Neuroketals in the Cerebrospinal Fluid of Multiple Sclerosis Patients.

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BACKGROUND

Oxidative stress is increasingly being recognized as a contributing factor in neurological diseases including multiple sclerosis (MS). The brain is especially susceptible to oxidative damage due to its high lipid content, high energy consumption and low antioxidant defenses. Reactive oxygen species (ROS) can react non-specifically and rapidly with all cellular biomolecules; however, lipids are the major target of free radicals.

We are investigating the involvement of a novel class of lipid peroxidation in the brain, i.e., Neuroketals (NKs). NKs are the generated from the ROS action on docosahexenoic acid (DHA) which is highly enriched in the nervous system. NKs are believed to be detrimental to brain function because they adduct to critical proteins.

OBJECTIVE

The current study sought to determine the levels of neuroketals in the cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients as a biomarker for lipid peroxidation/oxidative stress and to establish if these levels correlate with disease activity.

METHODS

CSF was obtained by lumbar puncture or by aspiration from an access-port of implanted pumps from 59 patients with clinically definite MS at the International Multiple Sclerosis Management Practice (IMSMP). Informed consent was obtained using an IRB-approved protocol. Control CSF from 20 patients with other neurological diseases served was also obtained. NK levels in the CSF were measured by ELISA. using a commercially available antibody. Statistical analysis was done using Graphpad Prism 5 software.

RESULTS

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

Table 1. Patient Demographics.

	Control	RRMS	SPMS	PPMS
Average age (years)	46.5	43.18	52.8	51.4
Females/Males	14/6	7/4	16/11	15/6
Disease duration range (years)		1-20	6-31	3-30
EDSS	0	2	6.7	7.6
N	20	11	27	21

It was found that NK levels were nearly 4-fold higher in the CSF of MS patients as compared to the control CSF ($p < 0.001$) as determined by ANOVA using Graphpad Prism 5 (Figure 1). Thus NK levels was found to be significantly increased in all the three MS groups : Relapsing remitting MS (RRMS, n = 11; Secondary Progressive MS (SPMS, n = 27) and Primary Progressive MS (PPMS, n = 21), as compared to the control CSF (n = 20), as can be seen in Figure 2.

Figure 1. Neuroketal (NK) levels in CSF of control and MS patients as measured by ELISA.

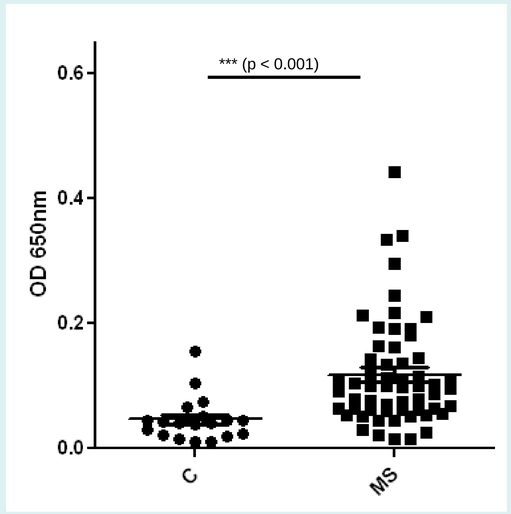
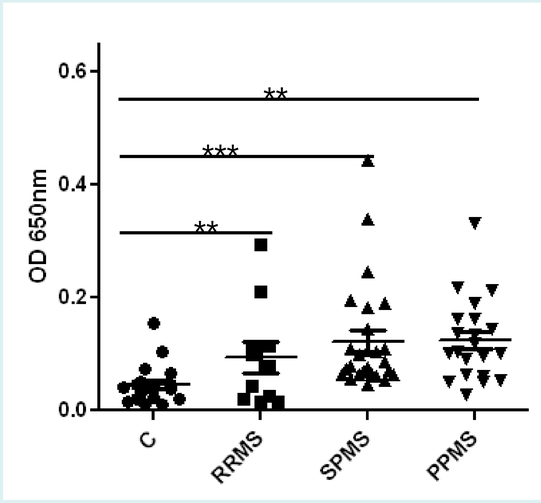


Figure 2. NK level in MS disease groups.



Furthermore, a comparison of twenty five clinically active versus stable patients in the SPMS group shows a positive correlation of NK levels with disease activity as shown in Figure 3.

Figure 3. NK levels in relation to disease activity in SPMS patients.

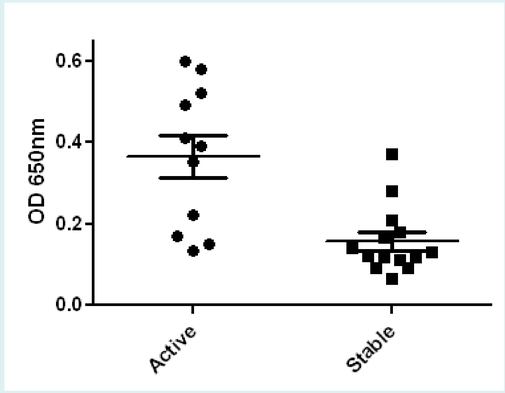
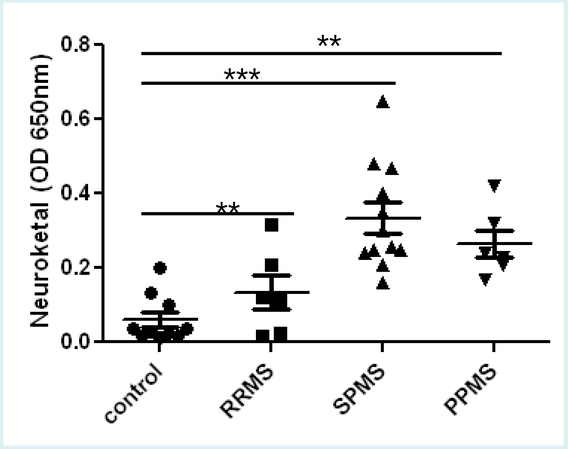


Figure 4. NK levels in untreated MS patient CSF.



In order to rule out the effects of disease modifying therapies on CSF NK levels, we analyzed samples from untreated MS patients. The results given in Figure 4, confirm our findings and show significant increases in the MS patients groups as compared to the control samples.

CONCLUSIONS

1. **NK levels are elevated in the CSF of MS patients as compared to controls.**
2. **NK levels in MS sub-groups show significant variation which seems to correlate with disease activity.**
3. **These results indicate that NKs may serve as a novel biomarker of disease activity and lipid peroxidation/oxidative stress in MS and warrant further investigation.**