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Clinical and Biological Markers for Outcome in Schizophrenia

A Review of a Longitudinal Follow-up Study in Uppsala Schizophrenia Research Project

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During a 10-year period, 120 drugfree DSM-III-R schizophrenic patients were consecutively and unselectively admitted to a ward for young psychotic patients and subjected to a battery of examinations including symptomatology, cerebrospiral fluid (CSF)-biochemistry, computed tomography (CT)-scan, neurophysiologic and psychophysiologic (Electrodermal activity, EDA) parameters before antipsychotic treatment was initiated. After discharge, the patients were longitudinally followed with ratings of outcome (Strauss-Carpenters outcome scale) at years 1, 3, and 5 after index admission. The aim of the study was to find possible early markers for outcome in schizophrenia. At 5 years, 30% of the patients had a good outcome (total score >13) and 15% a poor outcome (total score <8). Poor premorbid adjustment and low level of education as well as negative schizophrenic symptomatology at index admission were associated with a poor outcome 5 years later. Postive symptomatology and a family history of schizophrenia did not predict outcome. Patients with a poor outcome (total score <8) had a significantly more deviant CSF HVA/5-HIAA quotient than those with a very good outcome (total score >15) as compared with healthy controls. Further, the CSF-peptides neuropeptide Y, dynorphin A, and CRF were predictable for outcome at the 5-year follow-up evaluation. Male schizophrenics who were "nonresponders" on the EDA test showed an almost 100% poor outcome, which was not found in females. In summary, several clinical and biological variables seem to have a predictable value for outcome in schizophrenia and, early identification of them might be a challenge for our future treatment strategies. ***[Neuropsychopharmacology 14:23S–26S, 1996]***

KEY WORDS: *Schizophrenia; Outcome; Symptoms; Monoamines; Neuropeptides; Electrodermal activity (EDA)*

Originally the diagnostic concept of schizophrenia was to a great extent based on the outcome of the disorder, and Kraepelin (1919) considered it to be characterized by steady deterioration, an opinion that was still expressed in DSM-III (1980). However, several studies during the last decade have presented a more optimistic view pointing out that a substantial number of schizophrenic patients in fact have a good outcome if the length of the follow-up time is long enough (Harding et al. 1987; Ciompi 1988; Ram et al. 1992; Wieselgren and Lindström 1994). It could be argued, however, that the prognosis of schizophrenia has changed during this decade or that other factors like early drug treatment, deinstitutionalization, or other unknown influences have changed the picture. However, we have still no valid guidelines about the long-term prognosis for the single first-episode schizophrenic patient, so the effort to find early predictors for outcome is a challenge.

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This presentation is an overview of our own research strategy over the past 15 years that aimed to find early clinical and biological markers for short-term and long-term outcome in both first-episode and readmitted chronic schizophrenic patients (See Table 1). This is a prospective longitudinal study in which a group of drugfree schizophrenic patients were subjected to a battery of examinations at index admission including demographic data, clinical ratings of symptomatology, cerebrospiral fluid (CSF)-biochemistry, computed tomography (CT)-scan, neurophysiologic and psychophysiologic (Electrodermal activity, EDA) parameters. They were then treated with classic or atypical neuroleptics in combination with social skill straining and family support and subjected to a prospective follow-up study using the Strauss-Carpenters outcome scale 1, 3, and 5 years after index admission.

MATERIAL AND METHODS

The subjects were 120 DSM-III-R schizophrenic patients, 86 men and 34 women with a mean age of 27.1 years at index admission. Of the patients, 66 were first-admitted and never treated with antipsychotics. Mean age for the appearance of first symptoms was 22.5 years for the whole group of patients.

Demographic data were collected by a detailed and structured interview with one or more close relatives to assess deviant premorbid behavior (a 5-point scale dichotomized into a normal and a deviant group), family history for schizophrenia (complemented with hospital records), and age at first symptoms.

Symptomatology at index admission was assessed by use of 16 reported and 17 observed items from the Comprehesive Psychopathological Rating Scale (CPRS) (Åsberg et al. 1978) within 2 days after admission. Two subscales from the CPRS were used to cover positive and negative symptoms.

