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Indices of adrenal deficiency involved in brain plasticity and functional control reorganization in hemodialysis patients with polysulfone membrane: BOLD-fMRI study

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This work purpose was to estimate the implication of suspected adrenal function deficiencies, which was influenced by oxidative stress (OS) that are generating brain plasticity, and reorganization of the functional control. This phenomenon was revealed in two-hemodialysis patients described in this paper. Blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI) revealed a significant activation of the motor cortex. Hemodialysis seems to originate from the inflammatory state of the cerebral tissue reflected by increased OS, while expected to decrease since hemodialysis eliminates free radicals responsible for OS. Considering adrenal function deficiencies, sensitivity to OS and assessed hyponatremia and hypercalcemia, adrenal function deficiencies is strongly suspected in both patients. This probably contributes to amplify brain plasticity and a reorganization of functional control after hemodialysis that is compared to earlier reported studies. Brain plasticity and functional control reorganization was revealed by BOLD-fMRI with a remarkable sensitivity. Brain plastic changes are originated by elevated OS associating indices of adrenal function deficiencies. These results raise important issues about adrenal functional deficiencies impact on brain plasticity in chronic hemodialysis-patients. This motivates more global studies of plasticity induced factors in this category of patients including adrenal functional deficiencies and OS.

Keywords: Adrenal gland deficiency; chronic renal failure; BOLD-fMRI; brain plasticity; hemodialysis; oxidative stress.

1. Introduction

Controversial evidences are reported on possible association between adrenal function deficiencies and hemodialysis (HD) in patients suffering of chronic renal failure (CRF) (Barbour & Sevier, 1974; McDonald *et al.*, 1979; Wallace *et al.*, 1980; Nolan *et al.*, 1981; Ramirez *et al.*, 1982; Heaton *et al.*, 1985). Besides, recent studies are rare (Clodi *et al.*, 1998), since adrenal deficiency (AD) is an uncommon pathology with difficult diagnosis especially in patients suffering from CRF and following HD. The most clinical and biological symptoms of AD are similar to those encountered in patients suffering from CRF. These consist of low blood pressure, hyponatremia and hypercalcemia which are mostly frequent biological abnormalities (Malet-Pipo *et al.*, 2000). Loss of weight, anorexia, physical and psychic asthenia are all found in CRF patients (Gmar-Bouraoui *et al.*, 2001). CRF patients are often undergoing HD which is the most suitable treatment to survive during the disease (Himmelfarb & Ikizler, 2010; Montazerifar *et al.*, 2012). However HD technique presents drawback effects such as excessive generation of free radicals originating oxidative stress (OS) and released inflammatory factors (Kohen & Nyska, 2002; Pupim *et al.*, 2004; Libetta *et al.*, 2011; Belaïch *et al.*, 2013).

It is well established that OS phenomenon is involved in most brain metabolic processes (Noseworthy & Bray, 1998). Consequently, OS is also involved in brain plasticity and functional control reorganization (Kishida & Klann, 2007; Numakawa *et al.*, 2011). Besides, adrenal gland (AG) activity is potentially influenced by OS and other factors such as neuropeptides and neurotransmitters activated by pharmacological interactions and lower rate of lipoproteins (Bornstein, 2009).

Recently, it was demonstrated that blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI) was an efficient technique for evaluating OS in brain's chronic HD patients (Batta, 2011; Belaïch *et al.*, 2015a; Belaïch, *et al.*, 2015b; Belaïch *et al.*, 2016).

The purpose of this work was mainly to estimate indirect indices of AG dysfunction which is potentially influenced by OS that generates brain plasticity and a reorganization of the functional control. This phenomenon was revealed in two HD patients that we describe in this paper.

2. Patients and Methods

2.1. *Patients*

Both patients were recruited in Hemodialysis Center, University Hospital of Fez; Fez, Morocco. They gave consent to participate to an MRI study conducted by Clinical Neuroscience Laboratory, Faculty of Medicine and Pharmacy of Fez; University of Fez in collaboration with Nephrology Department, and Radiology and Clinical Imaging Department, University Hospital of Fez and Laboratory of Molecular Basis in Human Pathology and Therapeutical Tools, Faculty of Medicine and Pharmacy of Fez (Batta, 2011; Belaïch *et al.*, 2015a, 2015b, 2016).

