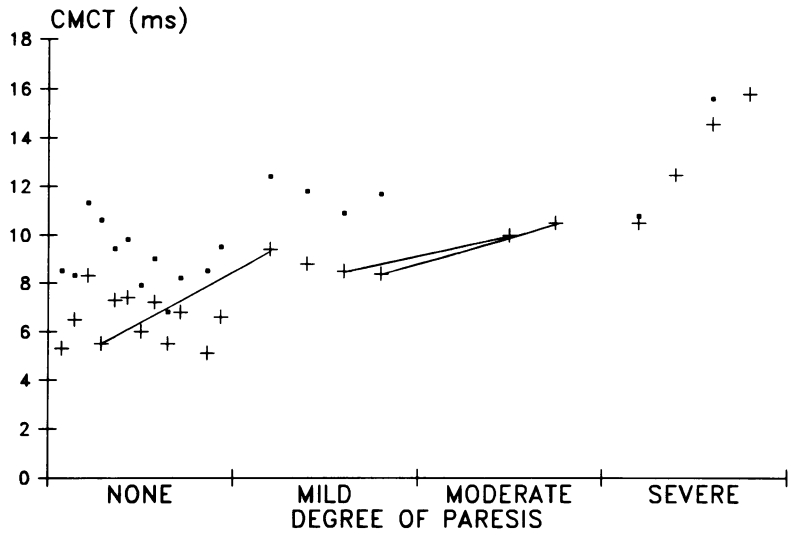

Figure 1 Central motor conduction time of the affected side with the APB active (crosses) and relaxed (dots). Serial recordings in a single patient were connected (solid lines) for contracted muscles. In two patients with moderate and in two with severe paresis a MEP could be obtained only with preactivation (see text). One patient with plegia had to be excluded from this analysis as CMCT could not be calculated.

degree of hand paresis with five categories (no paresis: mild, moderate, and severe paresis; plegia).

For TCMS we used a Novametrics stimulator (Magstim 200). A circular coil with an outer diameter of 14 cm was placed over the vertex. We checked for the threshold with slightly contracted muscles in the unaffected side and stimulated with currents 40% above threshold values with the current in both the clockwise and the anticlockwise direction. Recordings were taken from the abductor pollicis brevis (APB) muscles bilaterally using surface electrodes. Stimulation was performed with the target muscles relaxed as well as maintaining a slight contraction. The contraction was controlled on the screen of the amplifier and by a loudspeaker. Thus even in patients with moderate paresis a similar amount of background contraction could be achieved on both sides. Patients with severe paresis who could not maintain a voluntarily contraction comparable with that on the other side were given a cup to hold with their paretic hand; this resulted in a slightly better contraction in some patients.

Three stimuli were applied in each of the four conditions (active, relaxed; clockwise, anticlockwise). Right APB responses were evaluated only after anticlockwise stimulation and left APB responses after clockwise stimulation.[11] The shortest onset latency that definitely was not part of the background contraction was measured, as well as the largest peak to peak amplitude. An amplitude ratio was calculated for the motor evoked potentials (MEP) (MEP affected side to MEP unaffected side). Magnetic stimuli were also applied over the lower cervical spine for measuring peripheral conduction time and calculating central motor conduction time (CMCT). CMCT values were compared with results in a normative study (table 1) performed in our laboratory.[12]

For SEP the median nerve at the wrist was stimulated with an intensity that produced a well visible twitch. Needle recordings were made from C_3' and C_4' respectively using a frontal reference. Whereas TCMS was performed in seven patients during the acute state, SEP recordings were available in 16 for this period.

In all patients a pontine infarction was shown by magnetic resonance imaging (MRI, 1·5 Tesla; SE (2200/90)). If there was no lesion visible in the pons, or there was some doubt whether the lesion was responsible for the clinical syndrome, patients were excluded. Most of the patients had two MRI examinations, one in the acute and one in the chronic state. The lesion in the chronic state was often considerably smaller than that in the acute state, probably reflecting the disappearance of perifocal oedema.

