

responsible antigen so that we can compare our results with serological detection of specific anti-ganglioside antibodies. The results are remarkable as it is known that very many different carbohydrate antigenic determinants are present in different strains of *C jejuni* and our antigen was obtained from a single isolate, providing an extremely limited array of possible antigens. Whereas we anticipated such responses in patients with Guillain-Barré syndrome the positive results in patients with multiple sclerosis are also of interest. These results would accord with studies implicating immunity to non-protein antigens in multiple sclerosis, including a study in which it was possible to generate ganglioside specific clones from patients with multiple sclerosis that were restricted by CD1b.⁷

Further study of non-classic T cell responses in both Guillain-Barré syndrome and multiple sclerosis may prove informative.

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Changes in excitability of motor cortex in severe hepatic failure

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Severe liver failure causes accumulation of both albumin bound and water soluble substances that exhibit toxic effects on the brain and lead to hepatic encephalopathy. This is a complex neuropsychiatric syndrome determined by a neurotransmission failure rather than from primary energy deficit.¹ Transcranial magnetic stimulation represents a non-invasive method that can be used to study the physiology of the human brain.² Commonly used transcranial magnetic stimulation parameters include motor thresholds, cortical silent period (CSP), central motor conduction time (CMCT), intracortical inhibition (ICI), and intracortical facilitation. The threshold for producing motor evoked potentials reflects the excitability of a central core of neurons, which arises from the membrane excitability and a balance between inhibitory and excitatory input from local circuits. The CMCT provides information on the corticospinal tract anatomical integrity, CSP and ICI reflect the activity of GABAergic inhibitory circuits.²⁻⁶ Additional in vivo information on central motor circuits can be obtained using transcranial electrical stimulation of the motor cortex. Transcranial electrical stimulation stimulates the motor areas of the human brain deeply in the white matter and is therefore insensitive to changes in cortical excitability.⁶ Combining the data from transcranial electrical stimulation and transcranial magnetic stimulation it is possible to determine the site, cortical or subcortical, where brain functional changes have taken place. We used transcranial magnetic stimulation to explore function of the cerebral cortex in five patients affected by

severe liver failure. Recently, a molecular adsorbent recirculating system (MARS) has been proposed as a new extracorporeal detoxifying treatment.⁷ We used transcranial magnetic stimulation to evaluate the effects of MARS treatment on functions of the cerebral cortex in these patients and also the effects of orthotopic liver transplantation in one of them.

Clinical and neurophysiological examinations were recorded at baseline and 12-18 hours after the MARS procedure, combined with standard haemodialysis (Integra-Hospal) in patient 1, 3, 4, and 5 and with continuous venovenous haemodialysis (CVVHD) (BAXTER System BM11-BM14) in patient 2. Neurophysiological findings from the patients were compared with the data from 10 healthy age matched control subjects (mean age 35 (SD 17) years). Patients' relatives gave informed consent to participate in the study, which was approved by the local ethics committee. Patient 1, a 28 year old white woman developed a delayed graft dysfunction 3 days after orthotopic liver transplantation for a Budd-Chiari syndrome. On admission to the intensive care unit, her simplified acute physiology score II (SAPS II)⁸ was 67 and she was in a deep coma.

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Abbreviations: CSP, cortical silent period; CMCT, central motor conduction time; ICI, intracortical inhibition; MARS, molecular adsorbent recirculating system; CVVHD, continuous venovenous haemodialysis; SAPS, simplified acute physiology score II; RMT, resting motor threshold; AMT, active motor threshold; ISI, interstimulus interval

Table 1 Clinical and TMS findings in patients with SLF before and after MARS and OLT

