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Concordance of Positive and Negative Symptoms in Coaffected Sib-Pairs with Schizophrenia

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Positive and negative symptom (NGS) dimensions were examined for their concordance in 46 coaffected schizophrenic sib-pairs. Results showed that the symptom dimensions of negative symptoms (NGS), delusion-hallucination (DHS), and thought disorganization (TDS) could be formulated. Discrete genetic endowment of these three symptom dimensions was not found as shown by the low concordance in sib pair analysis (kappa = 0.20–0.30). Thirty-seven pairs (80.4%) and 21 pairs (45.7%) had liability, defined by the presence of NGS in any one member of the coaffected sib-pairs, of NGS of "any degree," and of "severe degree" in 46 sib-pairs, respectively. Both groups had high prevalence (59.1–81.0%) of positive symptoms. Another 9 (19.6%) and 25 (54.3%) pairs had no liability of NGS of "any degree" or of "severe degree" out of 46 sib-pairs, respectively. These two groups had high concordance (kappa = 0.45–1.00) of TDS or DHS between coaffected sib-pairs. Based on the results, it is hypothesized that schizophrenia, as defined by DSM-III-R, may consist of two subtypes: one has liability of NGS and a high prevalence of positive symptoms, while the other has only positive symptoms. *Am. J. Med. Genet. 74:1–6, 1997.*

KEY WORDS: positive symptom; negative symptom; schizophrenia; sib-pair

INTRODUCTION

Heterogeneity is an important issue in schizophrenic research. Resolution of the heterogeneity problem will determine the confusing nosological status of schizophrenia and provide a sound basis for the investigation of etiology, pathophysiology, and specific treatment of schizophrenia. However, schizophrenic researchers do not have a firm idea as to the exact number of causative etiological factors and the corresponding pathophysiological processes that form the phenomenological heterogeneity of schizophrenia. Precisely how the symptoms of schizophrenia should be grouped is unclear. Tsuang [1990] proposed that it is imperative to study the competing heterogeneity models of schizophrenia in order to determine valid subtypes of schizophrenia.

This study examines the dimensions of positive and negative symptoms to study the concordance between the coaffected sib-pair of schizophrenia under the hypothesis that the negative and positive symptom dimensions may have different pathophysiological processes and different genetic etiological factors. Schizophrenic cases with positive or negative symptoms were found to have different treatment response patterns and different clinical outcomes [Strauss et al., 1974a; Snezhnevsky, 1968; Crow, 1980; Hwu et al., 1995]. The negative symptoms were more stable than positive symptoms in the follow-up course [Addington and Addington, 1991]. Negative symptoms might be independent, at least partially, from positive symptoms [Kay, 1991; Greden and Tandon, 1991; Andreasen et al., 1995]. Liddle et al. [1992] found distinct features of cerebral blood flow in positron emission tomography of schizophrenic patients with negative symptoms and positive symptoms of reality distortion and thought disorganization.

In reviewing the genetic relationship between schizotypal disorder and schizophrenia, Torgersen [1985] showed that social function related to negative symptoms was more genetically related to schizophrenia. Sautter et al. [1987] found that a family history of schizophrenia correlated with negative symptoms. However, Fenton and McGlashan [1991] could not find this correlation. Kay et al. [1986a] reported that this

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correlation was found only in a long-term chronic population (>10 years), but not in a more acute sample (<3 years of illness). Kay et al. [1986b] also reported that the occurrence of negative symptoms was positively correlated with a family history of major psychiatric disorders, but negatively with a family history of affective disorders. Basett et al. [1993, 1994] found negative syndrome to be presented in coaffected schizophrenic cases in a family. Tsuang et al. [1991] reported that negative symptom scores in the relatives of schizophrenic cases were significantly higher than in the relatives of depressive controls.

Twin study by Dworkin and Lenzenweger [1984] found an increased concordance rate for schizophrenia in twins of probands with two or more negative symptom items. This relationship was not found in positive symptoms. It was also found that the negative symptom level, but not the positive symptom level, was correlated significantly between pairs concordant for schizophrenia. Corrigall and Murray [1994] found that early onset psychosis, a disease with prominent negative symptoms, had an excessive probandwise concordance rate in monozygotic twins (33.0%) as compared with that of the dizygotic twins (0.00%).

Family and twin studies suggest a strong tendency of genetic distinction between schizophrenic cases with and without negative syndrome. More genetic study data are needed in this area. However, two important facts, as presented in next paragraph, deserve attention in planning further genetic validity studies of positive and negative syndrome.

Strauss and Carpenter [1974b] found that there were three symptom clusters of delusion-hallucination, thought disorganization (thought process disorder), and function impairment (negative symptom), forming the central psychopathology of schizophrenia. Factor analysis of positive and negative symptoms had also consistently confirmed the existence of these three factors [Bilder et al., 1985; Andreasen, 1986; Thompson and Meltzer, 1993, Silver et al., 1993; Lin et al., 1996]. Liddle et al. [1992] also confirmed this hypothesis by cerebral blood flow study. Another important fact which needs to be considered is that acute state assessment of negative symptoms was found to be unstable over time [Lindenmayer et al., 1986; Ohita et al., 1990], and was stable in subsided state [Addington and Addington, 1991; Andreasen et al., 1991].