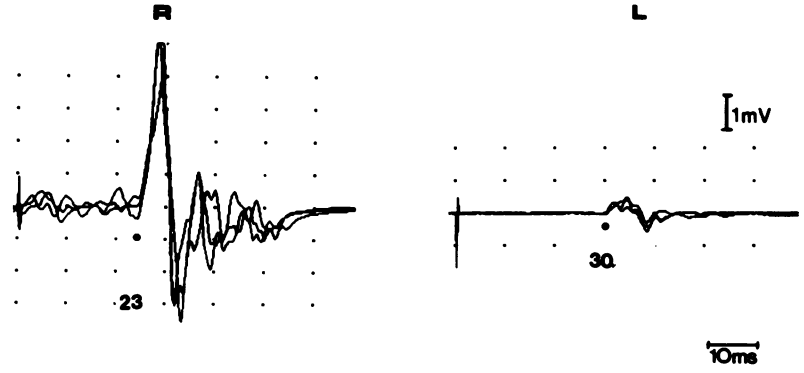

Figure 2 Severe left hemiparesis after pontine infarction. The response in the left APB is considerably delayed and reduced in amplitude. The patient was able to perform a slight preinnervation but it was much less than on the unaffected side as can be seen from the baseline values. However, without preinnervation no response could be evoked on the left, even with the highest stimulus intensities (not shown here).

Results

Clinical findings

At the time of the first TCMS investigation the degree of hand paresis was mild, moderate or severe in eight patients and one patient had plegia. In 11 patients the paresis had resolved at the time of the first TCMS investigation. All of these 11 patients initially had a hemiparesis of various degrees. Two patients with moderate paresis had mild paresis at repeat investigation and one patient improved from mild to none. In all cases the degree of proximal weakness was less pronounced than distally, taking into consideration also findings on admission in those patients whose paresis had resolved. In only one patient was the weakness more pronounced in the leg: in the remaining patients the arm was predominantly affected or weakness was balanced for arm and leg. Eleven patients in the chronic state showed increased tendon reflexes on the affected side, including the patients whose paresis had resolved. In four of these 11 patients manual dexterity was disturbed.

In addition to these motor findings, two patients had a transient gaze paresis, four gaze evoked nystagmus, two an incomplete sixth

Table 2 Clinical and electrophysiological data on selected, illustrative cases

Case No	Side, degree of paresis	Time after stroke (months)	Latency		CMCT		Amplitude	
			Right	Left	Right	Left	Right	Left
1	Left, severe	10	21·4	28·2	6·5	13·1	10·7	0·7
2	Left, severe	16	21·0	30·0	7·5	15·3	9·4	0·1
12	Left, moderate	0	19·7	24·7	6·1	10·2	5·4	1·4
	Left, mild	7	21·9	23·5	6·6	9·1	11·3	3·3
15	Right, moderate	0	26·5	19·5	9·0	3·9	0·3	9·9
	Right, mild	8	25·7	20·9	8·7	4·1	4·8	9·6
7	Left, none	5	21·4	20·6	5·8	5·2	8·8	3·9
9	Right, none	9	17·6	18·0	4·8	4·5	9·6	9·9
14	Left, none	18	21·0	22·1	6·4	6·8	11·7	7·9

nerve palsy, and one a Horner's syndrome and a skew deviation. Dysarthria was found in 12 patients, contralateral hemihypoesthesia in nine, lower cranial nerve paresis in seven, hemiataxia in five, ipsilateral facial hypoesthesia in three, and nuclear facial nerve paresis in one.

