VALIDATION OF TWO SUBTYPES OF SCHIZOPHRENIA DEFINED BY POLYUNSATURATED FATTY ACIDS IN BLOOD CELLS DURING AN ACUTE PSYCHOTIC EPISODE

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Background*:* We have completed two studies (I, II) exploring a bimodal distribution of polyunsaturated fatty acids (PUFA) in red blood cells (RBC) in schizophrenia and related psychoses. At the Lipids and Brain 2011 conference we report observational data from study I (1: Bentsen H *et al, in press; 2:* Bentsen H *et al, submitted*). It was part of a 16 weeks randomized controlled trial of ethyl-EPA and vitamins E+C. We also present the design of study II, focusing on the relation between glutathione and PUFA in a cohort from study I.
STUDY I.

Material and Methods: Patients aged 18-39 years with DSM-IV schizophrenia, schizoaffective or schizophreniform disorders were consecutively included at admission to hospital. RBC fatty acids were measured in 97 patients at baseline, as well as in 20 healthy controls. The primary outcome measures: (1) the bimodality test statistic T; (2) negative subscale of the Positive and Negative Syndrome Scale (PANSS). **Results:** (1) At baseline, RBC PUFA were highly significantly bimodally distributed among patients. One third of patients constituted a group ("low PUFA") who had PUFA levels at one fifth ($p<0.001$) of those in "high PUFA" patients and healthy controls, which did not differ. Bimodality was mainly accounted for by docosahexaenoic acid and arachidonic acid. Bimodality was confirmed after 16 weeks. Alpha-tocopherol was a robust predictor of PUFA at both occasions. Desaturase and elongase indices differed between PUFA groups. Smoking, gender, antipsychotic medication and dietary factors did not explain the bimodal distribution. (2) Low PUFA patients had more negative symptoms than high PUFA patients ($p=0.04$). This difference was enduring. Hypertriglyceridaemia (44 % of patients) was 3.4 times more likely in low than in high PUFA patients ($p=0.009$). Clozapine/olanzapine entailed a higher risk than other antipsychotics only in the low PUFA group (interaction $p=0.08$). Among low PUFA patients, serum glucose was higher ($p=0.03$), men were heavier ($p=0.05$), and mean corpuscular haemoglobin was higher than among high PUFA patients ($p=0.001$).

Conclusions

STUDY I: RBC PUFA were bimodally distributed among acutely ill patients with schizophrenia and schizoaffective disorder. Endogenous deficiencies of redox regulation or synthesis of long-chain PUFA in the low PUFA group may explain our findings. Compared to high PUFA patients, low PUFA patients had more negative symptoms and increased morbidity and mortality risk.

STUDY II was undertaken 4-6 years later, in collaboration with K Do and M Cuenod at the University of Lausanne. We examine mortality of patients from study I. We have recruited 55 patients from this study, as well as 51 healthy controls. We analyze PUFA and their links to glutathione genotypes, amino acids, redox regulation biomarkers, PANSS, diet assessed by a questionnaire, and Brain Derived Neurotrophic Factor. Subjects were assessed twice.

References:

Bentsen H, Solberg DK, Refsum H, Gran JM, Bøhmer T, Torjesen PA, Halvorsen O, Lingjærde O. Bimodal distribution of polyunsaturated fatty acids in schizophrenia suggests two endophenotypes of the disorder. Biological Psychiatry, *in press*.

Bentsen H, Solberg DK, Refsum H, Bøhmer T, Lingjærde O. Clinical validation of two subtypes of schizophrenia defined by levels of polyunsaturated fatty acids in red blood cells. Submitted 2011.