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Two men following chronic HD for longer than six months were recruited. Their ages were respectively 25 and 29 years-old. Both patients did not prove any sign of diabetic, tobacco use, infection episodes or treatment with iron or erythropoietin injection. Their duration of HD before recruitment was respectively 48 and 24 months.

Both patients underwent identical assessment protocol immediately before starting HD session and immediately after achieving a full HD session.

Blood ionogram assessing Na and Ca were achieved using Olympus AU640/ AU400 apparatus in the central laboratory of the University Hospital of Fez; Fez, Morocco. The detailed results were reported in Medical Doctor Thesis (Batta, 2011).

We have not been able to assess AG hormones of both patients; and inspection of AD was made from blood ionogram and was revealed after months of patient's recruitment.

The contact with these patients was cut and there was no way to call them back for advanced assessment to confirm our hypotheses.

2.2. *Methods*

2.2.1. *BOLD-fMRI acquisition protocol*

Both patients underwent identical brain BOLD-fMRI protocol before starting HD session and after achieving a full HD session in Hemodialysis Center of the University Hospital of Fez; Fez, Morocco. The image data was acquired in Radiology and Clinical Imaging Department of the University Hospital of Fez; Fez, Morocco. Brain BOLD functional and anatomical magnetic resonance images were acquired using a 1.5 Tesla MRI system (Sigma, General Electric; Milwaukee, United States). The acquisition of images was done using single shot gradient-echo echo-planer imaging (GE-EPI) sequence. This approach was shown to be very sensitive to T2* effect generated during BOLD effect reflecting functional activity of cortical brain tissue (Boujraf *et al.*, 2006, 2009; Housni *et al.*, 2013, 2014).

BOLD-fMRI acquisition parameters were: echo time TE = 55 ms, repetition time TR = 3000 ms, slice thickness = 5 mm, field of view FOV = 240 mm, 31 axial slices were acquired covering the entire brain. The acquisition matrix size was 128×128. Each brain volume was acquired within 3 s, while during whole BOLD-fMRI acquisition protocol 60 brain volumes were acquired within 3 min. BOLD-fMRI paradigm consists of a very simple motor task, where patients are asked to perform finger taping of right hand during a continuous scanning session, in blocks of 30 s ON, alternating with 30 s rest. Target forces and rates of finger taping were constant within each 30 s block, for 10 repetitions.

2.2.2. *Data post-processing and imaging result generation*

Image processing and statistical analysis were conducted with Statistical Parametric Mapping package version 8 (SPM8, 2008), (http://www.fil.ion.ucl.ac.uk/ spm; Wellcome Department of Cognitive Neurology, London UK). All fMRI data

were analyzed using general linear model (GLM) approach as in SPM and all volumes obtained were used for data analysis. The pre-processing with SPM8 included re-alignment, co-registration and spatial normalization in the template of Montreal Neurological Institute (MNI). The gradient-echo echo-planar images were realigned using a rigid body transformation to the first volume of the time series for each subject. After this, data were spatially smoothed with a Gaussian filter (FWHM $8 \times 8 \times 8$ mm), and spatially normalized. The cerebral activation was rendered either onto T1-weighted brain slices or on the surface of a standard MNI brain. The box-car designed task was used and convolved with the functional hemodynamic response.

T-statistics was calculated for each voxel element and $p < 0.01$ was considered to be a statistically significant threshold for significantly activated areas that were correlated for multiple comparisons. The maximal BOLD signal changes were calculated for each subject in the motor area M1 before and after HD sessions. Activation maps were calculated and overlaid on anatomical images.

3. Results

Blood ionogram revealed a significant change of sodium (Na) and calcium (Ca) rates that expressed hyponatremia and hypercalcemia after HD session (Figs. 1 and 2).

3.1. *Quantitative BOLD-fMRI study results*

BOLD-fMRI signal measurements of activated motor area were quantified. They included the volume of activated brain area during functional control that is expressing an expansion of hyper oxygenated volume of brain area; and the maximal intensity of activated cortical area that is reflecting the highest density of cortical oxygenation following the execution and control of used functional motor task.

