ELSEVIER

Clinical Neurophysiology 116 (2005) 1507–1514

www.elsevier.com/locate/clinph

Brain dysfunction in uremia: a question of cortical hyperexcitability?

Fortunato Battaglia[a,*], Angelo Quartarone[b], Sergio Bagnato[b,c], Vincenzo Rizzo[b], Francesca Morgante[b], Francesco Floccari[d], Adolfo Romeo[d], Antonio Sant'Angelo[b], Giovanni Grasso[b], Paolo Girlanda[b], Michele Buemi[d]

[a]*Department of Physiology and Pharmacology, City University of New York Medical School, New York, NY, USA*
[b]*Department of Neurosciences, Psychiatric and Anaesthesiological Sciences, University of Messina, Messina, Italy*
[c]*Department of Neurological Sciences and Istituto Neurologico Mediterraneo, Neuromed IRCCS, University of Roma "La Sapienza", Roma, Italy*
[d]*Department of Internal Medicine, University of Messina, Messina, Italy*

Accepted 15 February 2005

Abstract

Objective: To investigate whether patients with end-stage renal disease (ESRD) in different stages of the disease and undergoing different treatments display alterations in cortical excitability.

Method: A total of 36 patients with ESRD were evaluated at different stages of the disease and under different treatment by using standard transcranial magnetic stimulation (TMS) parameters. Moreover patients under haemodialysis underwent a double-blind crossover study (mannitol vs placebo) in order to better elucidate the pathophysiology of the acute effects of haemodialysis on cortical excitability.

Results: Patients with ESRD in conservative therapy showed a significant reduction of short-interval intra-cortical inhibition (SICI). This alteration could be reversed by haemodialysis, peritoneal dialysis and by renal transplantation. After haemodialysis there was a significant increase of intra-cortical facilitation (ICF) inversely correlated with the drop in plasma osmolarity induced by the dialytic procedure. Mannitol infusion prevented the drop in plasma osmolarity and the haemodialysis-related changes in ICF.

Conclusions: ESRD patients showed alterations in cortical excitability that can be reversed by replacement therapies. We propose that the drop in plasma osmolarity is a key to the mechanism underlying post-haemodialysis cortical hyperexcitability.

Significance: The results of this study give further insight to the pathophysiology of brain abnormalities in patients with chronic renal failure.

Keywords: TMS; Dialysis dysequilibrium syndrome; ICF; End-stage renal disease (ESRD); SICI

1. Introduction

End-stage renal disease (ESRD) occurs when chronic renal failure progresses to the point at which the kidneys are permanently functioning at less than 10% of their capacity and is characterized by multi-organ dysfunction. Patients with ESRD frequently present central nervous system (CNS) abnormalities, such as uremic encephalopathy. This condition is characterized by cognitive and memory dysfunctions that may progress to delirium, convulsions, and coma (Burn and Bates, 1998; Fraser and Arieff, 1988; Lockwood, 1989). Although clinical symptoms of uremic encephalopathy are well known, its pathophysiology remains uncertain and is probably multi-factorial (D'Hooge et al., 1999; Silver et al., 1992).

The accumulation of several organic substances and metabolites can induce neuronal dysfunction in experimental models of ESRD (D'Hooge et al., 1999) and these abnormalities might lead to a distorted balance of excitatory and inhibitory effects that may be responsible for the neurological manifestations.

The role of the so-called 'uremic toxins' is further confirmed by the positive effects of the dialytic treatments and the success of renal transplantation in uremic encephalopathy (D'Hooge et al., 1999).

Although beneficial in improving multi-organ dysfunction in patients with ESRD, such treatments are

* Corresponding author. Tel.: +1 212 650 7964; fax: +1 212 650 7726.
E-mail address: fb@med.cuny.edu (F. Battaglia).

1388-2457/$30.00
doi:10.1016/j.clinph.2005.02.016

sometimes associated with severe neurological complications. Haemodialysis itself, for instance, is associated with neurological syndromes including Wernicke's encephalopathy, subdural haematoma, and the dialysis dysequilibrium syndrome (DDS). DDS refers to acute symptoms that develop during or immediately after haemodialysis. Early clinical manifestations include blurred vision, headache, disorientation, dizziness, nausea and in some patients seizures and coma. These symptoms are probably related to brain swelling occurring as a consequence of the dialysis procedure. Nevertheless, the mechanisms that lead to the formation of brain oedema are still controversial (Silver et al., 1992).