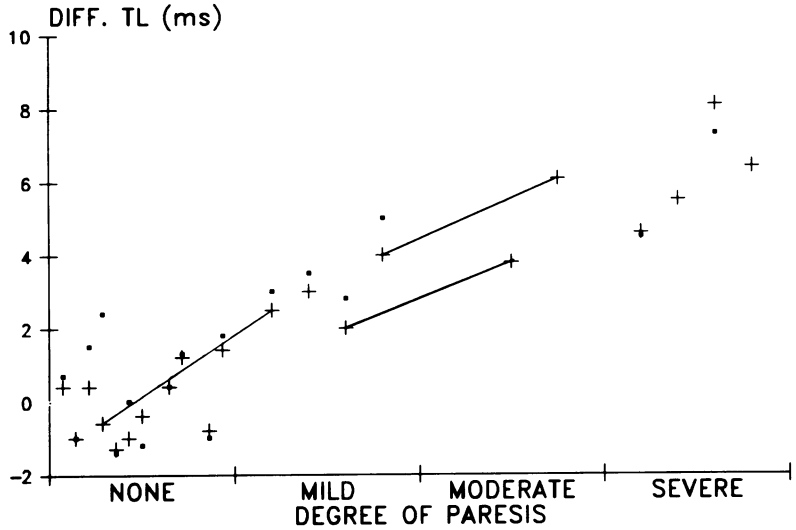

Figure 3 Difference between total latency (TL) calculated as affected minus unaffected side for preactivated (crosses) and relaxed (dots) APB. One patient with a carpal tunnel syndrome on the unaffected side and another patient with plegia had to be excluded from this analysis.

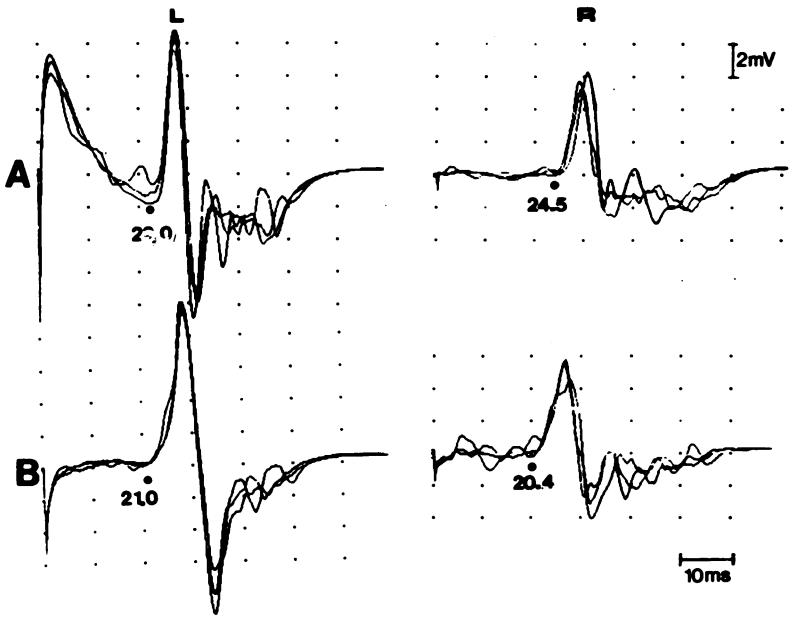

Figure 4 Patient with pontine infarction, pure motor hemiparesis, and dysarthria. No internuclear ophthalmoplegia. Paresis was initially moderate. (A) Five days after the stroke response on the affected right side was delayed and reduced in amplitude. The paresis at this time was only mild. (B) Four months later the paresis had resolved. The latency of the response is normal but the amplitude still reduced, indicating a subclinical involvement of the pyramidal tract.

MRI lesions

In 18 patients the hyperintense lesion was located mainly paramedially in the ventral pons, extending from the ventral pontine surface posteriorly and extending to a various degree laterally or into the tegmentum. In two patients most of the lesion was in the tegmentum, with the ventral pons being little affected.

TCMS findings

In patients whose paresis had resolved at the time of TCMS the CMCT was normal in active muscles and normal except in two patients with relaxed muscles on the affected side. Patients with mild to severe paresis had increasingly delayed CMCT up to 16 ms (figures 1 and 2). Data of some selective illustrative cases are given in table 2. In one patient with plegia a response could not be evoked in either the relaxed or the intensionally active state. Strong contraction of the opposite APB did not help to evoke a response. Two of the patients with moderate paresis and another two with severe paresis showed a response in the active state that was absent when the muscles were relaxed (figure 2), yet the degree of background contraction, particularly with severe paresis, was much smaller than the degree on the unaffected side. CMCT findings on the unaffected side were normal. Figure 3 shows the difference in the corticomuscular latency (affected minus unaffected side). With this kind of evaluation the results are quite similar to those using the CMCT as shown in figure 1.

Paresis was also associated with a drop in amplitude of the response (figure 4). The amplitude ratio of the affected to unaffected side is shown in figure 5. Patients with paresis had an amplitude ratio of less than 50%, and it was less than 40% if the degree of paresis was at least moderate. In patients whose paresis had resolved at the time of investigation (figure 4b) the amplitude ratio ranged from 40% to 120%.