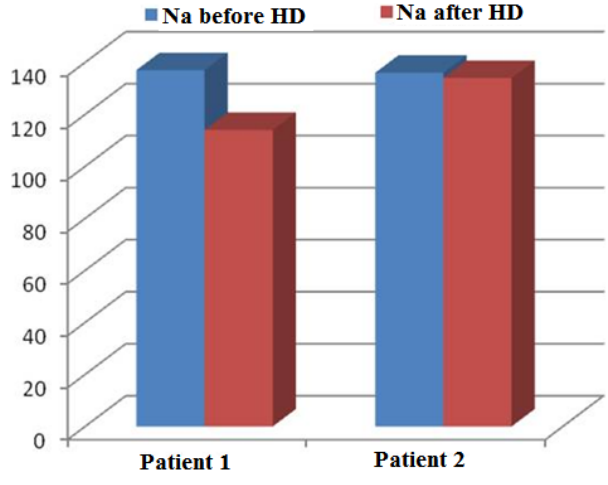

Fig. 1. (Color online) The ratio of Na is less than the normal after hemodialysis in both patients showing hyponatremia.

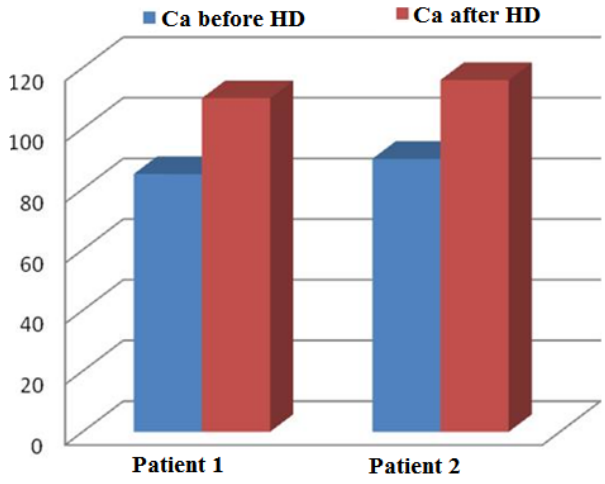

Fig. 2. (Color online) The rate of Ca is higher than normal after hemodialysis in two patients showing hypercalcemia.

The maximum BOLD-fMRI signal in individual activated brain areas have decreased in both patients after HD sessions (Fig. 3); this reflects a decrease of localized hemodynamic response strength and expresses much localized decrease of metabolic involvement in brain functional activity of involved motor area M1. In contrast, a systematic increase of activated brain volume area involved in functional control was recorded in both studied patients after HD sessions (Fig. 4). Indeed this reflects a localized expanding hemodynamic response expressing an enlargement of localized increase of metabolism involvement revealing an increased involvement of additional brain tissue in brain functional activity involving the motor area M1.

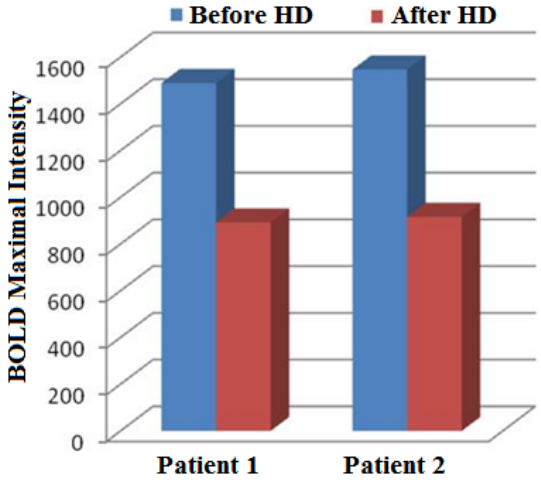

Fig. 3. (Color online) A systematic decrease of the individual maximum localized BOLD signal in the individual activated areas brain after HD sessions.

