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Serial evoked potentials in multiple sclerosis bouts. Relation to steroid treatment

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Serial recordings of multimodal sensory (visual, acoustic and somatosensory) evoked potentials were made in 19 relapsing-remitting Multiple Sclerosis patients enrolled in a clinical trial designed to evaluate the efficacy of dexamethasone versus high- and low-dose methylprednisolone in acute multiple sclerosis bouts. Electrophysiological and clinical evaluations were performed at the onset of therapy and until 6 months after the end of treatment. Using an arbitrary Evoked Potentials score that takes into account both latency and waveform alterations, we found a positive correlation between evoked potentials and clinical disability scores. Furthermore, different electrophysiological profiles were detected in the three therapeutic subgroups. Evoked potentials may be useful for monitoring acute Multiple Sclerosis bouts and evaluating the effect of therapy.

Key Words: multiple sclerosis — evoked potentials – steroids.

Introduction

The diagnostic value of Evoked Potentials (EPs) in Multiple Sclerosis (MS) is well known [5, 8, 11, 17, 22], but their usefulness in disease monitoring is controversial [1, 2, 16, 20]. Steroids are widely used in the treatment of MS exacerbations, but is still uncertain if their mechanisms of action are mainly antiedemic [14], antiinflammatory [6] or something else [3, 29].

In a previous study, we demonstrated that dexamethazone (DX) is more effective that ACTH or low-dose methylprednisolone (LDMP) in bout therapy [19]. No correlation has been found between clinical efficacy and short-term changes in visual (VEPs) or brain-stem auditory (BAEPs) EPs [26].

In this study, we evaluated the usefulness of short- and long-term serial EPs (VEPs, BAEPs, somatosensory EPs-SSEPs-) in a group of patients enrolled in a clinical trial evaluating steroid efficacy in MS bouts.

Patients and methods

Patients

Serial EPs were evaluated in 19 patients affected by relapsing-remitting MS consecutively included in a large clinical trial. Twelve patients had clinically definite and 6 probable MS, according to Mc Donald and Halliday's criteria [18]; the remaining patient had optic neuritis with CSF oligoclonal bands, and became probable MS during the study. All of the patients were in bout, defined according to Schumacher's criteria [27]. Bout onset had taken place during the 4 weeks before the patients were randomly allocated to one of the following therapeutic schedules: 1) DX, 8 mg/day for 7 days, 4 mg/day for 4 days, 2 mg/days for 3 days; 2) LDMP, 40 mg/day for 7 days,

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TABLE I. *Clinical features of patients and results of randomization.*

	DX	HDMP	LDMP
No. of patients	8	6	5
Mean age (yrs)	28.7±7.1	32.6±8.8	28.4±11.7
Sex	7 F, 1 M	5 F, 1 M	3 F, 2 M
Disease duration (mos)	42.2±30.1	106±125	47.8±41.3
Mean prebout DS	0.68±0.59	1.16±1.8	1.3±1.1
Bout syndrome*	3 BS, 2 SC, 1 ON, 2 CH	3 BS, 2 SC, 1 CH	2 BS, 1 SC, 1 CH, 1 ON

DX indicates dexamethasone; HDMP, high-dose methylprednisolone; LDMP, low-dose methylprednisolone, F, female; M, male; DS, disability score.
* Bout syndrome indicates clinical signs and symptoms compatible with brain stem (BS), spinal cord (SC), cerebral hemisphere (CH), and optic nerve (ON) involvement.
± = Standard Deviation.

20 mg/day for 4 days, 10 mg/day for 3 days); 3) high-dose MP (HDMP), 1000 mg/day for 3 days, 500 mg/day fof 3 days, 250 mg/day for 3 days, 125 mg/day for 3 days, 62.5 mg/day for 2 days. Each dose of the three different schedules was administered by intravenous infusion in 250 ml of saline. The patients were controlled by a blind observer 24 h before the onset of therapy, at 15 days and then 3 and 6 months after the end of treatment. Clinical evaluations included complete neurological examination, scored according to Kurtzke's Expanded Disability Status Scale (EDSS) and Functional Systems (FS) [15]. The clinical characteristics of the three therapeutic subgroups are shown in Table I.

