J Neurol (2012) 259:1490–1493
DOI 10.1007/s00415-012-6422-9

LETTER TO THE EDITORS

Abnormal sensory-motor integration in a patient with anti-NMDA-receptor encephalitis

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Received: 11 November 2011 / Revised: 24 December 2011 / Accepted: 13 January 2012 / Published online: 28 January 2012

Dear Sirs,

In this report, we describe the case of patient who showed abnormal corticomotor responses after peripheral afferent stimulation, namely sensory afferent inhibition (SAI) and sensory afferent facilitation (SAF), and its reversibility after treatment in a patient with anti-*N*-methyl D-aspartate receptor (NMDAR) encephalitis.

A 26-year-old woman was admitted to a hospital after experiencing fever and headache for 11 days. Comprehensive serological studies, a brain magnetic resonance imaging scan, and cerebrospinal fluid (CSF) analysis were unremarkable. In the following days, she developed hallucinations and generalized tonic seizures. A repeat CSF analysis showed lymphocytic pleocytosis (261 white blood cells/mm^3; 97% lymphocytes) and a normal protein concentration (63 mg/dl). She continued to have hyperkinetic movements and hyper-pyrexia despite receiving antibacterial and antiviral treatments. Electroencephalography showed diffuse slow waves with unremarkable somatosensory evoked potentials and brainstem auditory evoked potentials. After 30 days, she became unresponsive and had respiratory failure, and was then transferred to our hospital.

On examination, she presented with dystonic posturing, oro-lingual-facial dyskinesia, and myoclonic movements. A computed tomography scan of the chest and abdomen and a trans-vaginal sonogram disclosed no abnormalities. Her serum and CSF studies were positive for anti-NMDAR antibodies. Transcranial magnetic stimulation (TMS) demonstrated intact corticospinal tracts with normal latencies and thresholds for motor-evoked potentials (MEPs). However, the conditioned peripheral afferent stimulation failed to show an SAI response at inter-stimulus intervals (ISIs) in the range of 15–25 ms, while exaggerated SAF responses were observed at ISIs between 30 and 70 ms. These data are contrasted to data from a healthy control subject in Fig. 1a, b and Table 1. The patient's condition showed a little improvement in that she started to have some slow responses to verbal stimulation after steroid pulse therapy and plasmapheresis. Intravenous immunoglobulin was then started, and her condition improved dramatically. In a 3-week follow-up SAI/SAF study, the SAF had made notable progress toward normalization, but a normal SAI response was still absent (Fig. 1c; Table 1).

NMDARs are expressed at high levels in the central nervous system, and play an important role in excitatory synaptic transmission and synaptic plasticity. Patients with anti-NMDAR antibodies usually present with various neurological symptoms presumably resulting from an AMPA receptor-mediated hyperglutamatergic state [1]. The MEP amplitude and latency of the patient described herein were similar to normal values. Impaired SAI and exaggerated SAF, such as observed in the presently described case, are suggestive of abnormal motor-sensory