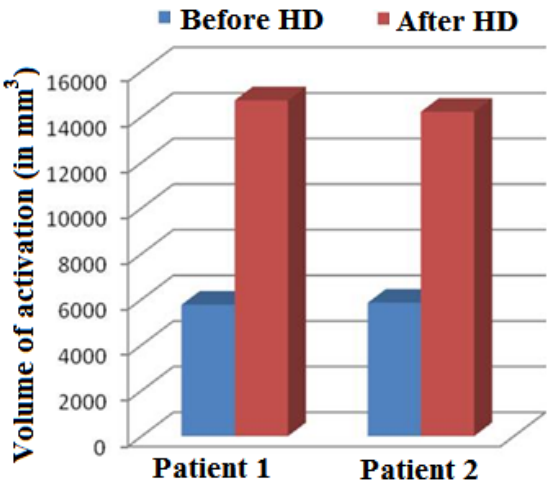

Fig. 4. (Color online) A systematic increase of the localized BOLD signal volume reflecting an increase of the volume of the activated brain area after HD sessions.

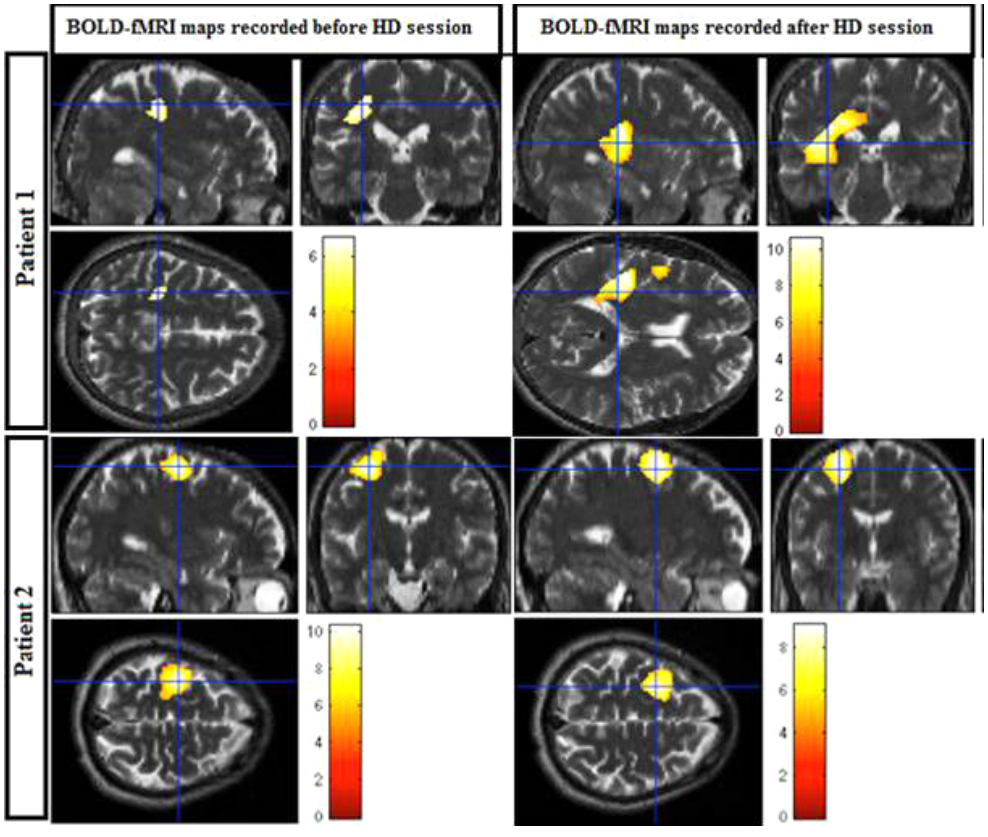

Fig. 5. (Color online) Typical individual activation maps of each patient in the motor cortex M1 overlaid on anatomical images obtained before and after HD.

The same coordinates are presented for both patients. Finally it is to consider that the maximum BOLD intensity is expressed in arbitrary unit (AU).

3.2. *Visual evaluation*

Typical functional 2D and 3D BOLD-fMRI maps were obtained for each patient before and after HD. These maps covered the same anatomic area (Figs. 5 and 6). Results of group analysis before and after HD sessions are also reported. The whole brain analysis comparing cerebral activation between both major conditions with respect to baseline/random navigation revealed important visual decrease of brain intensity activation in the motor area after HD and important visual increase of the size of brain volume activation after HD (Figs. 7 and 8).

