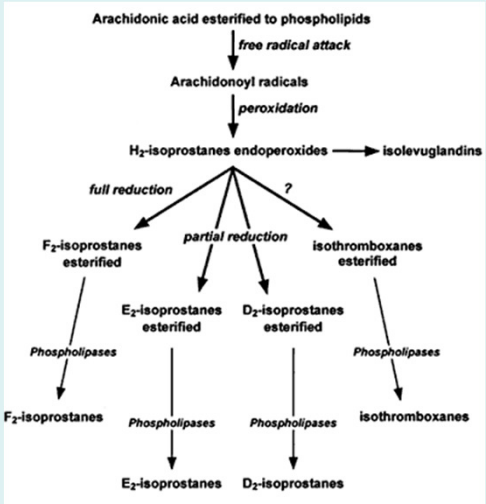
Elevated cerebrospinal fluid levels of an isoprostane, an oxidative stress biomarker in MS patients

Fozia Mir and Saud A. Sadiq
Multiple Sclerosis Research Center of New York, New York, NY, USA

BACKGROUND

Multiple Sclerosis (MS) is a multifactorial disease with several contributing pathophysiological processes. There is growing evidence of the involvement of oxidative stress to brain damage in MS. Oxidative stress, which is associated with increased free radical production, leads to lipid peroxidation. Indeed, due to the high concentration of polyunsaturated lipids in brain, this tissue is highly sensitive to cellular damage caused by increased lipid peroxidation. One major lipid peroxidation product produced in the brain is a class of eicosanoids called isoprostanes. Isoprostanes are prostaglandin-like compounds generated non-enzymatically by free radical catalyzed peroxidation of arachidonic acid that is esterified in membrane phospholipids. One of the most abundantly produced and stable isoprostanes is 8-iso-$PGF_{2\alpha}$, which is well recognized as a sensitive marker for oxidative stress and lipid peroxidation *in vivo*.

Schematic 1. Generation of 8-isoprostane F2α (8-isoPGF$_{2\alpha}$) from membrane associated a. rachidonic acid by free radical attack.



OBJECTIVE

In the current study, we investigated the potential of 8-iso-$PGF_{2\alpha}$ as a biomarker for oxidative stress and disease activity in the cerebrospinal fluid (CSF) of MS patients.

METHODS

8-isoPGF$_{2\alpha}$ levels in the CSF of 75 MS patients (25 each for relapsing remitting (RR), secondary progressive (SP) and primary progressive (PP) MS) and 25 controls were measured using a commercially available competition ELISA (Cayman Chemical). The samples were collected by either side port aspiration from implanted pumps or by lumbar puncture.
Statistical analysis was done using Graphpad Prism 5 software.

RESULTS

The demographics of the patients included in the study are shown in Table 1 below.

Table 1. Characteristics of study subjects

	Control	RRMS	SPMS	PPMS
Average age (years)	46.5	43.18	52.8	51.4
Females/Males	18/7	19/6	18/7	17/8
Disease duration range (years)		1-20	6-31	3-30
EDSS	0	2	6.7	7.6
N	25	25	25	25

It was found that levels of 8-iso-$PGF_{2\alpha}$ were significantly increased in the CSF of MS patients (P value of < 0.0001) as determined by ANOVA using Graphpad Prism 5 (Figure 1). The concentration of 8-iso-$PGF_{2\alpha}$ was found to vary significantly within the disease groups. Specifically, in all the three MS groups (RRMS, SPMS and PPMS), there were patients with 8-iso-$PGF_{2\alpha}$ levels comparable to those of control subjects; and there were patients whose levels were moderately increased (approximately 3 fold increase) in comparison to the control samples. Interestingly however, there was a subgroup of MS patients whose 8-iso-$PGF_{2\alpha}$ levels were found to be very high – more than a 15 fold increase over the control group. In the SPMS patients, this subgroup consisted of 10 out of the 25 patients screened. The observed variation in 8-iso-$PGF_{2\alpha}$ levels may be indicative of the heterologous disease pathogenesis in MS.

A comparison of the clinically active versus stable patients in the SPMS group shows a positive correlation of 8-iso-$PGF_{2\alpha}$ levels with disease activity (Figure 2).

The two control subjects showing moderately increased levels of 8-iso-$PGF_{2\alpha}$ are inflammatory disease controls.

Figure 1. 8-isoPGF$_{2\alpha}$ levels in CSF of control and MS patients as measured by ELISA.

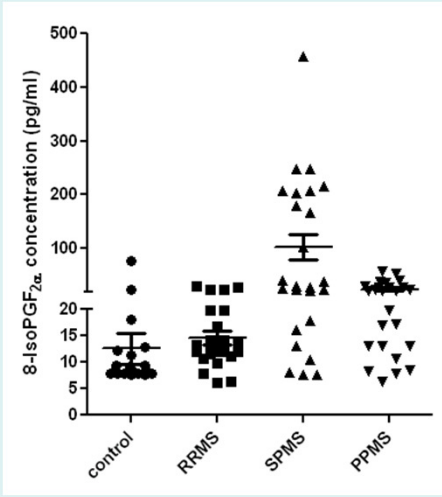
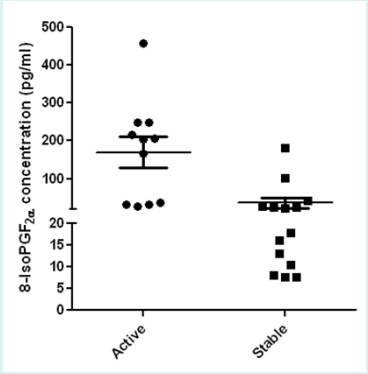


Figure 2. 8-isoPGF$_{2\alpha}$ levels in relation to disease activity in SPMS patients.



CONCLUSIONS

1. 8-iso-$PGF_{2\alpha}$ levels are elevated in the CSF of MS patients as compared to controls.
2. 8-isoPGF$_{2\alpha}$ levels in each sub-group show significant variation which seems to correlate with disease activity.
3. These results indicate that 8-isoPGF$_{2\alpha}$ may serve as a biomarker of disease activity and oxidative stress in MS.
4. Markedly increased levels of 8-iso-$PGF_{2\alpha}$ in a sub-group of Secondary Progressive MS patients identifies a group that might be well-suited for anti-oxidant therapy.
5. Taken together these results show that 8-iso-$PGF_{2\alpha}$ levels are indicative of oxidative stress and disease activity in MS and warrant further investigation.