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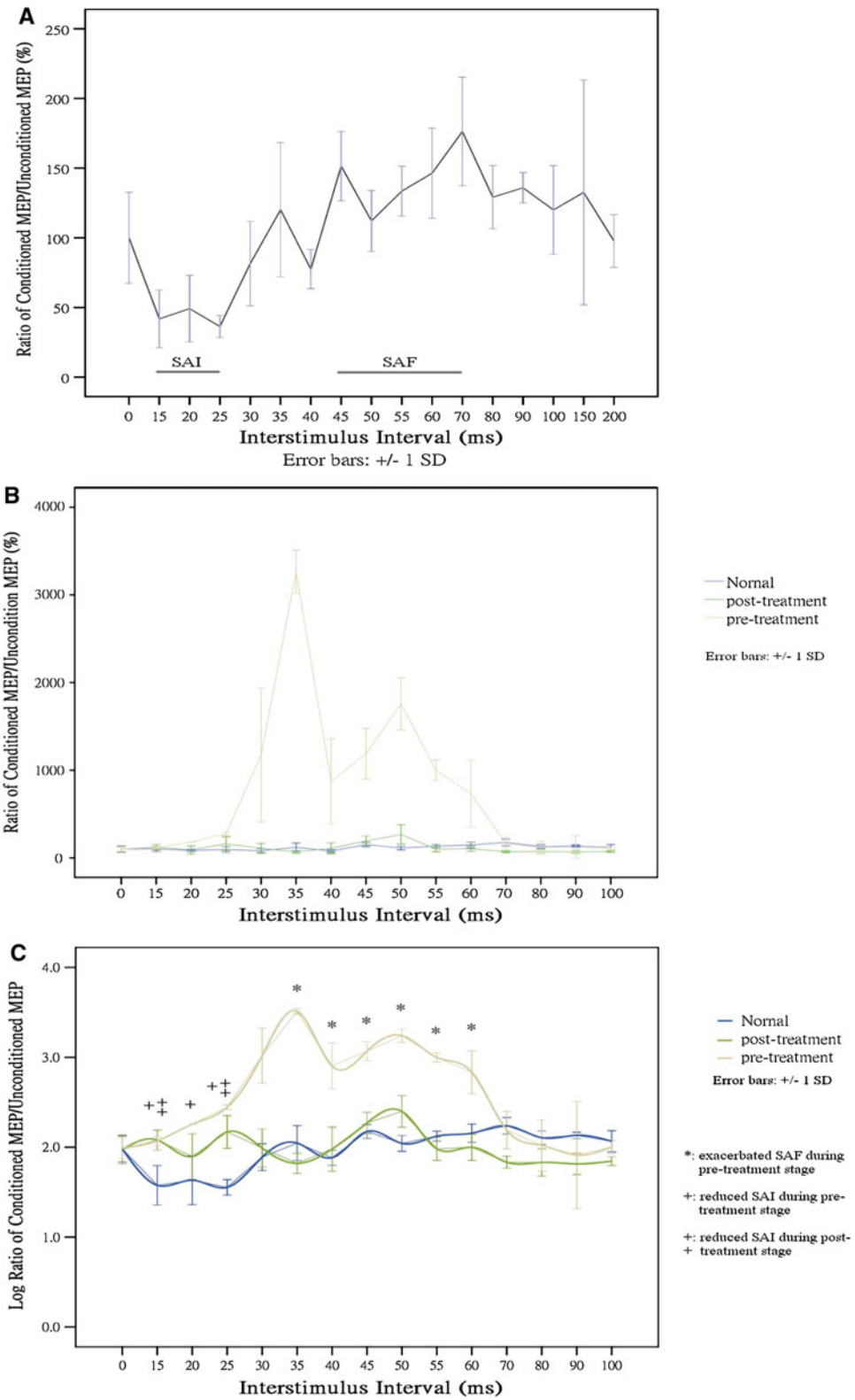

Fig. 1 **a** Typical pattern of SAI/SAF in a healthy control subject (26-year-old female). Transcranial magnetic stimulation was applied over the left primary motor cortex (M1) of the abductor pollicis brevis (APB). Firstly, the intensity to evoke a motor-evoked potential ~1 mV was determined. Then, a conditioned peripheral electric stimulation, twice the intensity of motor threshold, was given over the right median nerve at the wrist in different inter-stimulation intervals (ISI) prior to the TMS. At each ISI, six stimuli were tested, and the ratio (%) to unconditioned MEP was expressed (mean ± SD). SAI at ISI between 15 and 25 ms and SAF at ISI between 45 and 70 ms can be identified. **b** In the patient before treatment, the TMS of the SAI study failed to show an inhibitory pattern at ISI of 15–25 ms on gross inspection. A markedly exaggerated SAF response at ISI between 30 and 70 ms was observed. After the treatment, the SAF demonstrated changes toward normalization. **c** Logarithmic presentation of Fig. 1b. Significantly exacerbated SAF before treatment was marked with an *asterisk*, and significantly reduced SAIs before treatment and after treatment were marked with *plus* and a *double dagger*, respectively. (Kruskal-Wallis test, with post hoc Mann-Whitney *U* test; $p < 0.05$ indicates significance)

integration. After treatment, the patient's SAF appeared to be normalizing, though her SAI response remained absent. These results imply that NMDAR encephalitis is a reversible disinhibition-predominant syndrome.

