

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 antipsychotic drugs were 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 patients 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 various drug treatments.

## S48. Membrane abnormalities and psychiatric disorders

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### S48.1

Aberrant tyrosine transport across the cell membrane in schizophrenia

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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

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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 lipoxygenase 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?

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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

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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 phosphodiesterases 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

relating outcome and symptom severity of schizophrenia to fatty acid intake. An initial open pilot study suggested efficacy of n-3 fatty acids on schizophrenic symptoms and tardive dyskinesia. A subsequent double-blind placebo controlled trial suggested that eicosapentaenoic acid (EPA), but not decosahexaenoic acid (DHA) was effective. Four further placebo controlled trials have now been completed, three of them with positive findings. Evidence so far suggests that 2g per day is the most effective dose of EPA, and that the best efficacy is seen when EPA is added to Clozapine. There is also evidence that EPA is effective as a sole treatment for schizophrenia.

### S48.5

Phospholipid metabolism and depression: new clinical trials

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Highly unsaturated fatty acids, such as arachidonic acid (AA) and eicosapentaenoic acid (EPA), which are attached to the Sn2 position of membrane phospholipids are important components of the signal transduction responses to serotonin and catecholamines. Studies in Australia, Japan, Europe and North America are consistent in showing low blood levels of EPA in major depression. Moreover, Hibbeln and colleagues have shown that low dietary intakes of fish, the major source of EPA, are associated with a strikingly increased risk of major depression in both between country and within country studies. An open label study in severe treatment-resistant depression, and two randomised double blind, placebo-controlled trials in treatment-unresponsive depression have now been performed. In a UK study, Peet et al randomised 70 patients who had failed to respond to standard therapy to receive the highly purified ethyl ester of EPA (E-EPA, LAX-101) at 1g, 2g or 4g/d or placebo. Patients were assessed on the Hamilton, MADRS and Beck rating scales. 1g/d was highly significantly better than placebo on all three scales: every item on all scales was better on E-EPA than placebo. The higher doses also showed beneficial effects but these were smaller, possibly because EPA at higher doses may deplete AA. Belmaker in Israel conducted a randomised study of 2g/d LAX-101 or placebo in patients who had relapsed in spite of continuing standard therapy. Again E-EPA was highly significantly better than placebo. In both studies there were no important side effects. E-EPA represents a new treatment modality in depression.

## S49. Early laboratory diagnosis of Alzheimer's disease

Chair: K. Blennow (S)

### S49.1

Hippocampal atrophy on MRI in the diagnosis of Alzheimer's disease

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The hippocampus and the entorhinal cortex are most consistently and heavily implicated in Alzheimer's disease pathology, even in an early stage. This pathology can be visualised as volume-loss on MRI. Two ways of estimating the volume of the hippocampus are by volumetric measurements and by visual rating. In several studies it has become clear that volumetric measurement of the hippocampus as well as visual rating of the medial temporal lobe are highly sensitive for and add significantly to the diagnosis

of Alzheimer's disease, particularly when compared to control-subjects. Also, in subjects with mild cognitive impairment the hippocampal volume seems to have an added predictive value for deterioration in cognition. Atrophy of the hippocampus correlates well with neuropsychological performance, particularly delayed recall.

In longitudinal studies it has become clear that volume loss of the hippocampus is larger in AD compared to controls. Also, volume loss is likely to have added diagnostic value in an early stage of the disease.

Unfortunately, very few studies have investigated the correlation of hippocampal volume, measured on MRI, and hippocampal volume, measured histologically. One small post-mortem study showed a high correlation.

In conclusion, measuring the hippocampal volume on MRI has important added value for the clinical diagnosis of Alzheimer's disease.

### S49.2

Total-tau, A $\beta_{1-42}$  and Ubiquitin in CSF in the diagnosis of Alzheimer disease

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Alzheimer Disease (AD) is multifactorial and heterogenous both clinically and histopathologically. This heterogeneity is not only between the familial and the sporadic forms of the disease but also has been observed within the latter group. The heterogeneity within the sporadic AD, which accounts for over 95% of the cases, might represent different disease mechanisms at early stages that all end up in common end points of neurofibrillary degeneration and  $\beta$ -amyloidosis. Recognition and classification of AD into various subgroups based on CSF markers will help determine the therapeutic efficacy of a specific pharmacologic drug towards one or more specific subgroups of the disease. Towards this objective levels of tau, conjugated ubiquitin and A $\beta_{1-42}$  were assayed in retrospectively collected lumbar CSFs of patients clinically diagnosed as AD (275 patients) and as non-AD neurological or non-neurological cases (97 patients). Levels of tau and A $\beta_{1-42}$  were assayed by sandwich ELISA employing Tau-kits and A $\beta_{1-42}$  kits from Innogenetics NV (Ghent, Belgium). Conjugated ubiquitin levels were assayed by a competitive inhibition ELISA using as primary antibody, the monoclonal antibody 5-25, which recognizes the amino acid residues 64-76 of ubiquitin, preferably the conjugated site generated by glycine 76 of ubiquitin with the substrate protein. Consistent with previous reports, CSF tau and CSF A $\beta_{1-42}$  values in AD were significantly higher and lower respectively than the control cases. Based on clustering of AD and control cases, values of  $\geq 700$  pg/ml for tau,  $\geq 30$  ng/ml for ubiquitin and  $\leq 700$  pg/ml for A $\beta_{1-42}$  were treated as diagnostic of AD. With these cutoff values (i) tau, ubiquitin and A $\beta_{1-42}$  reached diagnostic levels in AD/controls in 63%/11%, 65%/35% and 79%/35% respectively; (ii) 93% of the AD cases studied had diagnostic values for tau, ubiquitin or A $\beta_{1-42}$ ; and (iii) the cases subgrouped in tau only (1%), ubiquitin only (8%), A $\beta_{1-42}$  only (10%), tau and ubiquitin (4%), tau and A $\beta_{1-42}$  (16%), ubiquitin and A $\beta_{1-42}$  (10%) and tau, ubiquitin and A $\beta_{1-42}$  (43%). These findings suggest that sporadic AD might result from more than one disease mechanism and that CSF markers might be employed to identify various subgroups of AD.