NON INVASIVE BLOOD FLOW MEASUREMENT BY ARTERIAL SPIN LABELING IN SEVERAL BRAIN REGIONS DETECTS MINIMAL HEPATIC ENCEPHALOPATHY

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INTRODUCTION & AIMS

Patients with minimal hepatic encephalopathy (MHE) show neurological impairment in specific tasks to which selective regional alterations in blood flow (BF) could contribute. The possible contribution of alterations in BF in specific brain areas to neurological alterations in patients with MHE remains unclear. Previous reports suggest that impairment of some motor coordination functions are early markers for cerebral dysfunction in some patients with MHE even prior to neuropsychometric alterations becoming detectable. These motor functions are mainly modulated in cerebellum, supporting that cerebellar alterations would contribute to these early alterations. Arterial spin labeling (ASL) is a non-invasive magnetic resonance technique that measures quantitatively cerebral perfusion by magnetically labeling protons in arterial blood water. This study assess whether non invasive BF measurement by ASLin several brain regions detects MHE and/or specific neurological alterations.

The AIM of this work was to assess whether non invasive blood flow measurement by ASL in several brain regions detects minimal hepatic encephalopathy.

METHODS

Blood flow (BF) was analyzed by ASL in different brain areas of 14 controls, 24 cirrhotic patients without and 16 cirrhotic patients with minimal hepatic encephalopathy (MHE). Images were collected using a 3 Tesla MR scanner (Achieva 3T-TX, Philips, Netherlands). Pulsed ASL was performed. Patients showing MHE were detected using the battery Psychometric Hepatic Encephalopathy Score (PHES) consisting of five tests. Different cognitive and motor functions were also assessed: alterations in selective attention were evaluated using the Stroop test. Patients and controls also performed visuo-motor and bimanual coordination tests. Several biochemical parameters were measured: serum pro-inflammatory interleukins (IL-6 and IL-18), 3-nitrotyrosine, cGMP and nitrates+nitrites in plasma, and blood ammonia. Bivariate correlations were evaluated. The diagnostic performance for MHE was assessed using a logistic regression analysis, followed by receiver operating characteristic (ROC) curve to determine sensitivity and specificity, and the optimal threshold value. Analyses sere performed using SPSS vs. 19.0.

RESULTS

Blood flow is increased in cerebellum and reduced in occipital lobe in MHE

In patients with MHE, BF was increased in cerebellar hemisphere (P=0.03) and vermis (P=0.012) and reduced in occipital lobe (P=0.017) (Figure 1A). BF in cerebellar hemisphere was also increased in patients without MHE (P=0.02).