EVOKED POTENTIALS

EPS studies were performed in all patients at the same time as the neurological evaluations (0, 15 days, 3 and 6 months), although 3 cases were lost at the last examination. The therapy was unknown to the examiner.

VEPs

Pattern-reversal VEPs with full-field checkerboard stimulation at 1.6 Hz and 50% contrast (check size 15 minutes of arc) were recorded from a midline electrode placed 5 cm above the inion and referenced to the vertex. Absolute and interpeak latencies of the N80 and P100 components and the N80-P100 peak-to-peak amplitude were considered. No refraction defects were detected in any of the patients.

BAEPs

BAEPs were elicited by 0.1 msec squarewave rarefaction clicks at 80 dB normal hearing level, presented at 10/sec to each ear. The responses were recorded in two separate channels from the vertex, respectively referenced to the ipsilateral and contralateral mastoid. Absolute latencies of waves I, III and V, interpeak I-III, III-V and I-V, and the I/V amplitude ratio were considered. All patients had normal hearing.

SSEPs

SSEPs were elicited by 0.1 msec electrical pulses just above the motor threshold and delivered percutaneously to the median nerve at the wrist for the upper limbs in all patients, and to the posterior tibial nerve at the medial malleolus for the lower limbs in 16 patients. Median SSEPs were simultaneously recorded from Erb's point and the sixth cervical spine with reference to a midfrontal electrode, and from a controlateral parietal scalp electrode located 2 cm posterior to a site 7 cm lateral to the vertex, referenced to linked mastoids, controlateral shoulder and midfrontal site. Tibial SSEPs were recorded from the cauda equina and lumbar spine with electrodes placed respectively over the L3 and L1 spinal processes (referenced over the contralateral iliac crest), and from the scalp with an electrode placed 2 cm behind the vertex and referenced to the midfrontal site.
Absolute latencies for the N9, N13 cervicomedullary and N20 cortical waves and the N9-N13 and N13-N20 interpeak latencies (Central conduction time) were considered in the evaluation of median SSEPs. The N24 and P40 absolute latencies and the N24-P40 interpeak latencies were considered in the evaluation of tibial SSEPs. The morphology of median SSEPs was defined by the following parameters: a) N13 onset-to-peak and N20-P27 peak-to-peak amplitude, respectively in the cervical spine-midfrontal and contralateral parietal-midfrontal derivations; b) duration defined by the N20-P27 peak interval. The morphology of tibial SSEPs was defined by the P40 onset-to-peak amplitude and interval values.

Abnormality criteria

Since a natural EP intertrial variability also occurs in normal subjects, we adopted very strict criteria for changes in order to increase the spe-

