NR22. Schizophrenia — aetiology and comorbid substance abuse

Chairmen: S Johnson, T Fahy

OBSTETRIC COMPLICATIONS AND PSYCHOPATHOLOGY IN SCHIZOPHRENIC PATIENTS

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Schizophrenics seem more likely than controls to have a history of obstetric complications (OCs). Therefore, OCs could play a a significant rôle in the following onset of schizophrenia. In a previous work we found out that more severe OCs were related to an increased risk for the development of schizophrenia. Thus, in the current work we firstly subdivided schizophrenic patients on the basis of a lower or higher risk of schizophrenia as evaluated by means of the overall severity of OCs and, secondly, we compared these subgroups to make evident any psychopathological difference between subgroups.

Fifty-eight consecutively admitted chronic schizophrenic male inpatients (DSM III-R diagnostic criteria) were evaluated through the Positive and Negative Syndrome Scale (PANSS). Information retrieval concerning gestations and births was obtained from mothers by using a semi-structured interview. Existence and severity of OCs were assessed through the OCs scale by Parnas et al (1982) based upon a midwife protocol.

Higher risk subjects (total score more than 2 on the OCs scale) had a significant lower score on the General Psychopathology and Negative Subscale. Neither the age of patients nor the duration of schizophrenic disorder nor the drug dosage in chlorpromazine equivalents, when a neuroleptic was administered, were significantly different between the subgroups.

By subdiving schizophrenics on the basis of an etiological factor as OCs it possible to underline the clinical significance of an higher severity of OCs in psychopathological terms.

ALCOHOL AND DRUG COMORBIDITY IN A FIRST ONSET PSYCHOSIS COHORT

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Alcohol and drug misuse among patients with psychotic disorders is increasingly recognised and poses particular diagnostic and management challenges. Studies to date have estimated a prevalence for comorbidity lying between 15% and 65% of patients with psychosis. Many studies are of North American origin and cannot necessarily be extrapolated to European populations. These studies have rarely addressed the confounding effect of duration of illness.

We have recently completed a two year prospective study of first onset psychosis in which an inception cohort was identified from a particular catchment area. Diagnoses were assigned in terms of ICD10-DCR operational criteria and further information on substance misuse obtained from structured interviews with relatives.

Of 155 subjects for whom data on substance misuse were available, alcohol and/or drug misuse was present in over one quarter. When those with any drug use were included, this rose to almost 40%. Those with a diagnosis of schizophrenia, or acute and transient psychosis were most likely to have comorbid substance misuse. 8% of subjects received a diagnosis of substance use disorder. Those with comorbidity were younger and more likely to be male. Misuse was less prevalent among African-Caribbean subjects.

This study confirms the high prevalence of substance misuse comorbidity in psychosis at first presentation, with important implications for detection, diagnosis and management.

CANNABIS AND SCHIZOPHRENIA — A FOLLOW-UP

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During a period of seven years 10.5% of 468 patients with a schizophrenic symptomatology who were treated for the first time at the Universitäts-Nervenklinik Homburg/Saar revealed a drug abuse. Substance abuse preceded the onset of psychotic symptoms for about five years. As compared with the complete group of schizophrenic patients those with drug abuse were six years younger at first occurrence of the disorder. They were predominantly men. More than 80% abused cannabis mainly or exclusively. The cannabis consuming patients were compared to a group of schizophrenics who had no history of alcohol or drug abuse. The control group was matched for age and sex. Cannabis abusing patients showed some characteristics in their anamnesis and psychosocial situation, but there were no differences between the two groups concerning psychopathology.

In a follow-up (on the average after 4.5 years) a majority (60%) of former cannabis consuming patients had continued their abuse or shifted to alcoholism. Psychosocial integration of most patients was poor often presenting with moderate to severe residual states. Moreover patients with on-going drug abuse exhibited more positive symptoms. Results of this study therefore confirm that cannabis abuse has an important impact on the long-term course of schizophrenia.

SCHIZOPHRENIA AND URBAN LIFE

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It has long been thought that rates of mental illness are higher in cities than elsewhere, because of crowding and resultant stress. In the case of schizophrenia, there are some exceptions to generally higher prevalence rates in industrialised cities. Factors such as migration, culture, infectious disease, demographic rates, and other social processes may affect geographical differences in rates. The excess of schizophrenia in central city areas has been given two contrasting explanations — the 'breeder' hypothesis and 'social driff'. Data on incidence from three cities are compared, but do not reveal a clear picture. Environmental factors connected with urban living are of two main types — social and non-social — which are not mutually exclusive; 'urban' living may also have a variety of meanings. Rather than 'urbanicity' being an independent aetiological factor in schizophrenia, its effect may perhaps be largely explained in terms of migration and social class.

DOES SUBSTANCE ABUSE PRECIPITATE SCHIZOPHRENIA?

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The high comorbidity of schizophrenia and substance abuse of up to 60% in chronic schizophrenic patients suggests a causal relationship between the two disorders. Some authors argued that substance abuse, particularly cannabis and amphetamine abuse, may precipitate schizophrenia, while others collected evidence that psychotropic substances are used for self-medication against schizophrenic symptoms. Studies of first-episode patients which could clarify the temporal order of first occurrences as a hint for a causal relationship are

scarce. Within the ABC Schizophrenia Study, the onset and course of schizophrenic symptoms and of alcohol and drug abuse was retrospectively investigated in a representative first-episode sample of 232 schizophrenic patients by means of the structured interview "IRAOS". Information given by relatives validated the patients' reports.