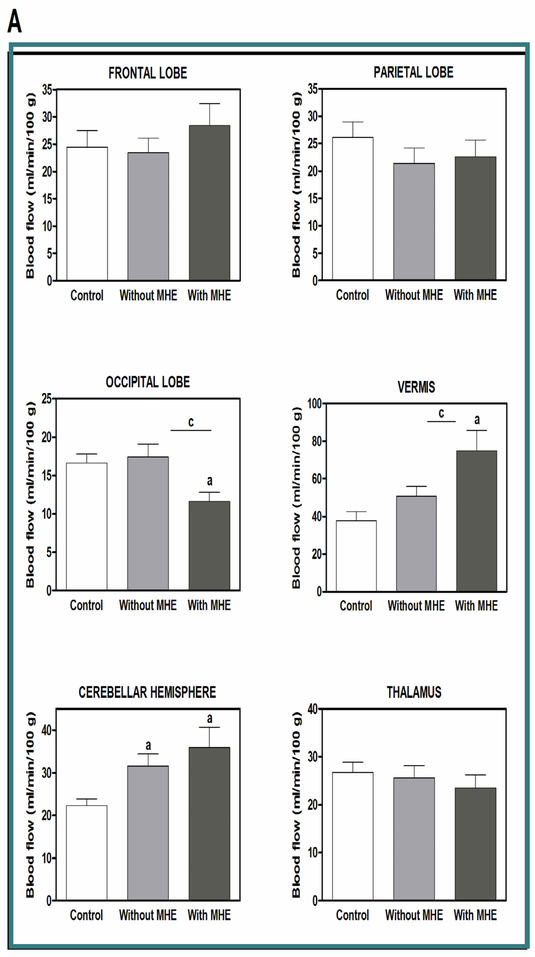

Fig. 1. Blood flow in the different brain regions studied. A: Blood flow in frontal lobe, parietal lobe, occipital lobe, vermis, cerebellar hemisphere and thalamus in controls and cirrhotic patients without and with minimal hepatic encephalopathy (MHE); B: Blood flow in cerebellar hemisphere and vermis including the patients (n = 7) showing Psychometric Hepatic Encephalopathy Score (PHES) = -3, considered as borderline. Data are expressed as mL of blood per minute per 100 g of brain tissue (mean ± SEM) of 14 controls, 24 patients without and 16 with MHE. [a]P<0.05; [b]P<0.01 vs control, Values significantly different between patients with and without MHE are indicated by [c]P<0.05.

Bimanual coordination was impaired in patients without MHE (P=0.05) and much more in patients with MHE (P<0.0001) (Figure 2A). Visuo-motor coordination was impaired only in patients with MHE (P<0.0001) (Figure 2B). Attention was slightly affected in patients without MHE and more strongly in patients with MHE (P<0.0001) (Figure 2C-E).

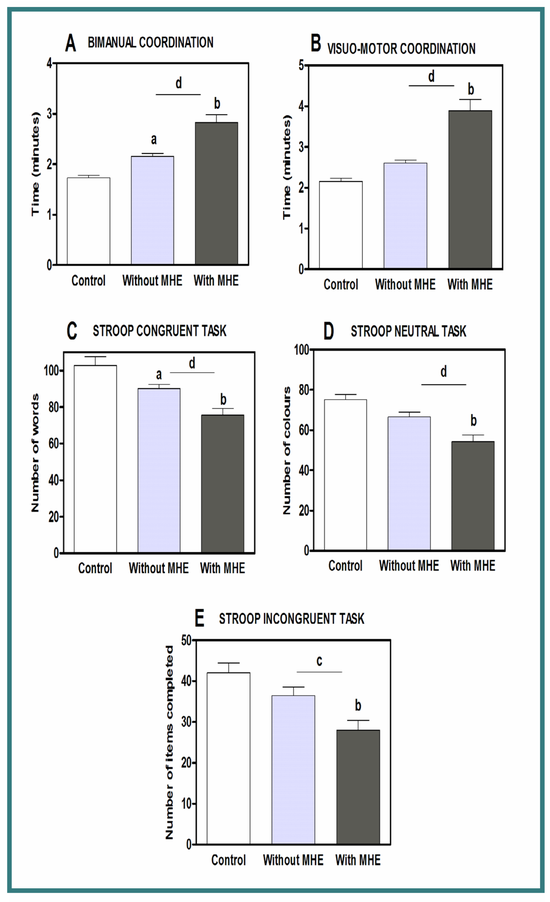

Fig. 2. Performance in the Stroop, bimanual and visuo-motor coordination tests. A. Bimanual coordination test; B. Visuo-motor coordination test; C-E. Congruent, neutral and incongruent tasks from Stroop test. Values are the mean±SEM of 14 controls, 24 patients without MHE and 16 with MHE. [a]P<0.05; [b]P<0.01 *vs* control, Values significantly different between patients with and without MHE are indicated by [c]P<0.05; [d]P<0.01.