	Baseline					After MARS					After OLT			
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean	Patient 3	
	Age	SAPS II	Child's score	HE*	Total bilirubin (mg/dl)	Conjugated bilirubin (mg/dl)	Bile acid (µmol/l)	Ammonia (µmol/l)	BUN (mg/dl)	Creatinine (mg/dl)	RMT (% of MSO) ^m	AMT (% of MSO) ^m	TES (% of MSO) ^f	CSP (150% AMT) (ms)
	28	21	45	49	71	35.2 (11)	NE	12	12	13	11	25.3 (9)	NE	
	67	59	42	61	33	28.8 (8)	3	3	3	1	1	17.1 (6)	Absent	
	4	4	2	1	1	161 (109)						88 (54)		
	22.3	48.4	43.8	32.9	28.6	90 (52)	12.6	35.2	32	25.5	21.2	25.3 (9)	1.5	
	20.1	34.7	39	26.3	24.1	69.2 (38)	9.9	20.7	25.2	18.3	11.6	17.1 (6)	1	
	39.9	193.2	21.5	60	298	3.1 (2)	15.3	92.8	109	63.7	160	88 (54)	8	
	176	101	45	72	56		173	114	54	85	47	95 (51)	22	
	64	21	100	115	46		47	21	71	70	25	46.8 (24)	58	
	1.1	1	5.4	5.4	2.4		0.8	0.7	3.9	3.4	1.3	2 (2)	3.5	
	75	100	78	78	81		59	76	64	70	74	68.6 (7)	57	
	NP	NP	51	46	67		NP	NP	47	48	57	47	47	
	NP	30'	15	20	25		NP	30'	15	20	25	20 (5)	15	
	NP	NP	66 (7)	NP	12.5 (55)		NP	NP	83 (5)	NP	184 (48)		83 (27)	
	NP	NP	40	NP	NP		NP	NP	48.9	NP	NP		49	

*According to Trey C *et al*; NE, not evaluable; NP, not performed; r, recording at rest; patient comatose, this value was not included in the mean; MSO, maximum stimulator output; (values in parentheses are SD. Normative data: RMT 51 (8.4); AMT 41(4); TES 18 (3); CSP (150%AMT) 97 (35); ICI 32 (14).

She underwent a MARS procedure with standard haemodialysis and after a single treatment we documented the improvement of hepatic encephalopathy. She was drowsy but responsive to verbal stimuli. The patient was discharged from our intensive care unit and died because of cardiac tamponade 3 months later.

Patient 2 was a 21 year old non-white woman affected by Wilson's disease and listed for orthotopic liver transplantation. On admission to the intensive care unit, her SAPS II was 59. The patient was in a deep coma and MARS treatment with CVVHDF was started. After a single MARS session, we documented a mild recovery of motor activity and gag reflexes. The patient died because of severe respiratory failure.

Patient 3 was a 45 year old white man affected by HBV related cirrhosis, listed for orthotopic liver transplantation. On admission to the intensive care unit, his SAPS II was 42. He was drowsy and responsive to verbal stimuli. Six MARS treatments with standard haemodialysis were performed. After each session, we noted neurological status improvement. On the 36th day from admission he was successfully transplanted. We report transcranial magnetic stimulation data recorded before and after the first of the six MARS treatments and 1 month after orthotopic liver transplantation.

Patient 4 was a 49 year old white man affected by alcoholic cirrhosis. On admission to the intensive care unit, his SAPS II was 61. He was drowsy and responsive to verbal stimuli. He underwent a MARS procedure with standard haemodialysis and after a single treatment the clinical picture was not modified. The patient died because of multiple organ failure.

Patient 5 was a 71 year old white man with subacute hepatic failure due to hepatotoxicity induced by antituberculosis treatment (isoniazide and rifampicine). On admission to the intensive care unit, his SAPS II was 33. He was drowsy and responsive to verbal stimuli. He underwent the MARS procedure with standard haemodialysis and after a single treatment the clinical picture was only slightly modified.

Magnetic stimulation was performed with a high power Magstim 200 (Magstim Co, Whitland, Dyfed). A figure of eight coil with external loop diameters of 9 cm was held over the right motor cortex at the optimum scalp position to elicit motor responses in the contralateral first dorsalis interosseus.

