Genetic Studies of the Schizoaffective Syndrome: A Selective Review

by Richard Abrams

Abstract

The diagnostic validity of the schizoaffective syndrome is assessed from a genetic vantage point. Five studies are reviewed that meet specific methodological requirements. No evidence is provided for the transmission of schizoaffective disorder as a diagnostic entity. The relationship of the schizoaffective syndrome to manic-depressive illness and to schizophrenia is unresolved, and genetic overlap exists between these two disorders in the transmission of the syndrome, with the larger contribution coming from affective disorder, and schizophrenia contributing primarily a severity of illness factor.

The diagnostic validity of schizoaffective disorder (more properly called the schizoaffective syndrome) remains undefined a half-century after Kasanin (1933) coined the term to describe nine young patients with acute remitting psychoses characterized by emotional turmoil.

The definition of the schizoaffective syndrome used in this review includes three groups of patients: (1) those who meet diagnostic criteria for schizophrenia but also have affective symptoms; (2) those who meet diagnostic criteria for affective disorder but also have schizophrenic symptoms; and (3) those who do not meet criteria for schizophrenia or affective disorder, but have a mixture of both schizophrenic and affective symptoms.

Designating a particular sign or symptom as “affective” or “schizophrenic” in no way implies diagnostic specificity for that clinical feature: no such specificity exists in psychiatric nosology. Formal thought disorder alone is no more diagnostic of schizophrenia than elated mood alone is diagnostic of mania. In the absence of any affective symptoms, however, formal thought disorder is highly predictive of a diagnosis of schizophrenia, just as elation in the absence of any schizophrenic features is highly predictive of a diagnosis of mania. Without a demonstrated etiology, the validity of separating the diagnostic categories of schizophrenia and mania is based upon observed differences between the groups for illness course, treatment response, laboratory studies, and familial illness patterns (Robins and Guze 1970). The present review assesses the validity of the schizoaffective syndrome in light of the relevant genetic studies.

The primary questions to be answered are whether relatives of schizoaffective probands are at greater risk for schizophrenia, affective disorder, or the schizoaffective syndrome than the general population, or than the relatives of schizophrenic or affective probands. These questions can only be answered by studies meeting the following methodological requirements:

- Probands must satisfy specified criteria for the schizoaffective syndrome. Studies of “atypical” or “reactive” psychoses are not included here as not all of their probands meet the requirements defined above for a diagnosis of schizoaffective disorder.

In the report of Tsuang, Dempsey, and Rauscher (1976), for example, probands with simple delusional disorder (Winokur 1977) could have satisfied the authors' criteria for atypical schizophrenia. Patients with...
simple delusional disorder do not have a mixture of affective and schizophrenic symptoms, nor do they exhibit a significant familial loading for any form of mental illness. Including such patients in a genetic study of schizoaffective disorder reduces the likelihood of detecting genuine evidence for transmission of this entity.

- **Age-corrected morbidity risks for secondary cases, or the data for calculating them, must be presented.** Prevalence rates (the simple proportion of ill relatives) are unsuitable for comparing familial risks for different disorders as the risk will be seriously underestimated in disorders with a later age at onset, and in the families of younger probands. Age-correcting the total sample of relatives to account for those who have not yet passed through the age at risk is therefore critical in comparing familial risks for disorders such as schizophrenia and affective disorder which have substantially different risk periods. The morbidity risk is the age-corrected prevalence statistic required for valid genetic comparisons. (Even less useful than simple prevalence is the characterization of risk merely as the number of probands with a positive family history.)

- **Diagnosis in relatives must be made without knowledge of proband diagnosis.** Diagnosing relatives while having full knowledge of the proband's diagnosis introduces a scientifically unacceptable bias into any genetic study. Thus, the present review excludes the widely cited report of Angst, Felder, and Lohmeyer (1979), in which the diagnoses in relatives were not made blindly to proband diagnoses.