Table 1. Correlations between tests and blood flow in the brain areas

PARAMETER/ TEST	SUB-TEST	FRONTAL LOBE	OCCIPITAL	VERMIS	CEREBELLAR HEMISPHERE
CFF		ns	r=0.353 *P*=0.017	r=-0.326 *P*=0.025	ns
PHES Global score		r=-0.36 p=0.007	r=0.309 *P*=0.031	r=-0.504 *P*<0.001	r=-0.348 *P*=0.01
	Symbol Digit Test	ns	ns	ns	ns
	NCT-A	r=-0.469 *P*<0.001	ns	r=-0.530 *P*<0.001	r=-0.320 *P*=0.018
	NCT-B	ns	ns	r= -0.531 *P*<0.001	r= -0.307 *P*=0.027
	Serial Dotting Test	ns	ns	ns	ns
	Line Tracing Test	ns	ns	r=-0.330 *P*=0.018	r=-0.364 *P*=0.007
STROOP	Congruent Task	ns	ns	r=-0.320 *P*=0.027	r=-0.354 *P*=0.012
BIMANUAL COORDINATION		ns	ns	ns	r=0.362 *P*=0.011
VISUO-MOTOR COORDINATION		ns	ns	ns	r=0.335 *P*=0.017

BF in cerebellar hemisphere and vermis correlated with performance in most tests of PHES [(number connection tests A (NCT-A), B (NCT-B) and line tracing test] and in the congruent task of Stroop test. BF in frontal lobe correlated with NCT-A. Performance in bimanual and visuomotor coordination tests correlated only with BF in cerebellar hemisphere. BF in occipital lobe correlates with performance in the PHES battery and with CFF.

Table 2. Correlations biochemical parameters and blood flow in the brain areas

PARAMETER	FRONTAL LOBE	OCCIPITAL	VERMIS	CEREBELLAR HEMISPHERE
cGMP in plasma (pmoles/ml)	ns	ns	r=0.301 *P*=0.034	ns
Nitrates + Nitrites (μM)	ns	r=0.339 *P*=0.043	r=0.362 *P*=0.023	ns
3-Nitro-tyrosine (nM)	ns	r=0.358 *P*=0.011	ns	ns
IL-6 (pg/ml)	ns	ns	ns	ns
IL-18 (pg/ml)	r=-0.353 *P*=0.041	ns	ns	r=-0.405 *P*=0.032
Ammonia (μM)	ns	ns	ns	ns

BF in cerebellar hemisphere correlates with plasma cGMP and nitric oxide (NO) metabolites. BF in cerebellar vermis also correlates with NO metabolites and with 3-nitrotyrosine. IL-18 in plasma correlates with BF in thalamus and occipital lobe.

Blood flow in cerebellar vermis is predictive for MHE

Univariate logistic regression analysis using the presence of MHE as the dependent variable and BF in *vermis* as independent variable shows that BF significantly predicts MHE, with an OR=1.042 (95%CI: 1.006-1.078, *P*=0.021). ROC curve analysis: AUC=0.714 (95%CI:0.54-0.88, *P*=0.027) for BF in vermis. At the cut-off of 46 mL/min/100g, specificity was 57%and sensitivity was 69%.

Although these values are not excellent for diagnosis, the data show that BF in cerebellum is altered in patients with MHE and also in some patients without MHE who also show impaired bimanual coordination. This supports that altered BF in cerebellum detects some motor deficits earlier that the PHES battery.

We sub-classified the patients showing a PHES of -3 (who are usually classified as without MHE) as "borderline" patients. There were 7 patients with PHES-3. BF in vermis was 60 ± 12 mL/min/100 g, which was nearly significantly different (*P*=0.055) from controls (Figure 1B). BF in cerebellar hemisphere of these "borderline patients" was 37 ± 6 mL/min/100 g which was significantly different (P < 0.01) from controls and not different from patients with MHE (Figure 1B).

CONCLUSIONS

Non invasive BF determination in cerebellum using ASL may detect MHE earlier than the PHES. Altered NO-cGMP pathway seems to be associated to altered BF in cerebellum