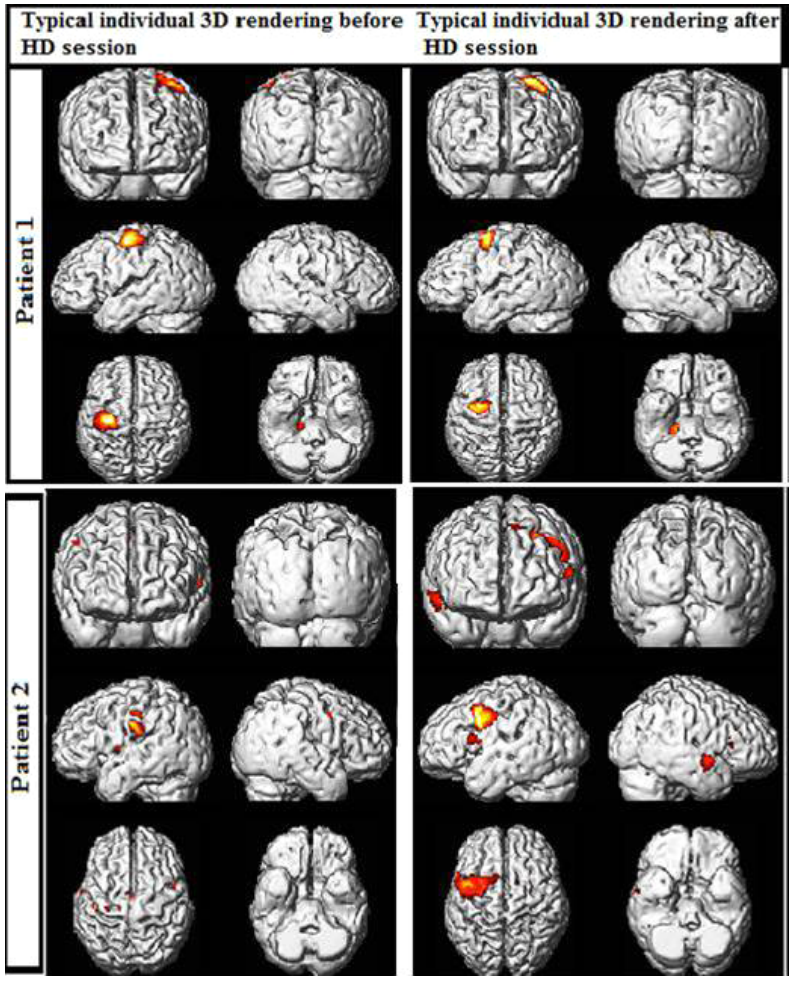

Fig. 6. (Color online) Typical individual 3D rendering on a standard brain showing each patient activation in the motor cortex M1 and projections in the stereotactic Tailarach space obtained before (first column) and after (second column) HD sessions.

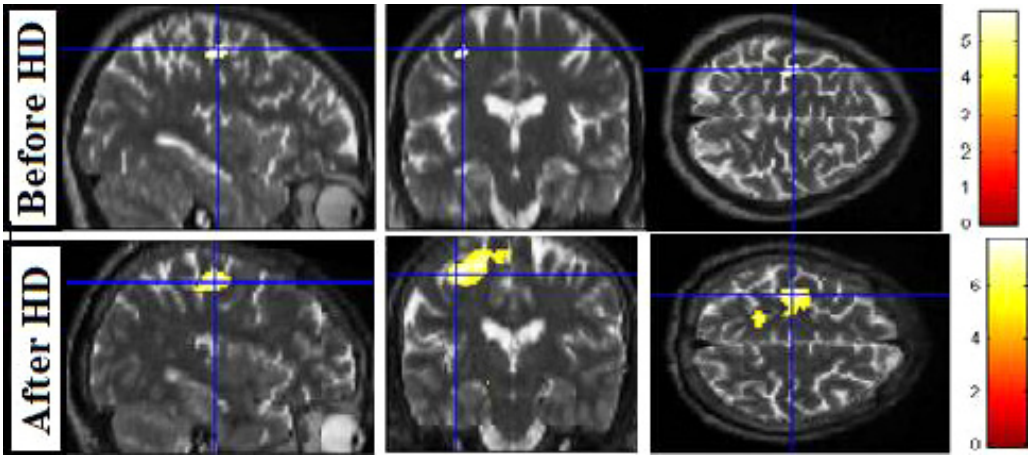

Fig. 7. (Color online) 2D results maps of group analysis are well revealing important visual decrease in the intensity of brain activation of the motor area after HD, and important visual increase of the size of the volume of brain activation.