The wide range of the amplitude ratio in the group with no paresis precluded a clear separation to the group with mild paresis. However, there was no overlap between the no paresis and moderate paresis groups. In active muscles the amplitude ratio was mostly higher, suggesting that the facilitating effect of preactivation was more pronounced on the paretic side (figure 5).

SEP recordings

Figure 6 shows the results of 31 SEP recordings in our 20 patients. Latency differences in the affected minus the unaffected side hardly exceeded 1 ms even in cases with an amplitude ratio of affected to unaffected side of less than 50%. With 50% as the lower limit of normal of the N20/P25 amplitude ratio, three patients had abnormal SEP and normal sensory examination results and four patients had normal SEP and abnormal sensory examination results. In the other patients both variables were in accordance.

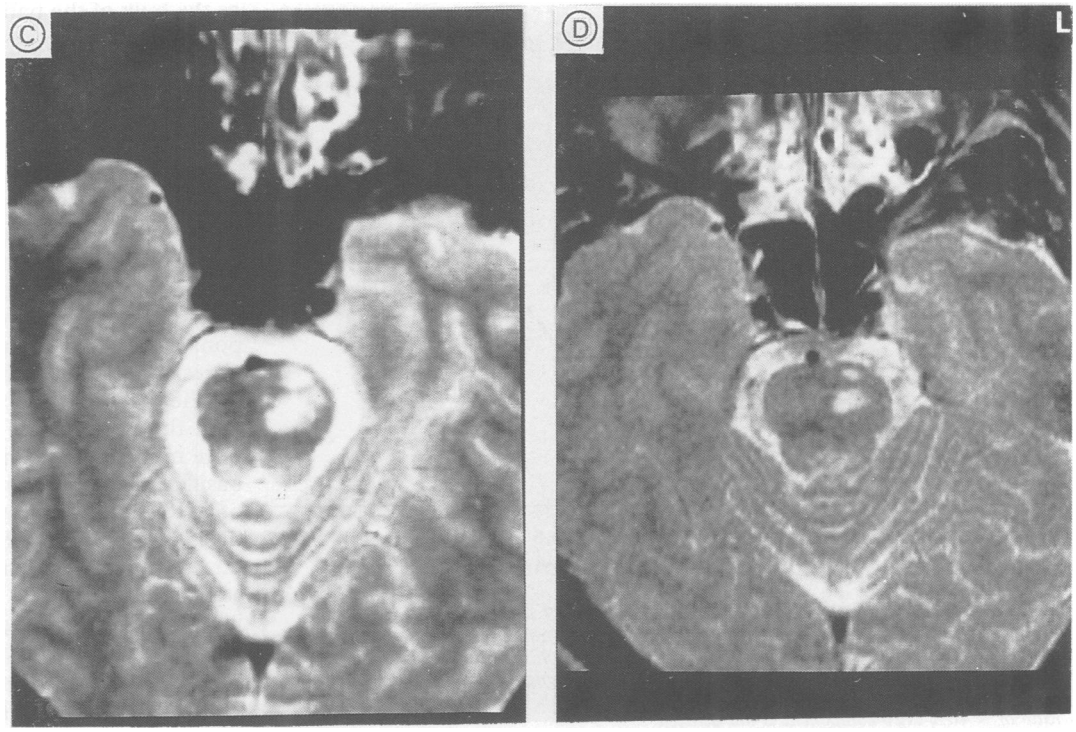

Figure 4(C) MRI at the time of the recording in (A) shows a large hyperintense area in the left ventral pons. (D) Repeat MRI at the time of the second recording in (B) shows marked retraction, indicating that the lesion in (C) consisted not only of infarcted tissue but also of oedema.