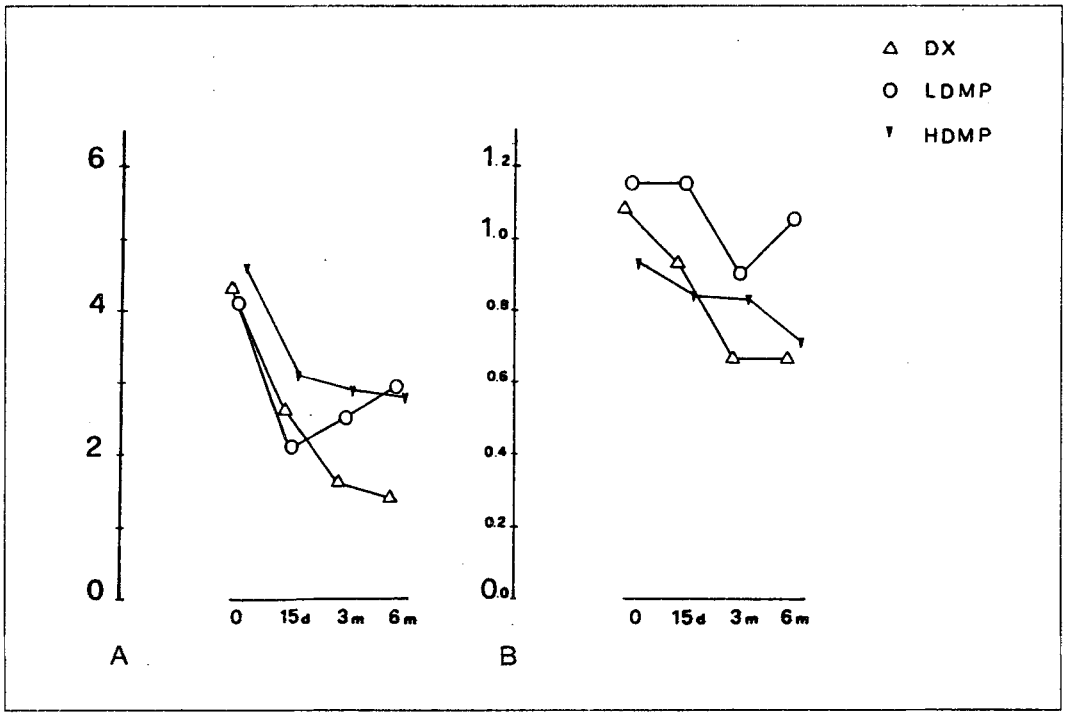

Fig. 1. *A) Mean disability score and B) mean evoked potentials score in multiple sclerosis patients over time (at bout onset 0, at 15 days, 3 and 6 months after trial onset).*

cificity of our analysis. Latency values were considered significantly increased when they exceeded mean control values by 2.5 SD. Alterations in morphology were defined according to the suppression, interside amplitude asymmetry (expressed as the percentage difference between the lower and higher value), or intertrial amplitude change of at least one component. Asymmetry and intertrial differences were considered significant when they exceeded 50% of the reference value. According to these criteria, the EP findings were classified as normal, latency-altered, waveform-altered or extinct. When there were both latency and waveform changes, the latter were arbitrarily considered prominent. A delayed-distorted EP was thus scored as waveform-altered. A numerical score was associated with the EP findings: 0 to normal, 1 to latency-altered, 2 to waveform-altered, 3 to extinct EPs. Mean overall and within-therapeutic group electrophysiological score values were calculated by dividing the sum of all individual EP scores by the number of tested sides in the four modalities at eache trial time.
Follow-up EPs were considered "stable", "improved" or "worsened" according to the same numerical scores. Variations in at least 1 point were considered significant. Changes in latency were considered significant when they exceeded 2 SD of our healthy controls for each EP modality.

Statistical analysis

Clinical and electrophysiological findings were correlated using Spearman's rank correlation test. Between-group comparisons were made using the chi-square and Mann-Whitney U tests.

Results

Clinical results

At 15 days, a clinical improvement (a decrease of at least 1 point in Kurtzke EDSS) was observed in 18 of the 19 patients (except one DX-treated case), at 3 months in 17 (except 1 LDMP and 1 HDMP-treated case), and at 6 months in 18 (except 1 LDMP-treated case). The mean EDSS at 15 days was similarly reduced in all the three therapeutic subgroups. However, whereas DX-treated patients continued to improve until the end of follow-up, HDMP-treated patients remained stable and LDMP-treated cases worsened (see Fig. 1 A). In fact, 4 of the LDMP patients had further relapses (2 cases within 1 months, 1 had 2 new

TABLE II. *Baseline abnormal evoked potentials in relation to clinical bout syndrome.*