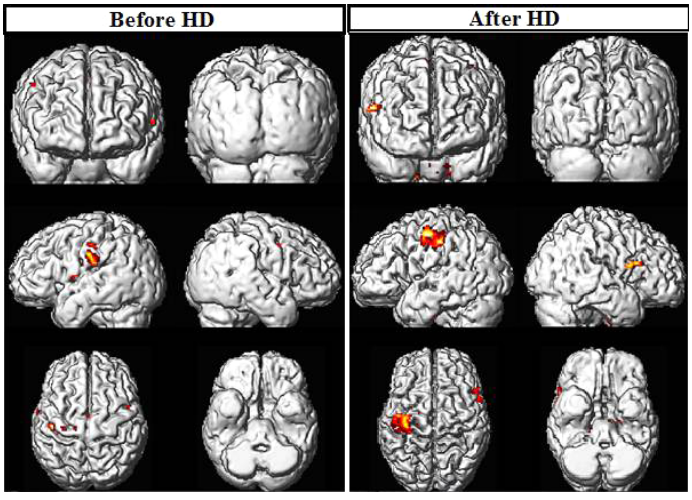

Fig. 8. (Color online) 3D rendering results of group analysis are well revealing important visual decrease in the intensity of brain activation of the motor area after HD, and important visual increase of the size of the volume of brain activation.

4. Discussion

This study consisted of assessing solely indirect indices of AD without assessing AG hormones. Indeed suspicion of adrenal insufficiency was essentially based on blood ionogram and has occurred after months of patient recruitment and contact cut with these patients. Besides, only two patients were recruited. Such critical aspects would constitute limitation of this study. However, the strength of this study consists of being the first to demonstrate changes in brain function secondary to HD associating AD shown by indirect indices.

Indeed raised issue in this paper is suggesting new paths for research in OS and AD in HD patients while proposing our hypotheses in this regards. Furthermore, the used BOLD-fMRI method revealed a higher OS in both patients, since it was demonstrated that it is an efficient approach for evaluating OS in chronic HD patients (Batta, 2011; Belaïch *et al.*, 2015a). The blood oxygenation is known to be systematically modified after HD session due to increased OS (Belaïch *et al.*, 2015a). Indeed the blood contact with HD Polysulfone membrane and the extra-human body blood circuit increase the production of free radicals and originate important inflammatory state associating a decrease of the oxygenation density, which is in accordance with earlier reported literature (Belaïch *et al.*, 2015a; Descamps-Latscha & Witko-Sarsat, 2003; Reuter *et al.*, 2010; Coombes & Fassett, 2012).

The CRF disease itself is a direct factor originating OS before HD session (Wratten *et al.*, 2000; Libetta *et al.*, 2011). However, HD process is enhancing the level of OS, and mostly amplified in brain tissue considering the higher oxidative metabolism engaged and lower antioxidant availability in the cerebral tissue (Christen *et al.*, 2013; Massaad & Klann, 2011).

Indeed this oxygenation density change was demonstrated through BOLD-fMRI by studying cortical motor area before and after HD (Belaïch *et al.*, 2015a). Thus, our earlier study demonstrated the involvement of OS in brain tissue, which is well confirmed by BOLD-fMRI that is a very sensitive technique to localized changes in oxygenation level in the microvasculature originated by changes in neuronal activity insuring the functional control (Belaïch *et al.*, 2015a; Huang *et al.*, 2012).

