Very early onset schizophrenic patients only partially benefit from conventional antipsychotic treatment and are at increased risk for developing neuroleptic- induced extrapyramidal symptoms and tardive dyskinesia (CAMPBELL ET al, 1999). Over the past decade novel atypical antipychotic drugs where introduced. These agents are associated with better efficacy in the treatment of positive and negative symptoms and less extrapyramidal symptoms. (TOREN ET al, 1998). Since 1990 , 48 childhood onset schizophrenic patient have been hospitalized in the children's department of the Ness- Ziona Mental Health Center. 14 patients were treated with Risperdal, 18 with Olanzapine and 25 with Clozapine. (Clearly some children were treated with more than one drug). Prior to the treatment with atypical antipsychotics, most patients were treated with conventional anti-psychotic drugs. In this lecture we will review the current literature and present the outcomes and side effects of the verious drug treatments.

# S48. Membrane abnormalities and psychiatric disorders

*Chairs*: L. Bjerkenstedt (S), J. Assies (NL)

## S48.1

Aberrant tyrosine transport across the cell membrane in schizophrenia

F.-A. Wiesel[1]*, L. Flyckt[2], N. Venizelos[3], G. Edman[4], L. Bjerkenstedt[2], L. Hagenfeldt[3]. [1]*Uppsala University, Department of Neuroscience Psychiatry;* [2]*Karolinska Institute, Stockholm;* [3]*Huddinge Hospital, Karolinska Institute;* [4]*Danderyd Hospital, Karolinska Institute, Sweden*

Schizophrenia is a complex disease involving changes in different biological systems. Any hypothesis of the disease must explain biological disturbances causing both peripheral and brain changes. In our research we have obtained results which have demonstrated an altered tyrosine transport across the cell membrane. These findings have led to the hypothesis of aberrant membrane function as a major cause to schizophrenia.

In vitro studies of tyrosine transport across the fibroblast membrane have shown decreased influx of tyrosine as well as increased affinity. However, the L-system functioned normally. That the in vitro findings have a physiological relevance is confirmed in PET-studies showing an aberrant tyrosine transport across the blood-brain barrier in vivo in patients with schizophrenia. The background of the transport changes was not related to clinical variables. However, since the aberrant tyrosine transport was transmitted through several cell generations of cultured fibroblasts a genetic background is plausible.

In conclusion Tyrosine transport is aberrant in schizophrenia probably reflecting a genetic trait, which may involve membrane function, like energy processes and transport proteins.

## S48.2

Fatty acid composition of membranes in psychiatric patients

J. Assies[1]*, R. Lieverse[2]. [1]*Academic Medical Center, Amsterdam;* [2]*GGZ Buitenamstel, The Netherlands*

Fatty acids (FAs) modulate energy balance and regulate important membrane functions as electrical signalling, receptor sensitivity, and neurotransmitter release. Perturbations of PUFAs are involved in the pathophysiology of neurodevelopmental and degenerative disorders. We found significantly reduced eicosapentaenoic and docosahexaenoic acid concentrations in erythrocyte membranes of 19 schizophrenic patients.

Twelve of our 19 patients showed comorbid cannabis abuse. Cannabis-using patients had significant increases in the n-3 and n-9 series and also in the saturated fatty acids. However, the changes induced by cannabis could not explain the schizophrenia associated FA depletions.

Peroxisome proliferator-activated receptors (PPARs) are activated by a variety of FAs, their cyclooxygenase and lipooxygenase metabolites, and (neuro)steroids like dehydroepiandrosterone(DHEA) and oestrogens.

PUFAs are also ligands for retinoid X receptors (RXRs), which interact as heterodimeric partners with the PPARs and with nuclear related receptors that regulate the expression of multiple schizophrenia candidate genes like dopamine-, serotonin-and glutamate receptors, choline acetyltransferase and phospholipase A2.

Hormones are involved in all stages of fatty acid metabolism.

In conclusion, the membrane composition is useful as a biological phenotypic expression of (psychiatric) diseases.

## S48.3

Increased lipid peroxidation in schizophrenia; a marker of membrane breakdown?

O. Akyol*. *Inonu University Faculty of Medicine, Malatya, Turkey*

The hypothesis that reactive oxygen species (ROS) play an important role in schizophrenia as well as neurodegenerative disorders remains speculative and there have been no detailed studies to test this hypothesis. ROS including superoxide, hydroxyl radical, hydrogen peroxide, singlet oxygen and nitric oxide can cause cellular injury when they are generated excessively or the enzymatic and non enzymatic antioxidant defense systems are impaired. Endogenous antioxidants provide important defence mechanisms that allow organism to cope with the daily challenges of oxidative stress. A number of oxygenated compounds, particularly aldehydes including malondialdehyde (MDA), are produced during the attack of free radicals against membrane lipoproteins and polyunsaturated fatty acids. Increased lipid peroxidation, demonstrated by measuring thiobarbituric acid reactant substances (TBARS) or MDA concentrations in plasma, serum, and erythrocytes, has been proved in several clinical situations. Our studies and the others provide evidence that the increased production of ROS through catecholamine metabolism, neuroleptic treatment, activation of oxidant enzymes, inactivation of antioxidant enzymes, or the other mechanisms might be one of the mechanisms that can lead to decreased phospholipid amount in the membranes and increased TBARS level in both plasma and red blood cell from patients with schizophrenia.

## S48.4

Phospholipid metabolism and schizophrenia: new clinical trials

M. Peet*. *Rotherham Priority Health NHS Trust, Sheffield, UK*

Evidence that phospholipid metabolism is abnormal in schizophrenia includes: reduced levels of n-3 and n-6 fatty acids in cell membranes from erythrocytes and brain of schizophrenic patients; increased levels of calcium independent phospholipase A2 in blood and brain; increased levels of phosphodiesters in brain according to 31P magnetic resonance spectroscopy; reduced skin flush to topical niacin; and abnormal electroretinogram. The possibility of treating schizophrenia with n-3 fatty acids was suggested by studies

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