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Familial liability and schizophrenia phenotypes: A polydiagnostic approach

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Abstract

Background: There are conflicting results about the correspondence between the diagnostic phenotype of schizophrenia and genetic factors. Using a polydiagnostic approach we examined the relationship between familial liability and alternative schizophrenia phenotypes.
Methods: The sample comprised of 660 psychotic probands and their 2987 first-degree relatives. Probands were assessed for 23 diagnostic systems of schizophrenia, 2 criteria for broadness of phenotype, 4 subtyping criteria and 16 clinical features, while relatives were assessed for familial morbid risk of schizophrenia. To quantify the predictive validity of familial liability against the alternative phenotypes we used the receiver operator characteristic curve analysis yielding an area under the curve (AUC) measure and logistic regression analysis.
Results: Although familial liability significantly predicted some diagnostic criteria for schizophrenia, their diagnostic performance was generally very poor (AUC .55 to .61 and OR 1.64 to 2.85). Overall, the most inclusive criteria performed better than the most restrictive ones. Subtyping schizophrenia according to both DSM-IV and negative or deficit subtypes was unrelated to familial liability. The best predictive ability of familial liability (AUC=.71, OR=4.54) was achieved against empirically-derived criteria consisting of (a) early onset *or* lack of a major mood syndrome *and* (b) presence of inappropriate affect, affective flattening *or* bizarre delusions.
Conclusion: Familial liability does have poor predictive validity regarding diagnostic systems of schizophrenia, although some differences existed among systems. Liability to schizophrenia performed better in predicting broad than restrictive phenotypes of the disorder.

Keywords: Schizophrenia; Diagnostic criteria; Phenotype; Familial liability; Diagnostic validity

1. Introduction

Decades of research into the etiology of schizophrenia has yielded only fragmentary results. The most consistent finding in this respect is the contribution of genetic factors, since having a first-degree relative with schizophrenia continues to be the single most powerful risk factor of the disorder. One of the most disappointing questions in schizophrenia research has been the failure to link the well established genetic background with a specific phenotype. Defining schizophrenia has been problematic since the earliest clinical descriptions of the disorder and existing diagnostic systems are based on assumptions about chronicity, diagnostic hierarchy

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rules, or symptom specificity with no or little empirical basis (Maj, 1998), and as a consequence the validity of that diagnosis remains subject to debate. In fact, we are confronted with a vicious circular reasoning in that we do not posses robust external validators to anchor the diagnosis, while at the same time unclear phenotypic boundaries impede the etiological research.

On the basis that a gold standard definition for schizophrenia is lacking, the so-called "polydiagnostic approach" (Kendell, 1982) has been advocated as a useful tool for examining the validity of alternative definitions of psychotic disorders (McGorry et al., 1990; McGuffin and Farmer, 2001). Given that familial liability is by far the most relevant risk factor of schizophrenia, it is important to know the extent to which liability is related to competing diagnostic systems of schizophrenia. Using a polydiagnostic approach, in this study we sought to examine the predictive validity of familial risk of schizophrenia against alternative phenotypes of the disorder with the aim of unraveling which of them are closer to familial liability. Phenotypic definitions of schizophrenia included: (i) 23 alternative diagnostic systems, (ii) 2 criteria for broadness of phenotype, (iii) 4 subtyping criteria, and (iv) 16 specific symptoms or clinical features.

2. Methods

2.1. Characteristics of the sample

The study sample comprised 660 psychotic inpatients who were consecutively admitted to the Psychiatric ward of the Virgen del Camino Hospital between 1988 and 1996. The hospital serves a predominantly urban geographic area of 250,000 inhabitants with no other psychiatric admissions wards in the area. Other psychiatric devices of this catchment area include four mental health outpatient centers and one day hospital. Patients were referred to by their attending psychiatrist or the emergency ward mainly because illness exacerbation. A minority of patients (<10%) were admitted because treatment refractoriness or for diagnostic clarification. The mean age at index assessment was 36.0 years (SD=14.0), the mean age at illness onset was 26.9 years (SD=10.6), and the average number of previous hospitalizations was 3.4 (SD=4.3). Three-hundred and eighty-four patients (58%) were male. DSM-IV diagnoses were as follows: schizophrenia (n=358, 54.2%), schizophreniform disorder (n=61, 9.2%), schizoaffective disorder (n=37, 5.6%), major affective disorder (n=88, 13.3%), delusional disorder (n=27, 4.1%), brief psychotic disorder (n=57, 8.6%) and psychotic disorder not otherwise specified (n=32, 4.8%).

All the patients were evaluated by the authors, each of them assessing approximately half of the patients. The study was carried out according to the declaration of Helsinki, it was approved by the local ethical committee and all subjects or their legal representatives provided informed consent to participate.

2.2. Diagnostic assessment

Each patient undertook an extensive clinical, diagnostic and psychopathological assessment, and for the purpose of the present study the main diagnostic instrument was an expanded version (Peralta and Cuesta, 1992) of the Manual for the Assessment of Schizophrenia (MAS, Landmark, 1982). A detailed description of the expanded MAS, assessment methodology and inter-rater reliability of symptoms and diagnoses may be found elsewhere (Peralta and Cuesta, 2005). The expanded MAS includes 23 diagnostic systems of schizophrenia, which cover virtually all the meaningful conceptualizations of the disorder from Kraepelin to nowadays. Inter-rater reliability for most clinical features, symptoms and diagnoses was good to excellent (Peralta and Cuesta, 2005). Diagnosis of specific psychotic disorders was also performed according to DSM-IV and RDC using a consensus best-estimate procedure on the basis of all available information sources including medical records and interviews with probands and at least a close relative.

For subtyping schizophrenia patients had to met the DSM-IV criteria for schizophrenia. The following classifications were used: (i) the DSM-IV classification in subtypes, (ii) the broad and (iii) restrictive criteria for negative schizophrenia (Andreasen et al., 1990), which were applied with the use of ratings from the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983), and (iv) the criteria for the deficit syndrome (Carpenter et al., 1988).

Lastly, we selected 13 lifetime symptoms and 3 clinical features from the MAS representing relevant domains of schizophrenia manifestations in order to examine their predictive validity as a previous step for developing tentative diagnostic criteria best predicting familial liability.

2.3. Assessment of familial liability to schizophrenia

A family history of schizophrenia was ascertained using the Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977) in the 2987 first-degree relatives of the probands aged 15 or greater. A detailed description of the family assessment procedure