The SAF phenomenon results from an interaction between afferent inputs and intracortical inhibition/intracortical facilitation (ICI/ICF) [2]. On the other hand, SAI is mediated through cholinergic circuits [3] and the

Table 1 Raw data of MEP amplitude in control and patient before and after treatment

ISI (ms)	0	15	20	25	30	35	40	45	50	55	60	70	80	90	100
Mean MEP amplitude (mV)															
Control	0.391	0.164	0.192	0.142	0.318	0.469	0.303	0.592	0.438	0.522	0.572	0.689	0.505	0.531	0.469
Patient before treatment	0.206	0.243	0.372	0.574	2.419	6.730	1.796	2.447	3.621	2.061	1.511	0.337	0.239	0.254	0.208
Patient after treatment	0.320	0.395	0.286	0.515	0.348	0.217	0.349	0.615	0.855	0.319	0.334	0.220	0.228	0.215	0.225
MEP (%) (compared to unconditioned MEP)															
Control	100.00	41.85	49.19	36.40	81.51	120.16	77.55	151.48	112.12	133.51	146.34	176.32	129.14	135.91	119.98
Patient before treatment	100.00	117.93	180.30	278.57	1,173.74	3,266.20	871.39	1,187.58	1,757.34	1,000.00	733.32	163.55	116.11	123.44	101.12
Patient after treatment	100.00	123.26	89.36	160.74	108.59	67.85	108.94	192.19	267.24	99.64	104.22	68.71	71.10	67.20	70.41

GABAergic system [4]. In normal subjects, a conditioned afferent input facilitates ICF and reduces ICI [2], resulting in a net MEP facilitation at ISIs between in the range of 45–70 ms. In a hyperglutamatergic state, such as stiff-person syndrome, ICF is enhanced while ICI is reduced [5]; these changes tend to normalize after treatment. Changes in ICI/ICF such as these may explain the exaggerated SAF, and its normalization after immunotherapy, in our patient. GABAergic interneurons that had become dysfunctional as a result of a hyperglutamatergic status [6] might have contributed to the reduced SAI observed in our patient.

An alternative TMS protocol (i.e., resting motor threshold, ICI/ICF, and a silent period) can be used to evaluate different excitatory and inhibitory mechanisms within the motor cortex. However, due to our patient's initial condition, a silent period study could not be performed in the present case. This study investigated the sensory afferent effect on the motor cortex because it is a good alternative for exploring the excitability of the motor cortex without the patient's conscious cooperation. In addition, we chose a paradigm that could be performed using traditional (mono-pulse) TMS equipment, which has high clinical availability, instead of the paired-pulse paradigm, which requires specialized Bi-TMS equipment, to increase the feasibility of subsequent studies that may replicate our findings.

During the patient's hospital stay, she was prescribed leveriacetam (500 mg per day) to alleviate her hyperkinetic movements. Consistent with a prior report [7], leveriacetam treatment did not significantly affect the ICF, ICI, or mean MEP amplitude in our patient. Thus, medication effects on cortical excitability should have been minimal to negligible in our study.

In conclusion, our study uncovered a possible effect of NMDA antibodies on central functional circuits in vivo that was coherent with clinical phenomenology. Our findings suggest that the extent of abnormal SAF could be an objective marker for treatment response.

Acknowledgments The authors thank Prof. Dalmau and his laboratory at the University of Pennsylvania for analysis of anti-NMDA-receptor antibodies.

Conflicts of interest This study was supported in part by grants from Taipei Veterans General Hospital (V99B1-002). Dr. Dou and Dr. Lai report no disclosures. Dr. Liao and Dr. Chen received grants from Taipei Veterans General Hospital and National Science Councils, Taiwan, R.O.C.

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