- **Diagnostic criteria must specify the precise rules for including and excluding each case (operational criteria).** This stipulation is required to avoid the well-defined risk of contaminating the schizophrenic samples with large numbers of patients actually suffering from affective disorder (Pope and Lipinski 1978; Taylor and Abrams 1978), thus entirely defeating the genetic strategy.

**Review of Studies**

**Tsuang (1979).** This was a case history study of 35 sib-pairs who were both hospitalized for "mental disorders" at the Genetics Research Unit of the Maudsley Hospital in London. Each sib was blindly and independently diagnosed from case records as having schizophrenia or affective disorder according to the criteria of Feighner et al. (1972), or schizoaffective disorder if he had (1) both schizophrenic and affective features or (2) an affective episode for the index admission but some schizophrenic symptoms in a prior episode. On the basis of the distribution of the 70 proband diagnoses (17 schizophrenics, 32 affectives, and 21 schizoaffectives) it was determined that there was a dearth in the expected number of schizoaffective sib-pairs, which was not true for the two other diagnoses. These results suggest that schizophrenia and affective disorder are genetically distinct, but that schizoaffective disorder is not. Further analysis of "crossed pairs" (e.g., affective-schizophrenic) suggested that some schizoaffective cases are genetically related to affective disorder and some to schizophrenia.

**Mendlewicz, Linkowski, and Wilmotte (1980).** The authors studied a sample of 55 schizoaffective probands who were matched for age and sex with 55 schizophrenic, 55 bipolar, and 55 unipolar probands. Diagnoses were made according to the criteria of Feighner et al. (1972) for schizophrenia and schizoaffective illness, and according to criteria "similar to those" of Winokur, Clayton, and Reich (1969) for bipolar and unipolar illness. Specifically, the diagnosis of schizoaffective illness "required the presence of episodic affective syndromes of a manic or depressive type, as well as the presence of at least one schizophrenic episode not concurrent to an affective syndrome." Relative diagnoses were made without knowledge of proband diagnosis.

The morbid risk for schizoaffective illness in relatives of any of the groups was too low to be tabulated. The morbid risk for all affective illness in first degree relatives of schizoaffective probands (34.6 percent) was similar to that for bipolar (39.4 percent) and unipolar (28.5 percent) probands, but much higher than for schizophrenic probands (8.6 percent). Conversely, the morbid risk for schizophrenia in first degree relatives of schizoaffective probands (10.8 percent) was similar to that for schizophrenic probands (16.9 percent) but much higher than for bipolar (1.8 percent) or unipolar (3.2 percent) probands. Thus, schizoaffective disorder was clearly not a separate genetic entity but exhibited overlap with both affective disorders and schizophrenia.

**Abrams and Taylor (1980).** The authors examined a sample of 111 consecutive admissions who satisfied the inclusion criteria for mania of Feighner et al. (1972). These probands were further characterized as exhibiting one or more schizophrenic features (formal thought disorder, first rank symptoms, auditory hallucinations, persecutory delusions, catatonia). Family interview and family history data
were combined into a single research record and diagnoses in first degree relatives were then made without knowledge of proband diagnosis. No cases of schizophrenia were found in first degree relatives. The morbidity risk for affective disorder in first degree relatives of manic patients without any schizophrenic features (n = 41) was 9.35 percent; for manic patients with at least one such feature (n = 70), the risk was 9.77 percent (NS). However, when the latter group was divided into those with one, two, and three or more schizophrenic symptoms, the risk for affective disorder in first degree relatives increased in stepwise fashion from 5.7 to 8.8 to 18.2 percent, respectively $\chi^2 = 7.86, df = 2, p < .025$.

This sharply increased affective morbidity risk in relatives with increasing schizophrenic symptomatology in probands is consistent with a multifactorial model in which the schizophrenic features represent a diagnostically nonspecific severity factor.