Discussion

We found that increasing severity of hand paresis is associated with increasing CMCT in a cohort of 20 patients with pontine infarction. The increase in CMCT reached 8–10 ms in patients with severe paresis. Improvement of paresis was followed by shortening of CMCT of the affected side in the few subjects with serial recordings. The delay in CMCT could also be shown in a comparable way by calculating the latency difference on the affected side minus that on the unaffected side. Increased CMCT was also found in paretic muscles after stroke by Berardelli *et al* with electrical stimulation.[5] However, in most of their patients no response could be evoked at all so that no CMCT could be calculated. The CMCT in their patients as well as in ours was considerably prolonged but was still less delayed even with very small responses than it was in patients with multiple sclerosis.[2] Demyelination is probably not the cause for the delayed CMCT in patients with stroke but more likely the need for temporal summation on the alpha motor neuron.[13] This need emerges from the diminished spatial summation as a result of axonal damage. Further evidence for this mechanism is that SEPs were not delayed in our patients, even in those with clinical sensory involvement and an amplitude reduction in N20. Normal latency of SEP with increased CMCT has also been reported before.[6] The pyramidal tract lesion may have been more severe than that of the medial lemniscus in our patients. However, even in the most severe strokes due to basilar artery thrombosis or pontine haemorrhage, the main SEP abnormality is reduction of amplitude with normal latency.[14 15]

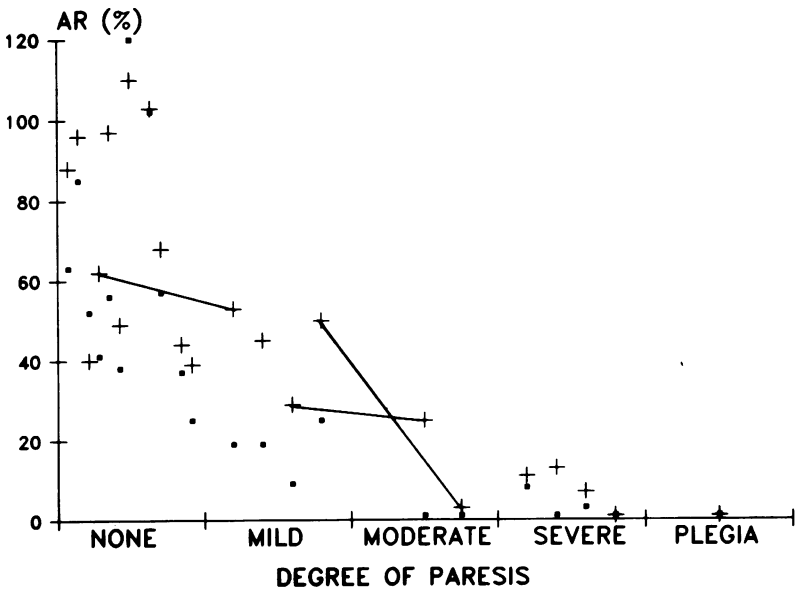

Figure 5 Amplitude ratio (affected to unaffected APB) in different degrees of paresis. Crosses represent contracted muscles, dots relaxed muscles. One patient with carpal tunnel syndrome was excluded from this analysis.

Amplitudes of motor evoked potentials have received only little attention in published work. This may be because of their inherent variability and the difference between sides of the body even in normal subjects, making their evaluation difficult in an individual patient. However, with respect to our group of hemiparetic patients there was a clear association between degree of paresis and amplitude reduction of the affected side expressed as the amplitude ratio. Complete loss of the potential was a common finding with electrical stimulation in patients with both cortical and capsular infarction and was observed even in patients with a mild paresis.[5] This is at variance with our