Bout syndrome*	VEPs		BAEPs		SSEPs	
	No. of patients	%	No. of patients	%	No. of patients	%
ON (n=2)	2	100	0	0	1	50
BS (n=8)	4	50	6	75	4	50
SC (n=5)	4	80	2	40	4	80
CH (n=4)	2	50	3	75	2	50

* Bout syndrome indicates clinical signs and symptoms compatible with brain stem (BS), spinal cord (SC), cerebral hemisphere (CH), and optic nerve (ON) involvement.

bouts at 2 and 6 months, and 1 at the end of follow-up). Only 2 of the 8 DX-treated patients and 1 of the 6 HDMP-treated patients had new relapses.

ELECTROPHYSIOLOGICAL RESULTS

Baseline results

VEPs were abnormal in 63.1%, BAEPs in 57.8% and SSEPs in 52.8% of the cases. No clear correspondence was found between the clinical syndrome and the abnormalities of the corresponding EP modality, except for the optic neuritis cases (see Table II).

Follow-up results

Significant changes in EPS during follow-up occurred in 11 of the 19 patients (57.9%). Improvements were more frequent in the first 3 months (95%), and worsenings in the last 3-6 months (75%). EP changes occurred in 6 of the 8 patients with brain stem relapses, in all 5 patients with clinical cerebral hemisphere involvement, and in the 2 cases of optic neuritis. All of the 5 spinal cord relapses showed stable electrophysiological parameters. Except for individual cases (see Fig. 2), no clear correlation emerged between clinical evolution and changes in the corresponding electrophysiological modality during the follow-up; moreover, modifications frequently occurred in other modalities not correlated with the clinical syndrome (see Table III). Furthermore, EP changes were never correlated with clinical signs or symptoms of new relapses occurring during follow-up, except in 1 ON case who had a new attack 1 month after trial entry with clinical signs compatible with spinal cord involvement and parallel SSEPs changes.

No significant findings were detected when the absolute latency and amplitude values at the various times of follow-up were analysed (data not shown). The mean EP scores at the various time points are shown in Fig. 1 B. In DX- and HDMP-treated patients, we observed a progressive decrease in EP score, parallel with their clinical improvement (see Fig. 1 A). On the contrary, in the LDMP-treated group, early (15 days) clinical improvement corresponded to a late (3 months) reduction in EP score, and the next clinical worsening corresponded to a clear electrophysiologial worsening at 6 months. The correlation between changes in EDSS and percentage changes in EP scores in comparison with baseline was found to be statistcally significant at both 3 ($P=0.008$) and 6 months ($P=0.02$). Clear differences in the number of normal, latency-, waveform-altered and extinct EPs, were found in the three therapeutic subgroups (see Fig. 3). The DX-treated group showed a progressive increase in the percentage of normal EPs and a reduction in the number of waveform-altered and extinct EPs, without any changes in the percentage of latency-altered EPs. HDMP-treated patients showed a similar pattern whereas, in the LDMP-treated cases, the percentage of normal EPs fluctuated (latency-altered EPs increased, along with opposite changes in waveform-altered and extinct EPs). None of these within-groups differences reached statistical significance.

Discussion

Previous serial EP studies in MS have suggested a relationship between EP changes and the clinical course of the disease. Stable patients are electrophysiologically stable [9, 24], whereas progression of disability seems to be associated with a progressive increase in latency [9, 30]; no or poor correlations can be found with clinical symptoms [1, 2, 12, 24]. In a long-term follow-up of chronic progressive azathioprine-methylprednisolone-treated MS patients, Nuwer et al. [20] were able to find a correlation between latency changes and clinical outcome. A significant improvement in central conduction time and clinical course after HDMP therapy has been found in acute MS patients [25], although no significant short-term EP changes were detected in steroid-treated MS patients [6, 7, 28), thus questioning the usefulness of EPs in monitoring disease activity in therapeutic trials [1, 2].