Lumbal puncture was performed before treatment had started between 8:00 A.M. and 9:00 A.M. with the patient in an erect position, and 18 ml of CSF was collected, centrifuged, well mixed and divided into 1-ml aliquots and immediatedly frozen at −70°C before assayed.

Monoamine analysis assays were performed by gas chromatography mass spectrometry using a LKB 2091 GC/MS equipped with a multiple ion detector following the procedure described by Swahn et al. (1976).

Opioid peptide analysis was performed by use of fractionation with reverse-phase silica gel column and subsequent radioimmunoassay, which followed a non-immune globuline pre-precipitating method.

Assessment of outcome was rated by use of the Strauss-Carpenter outcome scale with the following items scored on a five-point scale: hospitalization last year, social contacts, employment, psychotic symptoms, and medication. A total outcome score was constructed by adding the scores from the first four items mentioned yielding a lowest score of 4 and a highest of 20.

Electrodermal activity (EDA) was measured by standard silver/silver chloride electrodes attached to the second phalanges of the first and second fingers of the patient's left hand. Stimulation series involved 15 presentations of a 1,000 Hz, 80 dB 2-s tone, the number of skin conductance responses (SCRs) were rated, and the patients were dichotomized into two groups: nonresponders (0 SCR) and responders (>1 SCRs).

Table 1. Clinical Biochemical, and Psychophysiologic Candidate Markers for Poor Outcome in Schizophrenic Patients

Variables	Poor Outcome
Positive symptoms	0
Negative symptoms	⇑
Deviant premorbid adjustment	⇑
Education level	⇓
Family history of schizophrenia	0
CSF levels of HVA/5-HIAA	⇓
CSF levels of dynorphin A	⇑
Electrodermal activity, men	⇓
Electrodermal activity, women	0

RESULTS AND DISCUSSION

One year after index admission there was a relatively poor outcome with 70% of the patients scoring 8 or less on the total outcome score. Between year 1 and 5 after index admission, a clear-cut improvment was evident. At the 5-year evaluation, 30% of the patients were found to have a good outcome with a total score of >13 and only 15% with a poor outcome with a total score of <8. Women had a significantly better outcome compared to men. Seven patients had comitted suicide during the 5-year follow-up period. With regard to antipsychotic drug treatment, the follow-up data showed that 19% of the patients were without medication, 5% had taken neuroleptics sporadically during the last 6 months, 41% were on classic neuroleptics in antipsychotic doses, and 35% were treated with clozapine.

Patients with poor premorbid adjustment and low educational level had a poorer outcome at year 5, whereas high education and lack of premorbid deviation predicted a good outcome. Family history of schizophrenia was not related to outcome 5 years after index admission per se, but patients with a family history improved more between year 1 and 5 compared to those without.

Total degree of psychopathology as rated by the CPRS at index admission did not correlate with outcome scores at year 5 ($r = 0.0$, NS). In contrast, high

scores in CPRS on the sum of negative schizophrenic symptoms (indecision, withdrawal, reduced speech, lack of appropriate emotions, slowness of movements) were significantly correlated with a poorer outcome at year 5 ($r = 0.34$, $p < .05$). However, that was true only for those patients who had a duration of the illness of less than 24 months before the index admission, that is for patients with a more rapid onset of the disorder. In our study, high or low scores for positive symptoms (hallucinations, ideas of persecution, disrupted thoughts, flights of ideas and feelings controlled) had no predictive value for the outcome at 1, 3, or 5 years after index admission.

We have previously demonstrated low levels of the dopamine metabolite homovanillic acid (HVA) in CSF in schizophrenic patients compared with controls (Lindström 1986). In an extended sample (90 schizophrenic patients and 47 healthy controls) we have replicated our data with decreased CSF-levels of HVA ($t = 2.51$, $p = .013$) but normal levels of 5-HIAA ($t = 0.26$, NS). Consequently, the quotient HVA/5-HIAA was lower for schizophrenic patients compared to controls ($t = 2.47$, $p = 0.15$). The CSF-levels of the amine metabolites determined at index admission did not correlate with total outcome scores at years 1, 3, or 5. However, if the patients were subdivided into two extreme groups, one with a very poor outcome (total outcome scores <8) and one with a very good outcome (total outcome score >15) then a significant difference emerged. Patients with a very poor outcome had a significantly lower HVA/5-HIAA quotient compared to patients with a very good outcome ($t = 2.16$, $p < .05$), that is, a more deviant CSF-level of both HVA and 5-HIAA from healthy controls.