Thus, given the presence of symptoms that suggest abnormal cortical activity, we aimed to ascertain whether single or double TMS could disclose motor cortical dysfunction in patients with ESRD and in patients who undergo replacement therapies. TMS is a non-invasive tool for studying the human brain and can be used to measure different parameters of cortical excitability within the human motor cortex (Hallett, 2000). Furthermore paired-pulse studies can be used to assess short-interval intra-cortical inhibition (SICI) and intra-cortical facilitation (ICF). Those parameters reflect the activity of cortical inter-neurons and have been extensively evaluated in patients with different neurological diseases (Hallett, 2000).

In the present paper, we aimed to characterize the imbalance between excitation and inhibition in motor cortex of patients with ESRD and to study the changes induced by replacement therapies. The data obtained may be relevant in understanding the pathophysiology of cortical dysfunctions and ultimately minimize treatment-related neurological complications.

2. Methods

We investigated 36 ESRD patients (16 women, 20 men, mean age 58 ± 6.7 years). Patients were in different stages of the disease and were treated with different therapeutic procedures. None of them was under treatment with central nervous CNS-acting drugs. Ten patients were in conservative therapy (group a), 8 received haemodialysis (HD) three times a week (group b); 8 patients received continuous ambulatory peritoneal dialysis (CAPD) four times a day (group c), 10 patients were renal allograft recipients (group d).

The causes of ESRD were chronic glomerulonephritis ($n = 20$) and chronic interstitial nephritis ($n = 16$) (Table 1).

The subjects enrolled in the study underwent neurological examination, EEG, EMG, Mini Mental State Examination and brain MRI in order to exclude central and peripheral nervous system involvement.

Ten healthy volunteers (5 women, 5 men, mean age 55 ± 6.0 years) served as control group. Patients in groups (a)–(c) received treatment with subcutaneous erythropoietin three times a week (mean dosage 23 ± 7 UI/kg body weight).

Patients in group (b) underwent regular HD, performed with polyacrilonitrile filters for 3, 5 h 3 times a week, for 27 ± 9 months (Daugirdas, 1993). Eight patients (residual diuresis < 700 ml/24 h) were on CAPD from 1 to 24 (median 8) months, and just one of them experienced an episode of peritonitis, 15 months prior the study. Patients were hospitalized for the study. They received standardized CAPD (4 cycles a day, 1000 ml/m^2 BSA of dextran-free solution) with a lactate-buffered solution (35 mmol/l lactate, pH 5.5; Baxter HealthCare). The total ultrafiltrated volume in a single session was < 600 ml for each patient.

For transplanted patients, the inclusion criteria required at least 2 years post-transplantation without episodes of clinical rejection that required adjustment of the immunosuppressive therapy for at least 6 months prior to the enrolment. None of the patients showed neurological complications related to the transplant procedure. Ethic's Committee of our Institution approved the protocol and study design. Patients and control subjects were enrolled in the study after signing informed consent. They were strictly right handed according to the Edinburgh Inventory.

3. Experimental procedure

Motor evoked potentials were recorded with surface electrodes from the right first dorsal interosseous (FDI). The EMG amplified and bandpass filtered (0.1–2 kHz) raw signal was acquired through the 'Neurolog system' supplied by Digitimer. The signal was then digitized for offline analysis. TMS was delivered through a focal figure of eight shaped coil (each loop measured 70 mm in diameter) connected to two magnetic stimulators via a Bistim Module

Table 1
Characteristics of controls and uremic patients

	Total	Controls	Conservative treatment	CAPD	HD	Transplant
Number	46	10	10	8	8	10
Age	–	62.5 ± 14.6	61.9 ± 13.4	60.2 ± 14.8	64 ± 15.7	44 ± 12
Male/female	23/23	5/5	5/5	4/4	4/4	5/5
Haemoglobin (g/dl)	–	12.7 ± 1.4	10.9 ± 1.6	10.7 ± 1.4	10.4 ± 1.3	12.7 ± 1.6
Kt/V (weekly)	–	–	–	1.6 ± 0.1	3.4 ± 0.6	–
Chronic glomerulonephritis	21	–	6	5	5	5
Interstitial nephritis	15	–	4	3	3	5