Definitely, the activated neuronal network consumes massive oxygen quantities, while producing higher rate of free radicals (De Magalhaes & Sandberg, 2005). This might lead to an intermittent neuronal apoptosis while reducing the potential strength of activation of neurons (Suzuki *et al.*, 2010). This might activate plastic mechanisms that would compensate for former high neuronal activation (Luger *et al.*, 1987; Suzuki *et al.*, 2010). Indeed, these aspects were expressed in both patients' brain by expanding the brain activation and decreased intensity of activation after HD. Very localized changes of brain oxygenation were demonstrated while achieving identical functional activity, this aspect was shown systematically in both studied patients. This reflects formally a brain plasticity and functional control reorganization (Belaïch *et al.*, 2015a, 2015b; 2016). In fact studies showed an implication of free radicals in modulation of the synaptic plasticity (Luger *et al.*, 1987).

The blood ionogram of both patients revealed hypercalcemia and hyponatremia which are both important indirect indices of AD. This association enhanced strong inflammatory and oxidative processes compared to other patients of earlier study (Belaïch *et al.*, 2015a; 2015b; 2016). This would potentially impact the hypothalamic-pituitary-AGs and might originate its dysfunction (Bornstein, 2009). It is well established that pharmaceutical products might induce AD (Ramirez *et al.*, 1994). Previous studies demonstrated that HD would lead to AD (Luger *et al.*, 1987; Ramirez *et al.*, 1994; Clodi *et al.*, 1998). Recent study has confirmed the same

hypothesis (Ramirez *et al.*, 1994), and our findings in both suspected AD patients were in perfect accordance.

The AD diagnosis is often confirmed by assessing the cortisol and the adrenocorticotrophic hormone rates. Unfortunately, these evaluations were not achieved in these patients and should be done in further study. Correspondingly, both patients demonstrated brain plasticity and functional control reorganization after HD which was amplified compared to similar patients subjects (Batta, 2011; Belaïch *et al.*, 2015a). Earlier reported study demonstrated that OS plays a crucial role in brain plasticity and functional control reorganization. Hence it is to underline that BOLD-fMRI results including activation volume enhancement and decreased maximal BOLD signal are amplified by AD. The unique feature found in both patients explains that the enhanced brain plasticity in both patients is amplified by adrenal function deficiency assessed by indirect indices including rates of Na and Ca. This would induce tissue damage that might occur also at cells level including the cardiac and cerebral tissue. Indeed this is a real risk factor of cardiovascular complications, brain stroke and long-term neurodegenerative diseases (Weinstein *et al.*, 2000). Finally, it is to consider a systematic preventive AD assessment in HD patients to prevent avoidable complications.

5. Conclusion

Despite limited to only two patients this study is a first one to demonstrate changes in brain function control originated by HD associating AD assessed by indirect indices. Studied patients have expressed brain plasticity and a functional control reorganization that was revealed by BOLD-fMRI with a remarkable sensitivity. These brain plastic changes originated by higher OS associating AD. These indications raise important research issues about impact of AD on brain plasticity in chronic HD patients. Indeed this motivates a global study of plasticity induced factors in this category of patient including AD and OS. Indeed BOLD-fMRI is the approach of choice for evaluating brain plasticity involving advanced fMRI paradigms while investigating involvement of functional control of cognitive, motor and sensory, and visual cerebral cortex.

Consent

We do certify that the Moroccan legislation does not require patient's written consent for publishing scientific and medical data of patients; unless this might reveal directly or indirectly the identity of patients. However, we do certify that we obtained informed consent of patients.

Author Contributions

RB: First draft writing, study analysis; SB: Study design, writing, study analysis, reviewing; MM: Patient's management and reviewing; MB: Data interpretation and

reviewing; AH: Technical support and supply; FB: patients recruitment and management; TS: Early study design and patients recruitment and management; ST: Patient's management, technical and logistic support.

Conflicts of Interest

The initial BOLD-fMRI results were reported in Master Thesis achieved earlier by the first author (RB) under the supervision of SB. The initial OS and clinical biology results reported in this paper were obtained within framework of MD thesis that was achieved by one of co-authors (FB) that was officially supervised by one of co-authors (SB). The clinical biology assessment was done in the Central Laboratory of the University Hospital of Fez, Morocco; while the OS study was done in Pharmacology Department of the Faculty of Medicine and Pharmacy, University of Fez, Morocco. The Patient recruitment was supervised by the leader (TS) of the Nephrology Department, University Hospital of Fez, Morocco.

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