However, most of the studies have been carried out in MS populations which were hetergeneous

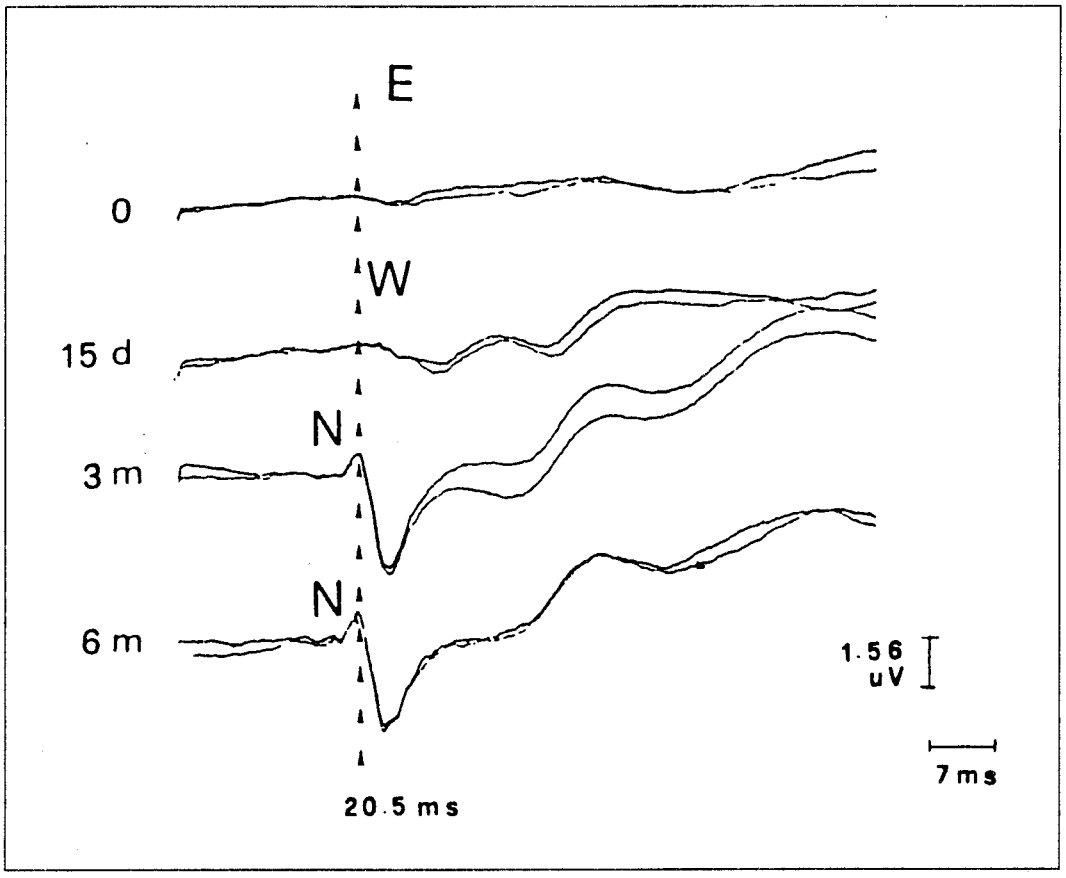

Fig. 2. *Evolution of median ssEPs. Right cortical derivations following left median nerve stimulation. This 18-year-old patient had an acute left hemiparesis with astereognosis of the left hand. She recovered completely within 15 days and remained stable during the next 6 months. The right cortical contralateral responses showed a temporarily concordant evolution: an extinct (E) N20 at baseline recording changed to latency-delayed and waveform-altered (W) after 15 days and to normal (N) after 3 and 6 months.*

in terms of clinical course (relapsing-remitting or progressive) and disease activity (relapse, stable or progressive phase). Furthermore, the information contained in EPs may not be fully exploited by insensitive scales, such as worse-better-unchanged. Latency measurements seem to be useful in long-term follow-up [20] and a clinico-electrophysiological correlation has been found in relapsing-remitting and progressive MS patients using an arbitrary EP abnormalities scale based on latency and waves extintion [4, 12].