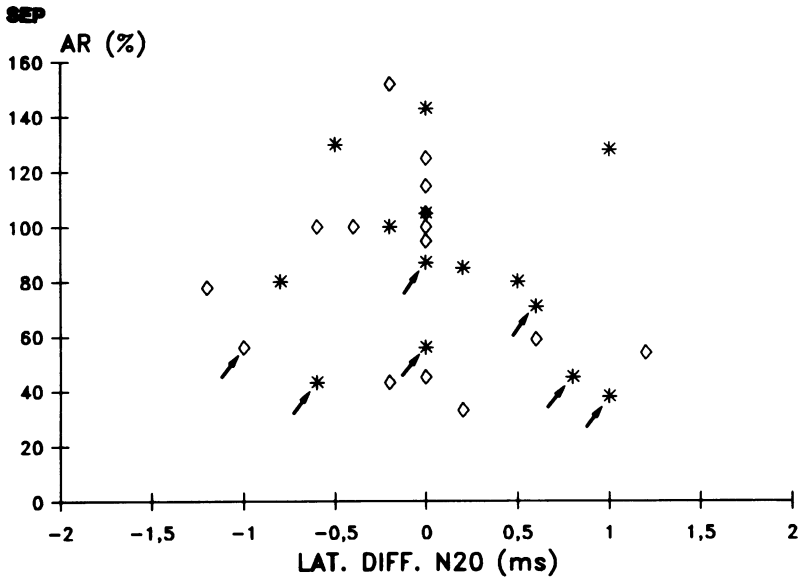

Figure 6 Amplitude ratio N20/P25 of median nerve SEP (affected/unaffected side). Recordings were made in the acute state (asterix) or the chronic state (rhombus). Values marked by an arrow represent patients with clinical signs of disturbed sensation. Two further patients with clinical sensory involvement had a complete loss of N20/P25 component and could therefore not be included in this graph. Even with an amplitude ratio of < 40% N20 component is not delayed.

results using magnetic stimulation, in which responses could be obtained even in patients with severe paresis. A possible explanation for this discrepancy is that in all our patients with pontine infarction the cortex was intact and was able to produce I waves. I waves appear as repetitive discharges of the pyramidal tract fibres and lead to temporal summation on the alpha motor neuron. On the contrary, patients with cortical infarction would lack not only the initial part of the pyramidal tract but also presynaptic afferent input to the pyramidal cells thereby supplying a less powerful activation of the alpha motor neuron.[13] As electrical stimulation produces fewer I waves than magnetic stimulation does, the frequent absence of the response even in less severe paresis in the patients of Berardelli *et al* may be due to both mode of stimulation and location of infarct.[5] Further reasons to suggest a differential effect of cortical versus subcortical—for example, capsular or brainstem—lesions on motor evoked potentials can be derived from experiments investigating transcallosal effects of focal hemispheric stimulation on to excitability of the contralateral motor cortex.[16]

Even in patients whose paresis had resolved we found a reduction in amplitude of the response in the previously affected APB. As the amplitude ratio of affected to unaffected side went down to 40% in these patients and exceeded 100% only in one patient it can clearly be separated from random variability. Thus for the first time a subclinical involvement after pyramidal tract lesion could be demonstrated for patients with stoke. Such subclinical involvement could also be shown in other conditions such as multiple sclerosis and hereditary ataxias.[2 3] The prognostic value of TCMS could not be investigated in this study as the bulk of the patients were studied only in the chronic state.

Apart from the electrophysiological findings, some interesting clinical findings emerged from this study. Somewhat surprising, our patients had a relatively moderate extent of paresis, even though we included only patients with a definite pontine infarct visible on MRI.[17] By doing so, we probably introduced a bias towards larger infarctions because small lesions cannot be detected by MRI. Moreover, most of the lesions were located in the ventral pons, which contains the pyramidal tract fibres. Occasionally the prominent MRI lesion in the basis pontis contrasted considerably with the mild degree of paresis. Even though pure motor hemiplegia was known to occur in basilar branch occlusion before the application of MRI,[18] clinicians tended to base the diagnosis of a pontine infarction with hemiparesis on additional oculomotor or cranial nerve signs and symptoms. These were rarely found in our patients, suggesting that most of our patients previously would have been diagnosed as suffering from capsular infarctions. On the other hand, if the pontine location of the infarct could be diagnosed by computed tomography the infarct was likely to be large because of the lower sensitivity of CT towards pontine lesions. Thus based on our findings, we suggest that hemiparesis due to pontine infarction in most cases has a relatively good prognosis. Moreover, pontine infarctions that lead to pure motor or sensomotor hemiparesis are more common than those associated with oculomotor abnormalities or crossed syndromes.

In conclusion, the degree of hand paresis in pontine infarction is accompanied by corresponding changes in CMCT as well as in the amplitude of the response. A precise prediction of clinical findings from the TCMS results is, however, not possible.

Professor Armin Thron kindly provided MRI data and figure 4 (c and d). We thank Mrs Seidel for secretarial help. Parts of this study will be included in SV's doctoral thesis.

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