Resting motor threshold (RMT) and active motor threshold (AMT) were defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 50 µV in 50% of trials) at rest and during isometric contraction of the tested muscle at about 20% maximum respectively. The AMT was evaluated only in patients 3, 4, and 5 because patients 1 and 2 were comatose. The CMCT was calculated by subtracting the peripheral conduction time from spinal cord to muscles from the latency of responses evoked by cortical stimulation. Silent period duration was evaluated only in patients 3 and 5. The silent period was elicited while the patients held a tonic voluntary contraction of about 50% of maximum voluntary contraction. Five stimuli at 150% AMT were given. Paired pulse stimulation to evaluate the intracortical inhibition was performed only in patient 3. Intracortical inhibition was studied using the technique of Kujirai *et al*.^{3,5} Interstimulus intervals (ISIs) between 1 and 5 ms were investigated. Five stimuli were delivered at each ISI. Amplitude of the conditioned EMG responses was expressed as percentage of the amplitude of the test EMG responses. The amplitude of the conditioned responses at the five different ISIs studied was averaged, obtaining a grand mean amplitude. In patients 2, 3, 4, and 5 we have also analysed the motor threshold of electrical anodal stimulation. Electrical stimulation was performed with a Digitimer D180A stimulator, with a 50 µs time constant. The cathode was located at the vertex and the anode 7 cm laterally (anodal stimulation). The stimulation was performed at rest in patient 2 and during voluntary contraction in patients 3, 4, and 5. Electrophysiological parameters were re-evaluated in the patients after extracorporeal treatment.

An unpaired *t* test was used to compare patient results with the data of 10 healthy age matched control subjects (mean age 35 (SD 17) years). Analysis of variance (ANOVA) for repeated measures was used to analyse the MARS effects on RMT, transcranial electrical stimulation, and AMT. If the effect of a given parameter was significant, data were further compared post hoc using Student's *t* test for paired samples.

Electrophysiological results are summarised in table 1. The RMT was significantly higher in the patients studied than in the control group (82.4 (SD 10)% *v* 51 (SD 8.4)%; *p*<0.01) and decreased significantly after MARS (68.6 (SD 7)% *v* 82.4 (SD 10)%, *p*=0.010). The AMT was higher in the three patients studied than in the control group (54.7 (SD 11)% *v* 41 (SD 4)%, *p*>0.05) but the difference was not statistically significant probably because of the restricted number. In the patients the AMT was slightly decreased after the MARS procedure (50.7 (SD 5.5)% *v* 54.7 (SD 11)%, *p*>0.05, paired *t* test). There was no difference between the CMCT and CSP and ICI of the studied patients and of controls. Active motor threshold to transcranial electrical stimulation was similar in the three studied patients and in the control group (20 (SD 5)% *v* 18 (SD 3)%, *p*>0.05). In patient 3 we found normalisation of all the parameters evaluated after orthotopic liver transplantation.

We demonstrated hypoexcitability of the motor cortex (increased RMT) in patients with severe liver failure. As transcranial electrical stimulation was normal, this hypoexcitability originates at the cortical level.²⁻⁶ Cortical hypoexcitability found using transcranial magnetic stimulation could be explained by decreased glutamatergic excitatory neurotransmission and/or increased GABAergic inhibitory neurotransmission, previously reported in severe liver failure.¹ Transcranial magnetic stimulation study led us to interpret the hypoexcitability of the motor cortex in severe liver failure as resulting from underactivity of cortical glutamatergic excitatory circuits rather than increased GABAergic activity (normal CSP and ICI). Electrophysiological abnormalities in our patients were reversed by MARS treatment or by orthotopic liver transplantation. However, the few patients presented does not allow us to express any consideration about the clinical implication of MARS treatment on the outcome of patients with severe liver failure.

These preliminary findings suggest that transcranial magnetic stimulation may be a useful tool in assessing patients with severe liver failure.

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Amnesia for childhood in patients with unexplained neurological symptoms

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In a preliminary study, we tested the hypothesis that patients with medically unexplained symptoms attending the clinic of a general adult neurologist would have delayed earliest and continuous memories compared with patients whose symptoms were explained by neurological disease. Depression, adverse childhood experience, and low socioeconomic status have all been associated both with poor memory of childhood. Because these variables are also associated with medically unexplained symptoms we hypothesised that we would find a link between unexplained symptoms and impaired memories of childhood.

One hundred consecutive neurology outpatients were asked the question "What is the very first thing that you can remember?" and "How old were you at the time?". They were

then asked "From what age from could you produce your own life story, biography, or CV without help from a parent or relative?" and "Do you have blanks in your memory?". Neurological diagnoses were recorded and the patient completed the brief assessment scale for depression cards (BASDEC) scale for depression.¹ This simple self rated measure is scored out of 21. A score of 7 or more is taken as the threshold for depression.

Fifty five patients were diagnosed with neurological disease and 45 were diagnosed with unexplained neurological symptoms by a consultant neurologist (GE). The neurological

Abbreviations: BASDEC, brief assessment scale for depression cards