**Baron et al. (1982).** These authors studied a sample of 50 schizoaffective, 40 bipolar, 45 unipolar, and 50 schizophrenic probands, all diagnosed according to the Research Diagnostic Criteria (RDC) of Spitzer and Endicott (1978). Personal interviews were obtained in 72 percent of first degree relatives, who were also diagnosed by RDC and without knowledge of proband diagnosis. The criteria for schizoaffective illness required an episode of illness that "qualifies for manic or depressive syndrome but that also includes at least one of the symptoms suggesting schizophrenia."

The morbid risk for schizoaffective disorder in first degree relatives of each proband group was similarly low: schizoaffective = 2.3 percent, affective = 3.0 percent, schizophrenic = 2.3 percent. The risk for affective disorder in relatives of schizoaffective and affective probands was equally high (19.5 percent and 25.4 percent, respectively), and much larger than that for schizophrenic probands (5.1 percent).

The risk for schizophrenia in relatives of schizoaffective and affective probands was equally low (2.0 percent and 0.4 percent, respectively), and much lower than that for schizophrenic probands (7.9 percent).

Thus, these data do not suggest a unique genetic transmission for schizoaffective disorder, but rather support the classification of schizoaffective disorder along with the affective disorders rather than with schizophrenia.

**Gershon et al. (1982).** The authors studied 11 schizoaffective probands and an unspecified number (but fewer than 161) of probands with affective disorder (bipolar I, bipolar II, and unipolar). Diagnoses in probands and relatives were made by the RDC (Endicott and Spitzer 1978), and 75 percent of relatives were interviewed, all interviews being conducted without knowledge of proband diagnosis. Specific criteria for schizoaffective disorder included "psychotic features during euthymia or mood-incongruent psychotic features during depression," with complete recovery between episodes for at least the first few attacks.

The morbid risk for affective disorder in first degree relatives of schizoaffective probands was higher than that for affective probands (31.3 vs. 22.2 percent), as was the morbid risk for schizophrenia (3.6 vs. 0.23 percent) and schizoaffective disorder (6.1 vs. 0.8 percent). These data suggest genetic overlap for affective disorder and schizophrenia in the transmission of schizoaffective disorder, with the preponderant effect deriving from affective disorder (there was a greater than 10:1 ratio of affective to schizophrenic relatives among schizoaffective probands).

**Discussion**

These studies provide no evidence for the transmission of schizoaffective disorder as a separate and specific diagnostic entity, and that issue must now be considered settled.

However, the relationship of the schizoaffective syndrome to manic-depressive illness on the one hand, and to schizophrenia on the other, remains unresolved. Genetic overlap in the transmission of the schizoaffective syndrome is suggested by the studies which report an increased risk for both affective disorder and schizophrenia in relatives of schizoaffective probands (Mendlewicz, Linkowski, and Wilmotte 1980; Gershon et al. 1982). In both of these studies the risk for affective disorder in relatives was 3.2 to 8.7 times greater than that for schizophrenia, suggesting that the main genetic effect derived from affective disorder.

In two studies (Abrams and Taylor 1980; Gershon et al. 1982) the presence of schizophrenic symptoms in schizoaffective probands reflected a dimension of severity: in one study (Gershon et al. 1982), the risk for affective disorder was greater in relatives of schizoaffective than in affective probands; in the other (Abrams and Taylor 1980), the morbid risk for affective disorder in relatives of schizoaffective probands increased in stepwise fashion with the number of schizophrenic symptoms exhibited by the proband. Both observations are consistent with a multifactorial, multiple-threshold model of inheritance in which schizoaffective disorder represents the most virulent form of illness.
The following statements about the schizoaffective syndrome summarize the weight of the genetic evidence to date:

- Schizoaffective disorder is not a distinct genetic entity.
- There is genetic overlap between affective disorder and schizophrenia in the transmission of the schizoaffective syndrome.
- The contribution of affective disorder in this transmission is much greater than that of schizophrenia.
- The contribution of schizophrenia in this transmission is primarily that of a severity of illness factor.

A definitive resolution of the genetic status of the schizoaffective syndrome awaits a methodologically appropriate study in a large sample of schizoaffective probands and their relatives.

References


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