We have found that schizophrenic patients have elevated levels of the opioid peptide dynorphin A in the CSF compared to healthy controls (Lindström et al., in preparation). Dynorphin A derives from the prohormone proenkephalin B and is further processed to leu-enkephalin-arg6 by the action of the peptidase dynorphin converting enzyme (DCE). Dynorphin A has a relatively high opioid kappa receptor agonistic selectivity and is therefore suggested to have psychotomimetic properties, whereas leu-enkephalin-arg6 has an agonist effect on δ receptors (Pfeiffer et al. 1986). With regard to outcome, we have found that the CSF-levels of dynorphin A were a predictor for the prognosis 5 years after index admission. If the total patient sample was dichotomized into two groups, one with a poor outcome (total outcome scores <11) and one with a good outcome (total outcome scores >10), then a difference was evident regarding the dynorphin levels. Patients with a poor outcome had significantly higher levels of dynorphin A compared to schizophrenic patients with a good outcome, who did not differ from healthy controls (poor: 68.1, good 40.0, controls 36.7 fmol/ml).

Electrodermal activity is a psychophysiologic technique measuring the "arousal" or "orienting response" to a sudden stimulus, in this case a tone of 80 dB, by registering sweating in the palm. Several studies have shown that about 50% of a population of schizophrenic patients are "nonresponders" compared with 5% to 10% of a normal population. A nonresponder does not react with arousal and palm sweating at the first tone or any of the following tones. In our outcome studies, it was evident that nonresponding male schizophrenic patients were associated with an almost 100% poor outcome 2 years after index admission (Öhlund et al. 1991). This clear-cut relationship was not found in female schizophrenics (Wieselgren et al. 1994). The reason for that gender difference is obscure.

By application of a broad clinical, neurophysiologic, biochemical, and psychophysiologic intervention in a group of both first-episode, never-treated, as well as readmitted schizophrenic patients in exacerbation in a drugfree phase, and by following the cohort over several years, we have been able to demonstrate that patients with a good outcome 5 years after index admission showed several differences from those with a poor outcome. Our data indicate that symptomatology might have a predictive value if the duration of the disorder before admission is less than 2 years. Negative symptomatology indicated by blunted affects, indecision, and withdrawal seem to predict a poor outcome. The role of biochemical deviations, as they can be assessed from analysis of CSF-samples, for the prognosis in schizophrenia is not so evident. However, it seems as if the balance between dopamine and serotonin in the brain, mirrored by their metabolites in the CSF, might be of some importance for outcome. Patients with a poor outcome have a more pronounced imbalance between the two transmitters. Also the opioid peptide system has to some extent a predictive value insofar that increased levels of the kappa-receptor opioid agonist dynorphin A was associated with a poorer prognosis 5 years after index admission.

A somewhat surprising finding was the fact that as many as 35% of the patient population was treated with clozapine 5 years after index admission. One explanation for that high figure is that we have a long tradition of giving clozapine at our clinic, and the psychiatrists participating in the study have extensive experience with that antipsychotic drug. The relatively high proportion of patients on clozapine could explain the good outcome figures in the present study. In our opinion, it is realistic to calculate that at least one-third of a group of unselected schizophrenic patients should be on clozapine after several years of illness.

It should be pointed out that any single symptom or biochemical or neurophysiologic abnormality by itself probably has a low predictive value for outcome in schizophrenia. The present study was conducted with

the aim of finding certain patterns or combinations of deviations that could tell us something about long-term prognosis in schizophrenia. In the study, we point out some probable candidates. To cover the problem of finding patterns of predictors, more comprehensive multivariate statistical techniques must be applied to our data. Such a work is in progress by us.

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