Severeal lines of evidence strongly suggest that a conduction block (whose EP marker is waveform distortion: [10]), rather than conduction slowing accounting for increased latency is related to clinical deficits [21, 23, 31]. Amplitude changes seem to be related to short-term clinical outcome [10, 13], but other authors have disregarded the analysis of abnormalities in amplitude and waveform morphology as scarcely quantitative or not reliable [2]. Conduction block may become irreversible because of the severity and extension of demyelination [23] and associated gliosis. On the contrary reversible neuropathological damage, such as oedema, inflammatory infiltration or variation of the biochemical environment of plaques, may be associated with an improvement in neurophysiological parameters.

In our study, we considered a homogeneous population of remitting-relapsing patients during an acute MS bout followed for 6 months; we also used an arbitrary EP score which takes into account all types of abnormalities and gives a higher score to waveform alterations and extinctions. In agreement with the literature, we did not find a consistent correlation between clinic data and baseline EP abnormalities or EP changes during follow-up, either for clinical syndrome or func-

TABLE III. *Changes in serial evoked potentials in comparison with baseline, and their relation to the evolution of clinical bout syndrome.*

Bout syndrome	Follow-up	Clinical outcome			VEPs			BAEPs			SSEPs		
		Im	St	Ws	Im	St	Ws	Im	St	Ws	Im	St	Ws
ON (n=2)	15 d	2	—	—	1	1	—	—	2	—	—	2	—
	3 m	2	—	—	2	—	—	—	2	—	—	1	1
	6 m	2	—	—	1	1	—	—	2	—	—	1	1
BS (n=8)$	15 d	8	—	—	3	4	1	—	8	—	2	6	—
	3 m	8	—	—	3	5	—	1	7	—	2	5	—
	6 m	8	—	—	2	4	1	1	6	—	2	5	—
SC (n=5)§	15 d	4	1	—	—	5	—	—	5	—	—	5	—
	3 m	3	2	—	—	5	—	—	5	—	—	5	—
	6 m	4	1	—	—	3	—	—	3	—	—	3	—
CH (n=4)	15 d	4	—	—	—	4	—	—	4	—	1	3	—
	3 m	4	—	—	1	2	1	1	3	—	2	2	—
	6 m	4	—	—	—	1	3	—	3	1	2	2	—

Im indicates improved; St, stable; Ws, worsened; ON, optic neuritis; BS, brain stem bout; SC, spinal cord bout; and CH, cerebral hemisphere bout.
$ one patient was lost at the last examination.
§ two patients were lost at the last examination.