In first-episode schizophrenics the rates of alcohol or drug abuse (24% and 14%) were twice the rates compared to a matched sample from the general population. Male sex and early symptom onset were major risk factors. Drug and alcohol abuse both significantly preceded the first positive symptom — on the average by more than 5 years. But neither the onset of alcohol abuse nor the onset of drug abuse significantly preceded the first symptom of schizophrenia. Alcohol abuse usually followed it, whereas drug abuse often emerged simultaneously with the first symptom. Only in one third of the comorbid cases substance abuse seemed to precipitate schizophrenia.

ALCOHOL USE AND ABUSE IN PATIENTS SUFFERING FROM SCHIZOPHRENIC DISORDERS IN CORFU ISLAND

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Alcoholism is frequently associated with schizophrenic disorders. Statistical analysis was conducted on the frequency of this coexistence as it is represented in the psychiatric population of the Psychiatric Hospital of Corfu during a period 3 years. For this research, a specialized questionnaire was administered for the recording of demographic and social characteristics, while the scales BPRS and BECK were used for the assessment of the psychopathology and the depression of the patients. The alcoholic schizophrenic patiens constitute the 4% percentage of the total admission of the hospital. And they are the 22% percentage of the total alcoholic treated inpatients during this period. The mean age of the inpatients was 29 years of age while a great portion (63%) of them was unmarried.

Finally we recorder the possible causes that lead schizophrenic patients to alcoholism and the effects that alcoholism has on the prognosis and the therapy of this disorder.

SCHIZOPHRENIC PSYCHOSES AND MUTATIONS OF THE CILIARY NEUROTROPHIC FACTOR (CNTF) AND NEUROTROPHIN 3 (NT3) GENES: EVIDENCE FOR THE MALDEVELOPMENTAL THEORY

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The maldevelopmental theory postulates that neurodevelopmental deficits, disturbances of cell migration and dysconnections of neural and glial structures are crucial factors in the etiopathogenesis of schizophrenic psychoses. Neurotrophic factors play a central role in the regulation of neural development and postnatal maintenance. For the CNTF gene, a null mutation has been described, whereby homozygote mutants lack CNTF completely, while for the NT3 gene, a missense mutation, Gly → Glu (GGG → GAG), is known. The aims of the present study were to investigate the frequencies of these mutations in psychiatric patients and to determine whether an association with schizophrenic psychoses is evident. Further, the allele frequencies were determined for the first time in a Caucasian population.

212 psychiatric inpatients (ICD-10 diagnoses) were examined with respect to CNTF mutation, of whom 188 were also examined for NT3 gene polymorphism; these genes were also examined in 60 healthy controls. Genotype determination involved extraction of genomic DNA from blood, PCR with primers flanking the gene region of interest, digestion of the PCR products with restriction endonucleases, fragment separation by gel electrophoresis and analysis under UV light. Previoulsy described primers have exhibited dimerization tendencies which interfere with genotype determination; we have therefore developed a new protocol for NT3 genotyping using more specific primers.

The schizophrenic psychosis group (n = 51) showed a significantly increased frequency of the CNTF null mutation allele when compared to healthy controls (0.250 vs. 0.122; χ^2 test, $p < 0.05$). Patients with other diagnoses exhibited no increased frequency of the mutated allele. Further, the CNTF mutation was not in Hardy-Weinberg equilibrium, as there were only 7 homozygote mutants, whereas 15 would be predicted. Concerning the NT3 polymorphism, we found a frequency of 0.006 for the allele *Glu* in the total sample. There were no homozygotes (*Glu/Glu*), and the three heterozygotes (*Gly/Glu*) belonged to the patient group (2× endogenous depression, 1× hebephrenia).

Neurotrophic factor genes have been considered as strong susceptibility loci in research into the etiopathogenesis of schizophrenia. Our results suggest mutation of the CNTF gene as a genetic factor which could increase an individual's risk for schizophrenic psychosis. The detected frequency of the NT3 allele *Glu* in Caucasians is far lower than that previously described for a Japanese population reference. An association of the mutant allele with schizophrenic psychoses was neither refuted nor confirmed, but all heterozygotes suffered from endogenous psychoses. Taken together, our findings lend further support for the maldevelopment theory of schizophrenic psychoses.

INCREASED MORBID RISK OF SCHIZOPHRENIA IN RELATIVES OF PATIENTS WITH SEVERE BIPOLAR DISORDER

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If "the familial liability to schizophrenia is, at least in part, a liability to develop psychosis" (Kendler et al., 1993), one would expect a higher morbid risk of schizophrenia in the relatives of bipolar disorder at the severest, psychotic end of the spectrum (Hypothesis 1). In addition, one would expect, analogous to findings in patients with schizophrenia, high familial morbid risk for schizophrenia to be associated with female gender (H2), early onset (H3) andpoor prognosis (H4).

We tested these hypotheses in a sample of 104 patients with severe DSMIIIR bipolar disorder requiring on average 6.13 admissions over 16 years. An average of 2 relatives for each proband were interviewed using the FH-RDC, and age and sex-adjusted morbidity risks were calculated according to the method of Strömgren.

H1: MR for not only bipolar disorder (5.2%), but also schizophrenia (3.0%), are much higher than reported population risks. H2/3: MR for schizophrenia in relatives of the female, early onset (below 50th percentile) group (7%) was significantly higher than in the other groups (female late onset: 1.0%; male early onset: 0.0%; male late onset: 3.1%). H4: familial morbid risk for schizophrenia, expressed as a continuous, age and sex-adjusted likelihood ratio score, was associated with the average number of hospital admissions per year (as a proxy of illness severity).