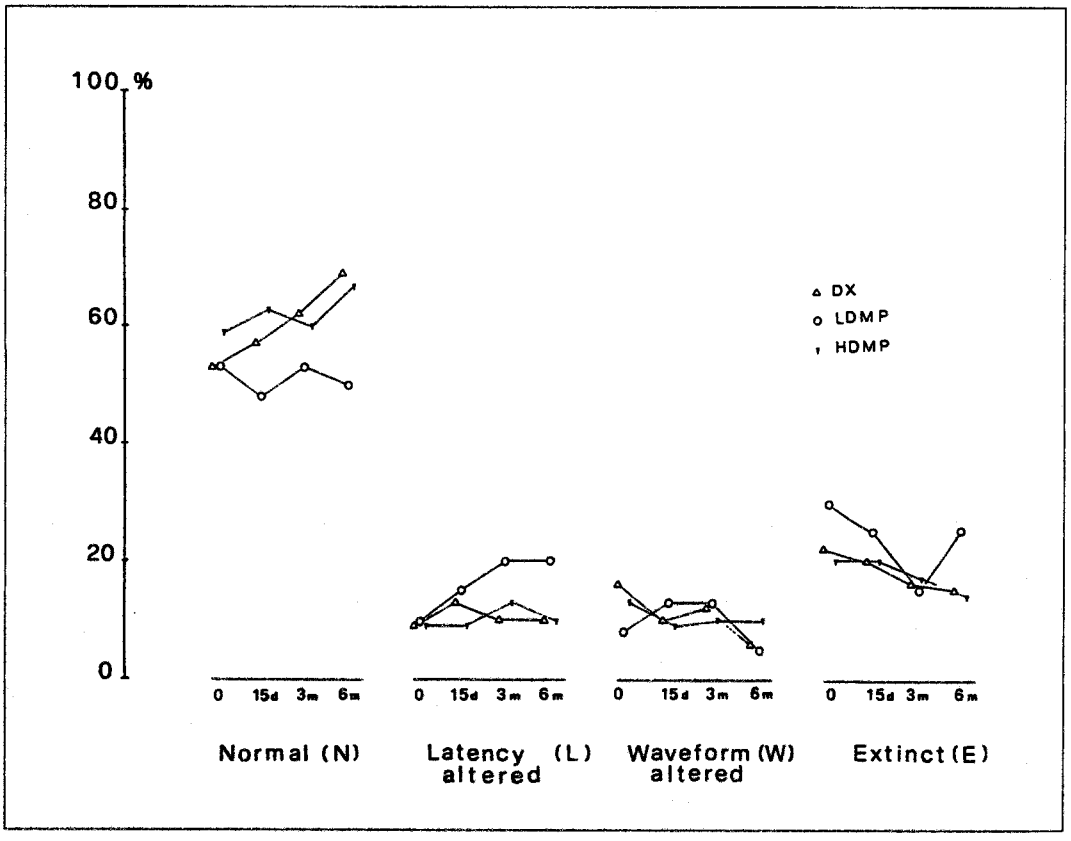

Fig. 3. *Percentages of normal (N), latency-altered (L), waveform-altered (W) and extinct (E) EPs in the three therapeutic subgroups during follow up.*

tional system. On the other hand, it is possible that EP changes unrelated to the clinical relapse syndrome may reflect the subclinical involvement of other central pathways. However, clinical disability was correlated to EP score, clinical improvement corresponding to a decrease in EP score and viceversa (see Fig. 1). Moreover, different electrophysiological profiles were found in the three therapeutic subgroups (Fig. 3): in particular, while DX and HDMP-treated patients showed a more frequent EP normalization parallel with their clinical improvement, LDMP-treated patients showed a higher percentage of delayed and extinct EPs parallel with their clinical worsening and more frequent attacks during follow-up.

Our data suggest that clinical outcome after an acute MS bout may be related to EP changes. Waveform-altered and extinct EPs may change to normal in improving patients, whereas clinical worsening is associated with an increase in latency and waveform alterations. Different steroid schedules may underlie these different clinical and electrophysiological outcomes.

A study in a larger population is needed to confirm these data.

Sommario

I potenziali evocati visivi, acustici e somatosensoriali sono stati monitorati in 19 pazienti affetti da Sclerosi Multipla, inclusi in un trial clinico volto alla valutazione dell'efficacia del desametazone e di basse e alte dosi di metilprednisolone nel trattamento delle riaccensioni della malattia. La valutazione clinica ed elettrofisiologica veniva effettuata all'inizio e alla fine del trattamento (a 15 giorni) e a 3 e 6 mesi dopo la sospensione. Utilizzando una scala arbitraria elettrofisiologica che prendeva in considerazione sia le alterazioni di latenza che di morfologia, abbiamo riscontrato una correlazione positiva tra punteggio elettrofisiologico e disabilità clinica. Inoltre differenti profili elettrofisiologici erano osservati nei tre sottogruppi terapeutici. Lo studio dei potenziali evocati appare utile nel monitoraggio delle riaccensioni della malattia e nella valutazione dell'effetto della terapia.

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