This study hypothesizes that the clustering of positive and negative symptoms may reveal 3 symptom dimensions in both the proband group and the coaffected sib group. These three symptom dimensions will have high concordance in the coaffected schizophrenic sib-pairs with the hypothesis of independent genetic endowment. Considering that negative symptom dimension is an integral part of the clinical manifestation in some proportion of schizophrenic patients [Rinh et al., 1991], negative and positive symptoms are dependent in some proportion of cases, and negative symptom cluster runs in a family, the authors assume that any affected sib having a negative symptom will imply the coexistence of negative symptoms in another coaffected sib, i.e., there exists a liability of negative symptoms in the coaffected sib-pairs, even though the negative symptom may not appear at the same time in these two coaffected sib-pair members. Under this assumption, the second hypothesis to be tested is that there is another group of schizophrenic patients who has only liability of positive symptoms, delusion-hallucination, or thought disorganization, which will have high concordance in coaffected sib-pairs. The positive symptom of this group is independent from the liability of the negative symptom.

MATERIALS AND METHODS

Forty-six schizophrenic probands (male 27, female 19) who had coaffected sibs (male 26, female 20) with the same clinical diagnosis of schizophrenia were recruited for study after informed consent was obtained. These cases were personally interviewed by the authors using the psychiatrist diagnostic assessment schedule [Hwu, 1991]. Medical charts were reviewed. These data were used together for diagnostic assessment according to DSM-III-R schizophrenic criteria [American Psychiatric Association, 1987]. Clinical and demographic variables were similar between the proband and coaffected sib groups who had a mean age of 28.7 (±5.8) and 29.2 (±6.2), mean age of onset at 19.5 (±5.9) and 19.2 (±4.6), and mean duration of illness of 9.0 (±4.5) years and 10.0 (±6.8) years, respectively. The educational level, history of medication, and clinical course were similar between the two groups. Cases of schizoaffective disorder, schizotypal disorder, and schizophreniform disorders were not included in the study.

Clinical psychopathological symptoms were assessed using the Chinese positive and negative symptom rating scale (PNSRS). The positive symptom items in the PNSRS included hallucination, delusion, unusual behavior, and thought disorganization; the negative symptom items included flat affect, alogia, avolition, and asociality. Definitions of these items followed those provided by Andreasen [1982, 1984a,b]. Items of the PNSRS were rated on a 6-point scale ranging from "0" to "5" (degree of severity of symptoms). Interrater reliability was examined using the Spearman rank correlation (SRC) and SRC values ranged from 0.73 to 0.92. The interrater reliability was considered to be satisfactory.

All these recruited probands and their coaffected schizophrenic sibs were at a subsided state of clinical condition when the positive symptoms and negative symptoms were rated. The ratings were used for correlation analysis. The presence of a positive symptom was considered a clear-out phenomenon, even if it was mild, and the rating score of being equal to or over "1" was considered as present. On the other hand, the presence of a negative symptom of mild degree is relatively unclear. For the definite presence of a negative symptom, a score equal to or over 2 was considered to be necessary. Thus, to categorize symptom dimensions, each positive symptom dimension was divided into an absent (rated 0) or present (rated 1, 2, 3, 4, and 5) category, and each negative symptom dimension was divided into an absent (rated 0 and 1) or present (rated ≥2) category.

Analyses were performed in three steps. In Step 1, the Spearman rank correlation of eight symptom items, including four positive and four negative ones, was performed. The global negative rating was also included in the correlation analysis. The degree of symptom correlation was examined. Those symptom items without significant correlation were considered to be of separate symptom dimensions. Those with high correlation were grouped together as a single dimension for sib pairwise concordance analysis. Step 2 was the sib pairwise analysis of degree of concordance of separate symptom dimensions. Step 3 of the analysis was performed by controlling the presence of the negative symptom dimension assuming the presence of liability of the negative symptom in the coaffected pairs who have the negative symptom in any member of the pairs, before analyzing the degree of concordance of separate positive symptom dimensions. Degree of concordance was examined using the statistics of kappa [Bartko and Carpenter, 1976] and random error coefficient [Maxwell, 1977].

RESULTS

Table I shows the values of correlation coefficients of all symptom items using Spearman rank correlation. The lower and upper halves of this matrix represent the correlation coeffeicients of the proband and coaffected sib groups, respectively. Both sample groups had a high correlation of delusion and hallucination. Neither delusion nor hallucination had significant correlation with thought disorganization and all negative items. Behavioral symptom was found to be correlated with all other positive dimensions. Thought disorder was found to have a mild to moderate degree of correlation with nearly all negative symptom items (correlation coefficients: 0.29–0.45). It is very interesting to note that all negative symptoms were highly correlated (correlation coefficient: 0.56–0.99) with each other, including the global rating. It is therefore reasonable to use the global rating of negative symptom as an indicator of negative symptom dimension (NGS). In sib pairwise analysis of concordance of symptom dimensions, delusion and hallucination were combined as a single dimension of delusion–hallucination symptom (DHS). The presence of either delusion or hallucination indicated the presence of DHS. Thought disorder symptom (TDS) was considered as a single symptom dimension. Behavior symptom was not used for pairwise categorical analysis of concordance.

Table II shows the summaried results of concordance analyses of DHS, TDS, and NGS between the proband and coaffected sib groups. Among 46 coaffected sib pairs, 30 pairs (65.2%) were concordant, and 16 pairs (34.8%) were discordant in the DHS, 30 (65.2%) concordant and 16 (34.8%) discordant pairs were found in the analysis of TDS, and 31 (67.4%) concordant and 15 (32.6%) disordant pairs were found in the analysis of NGS. All these analyses had a low degree of concordance in kappa and random error statistical analyses. It deserves attention that 22 (47.8%) out of 46 pairs had NGS in both pair members. Seventeen pairs (37.0%) and only 7 pairs (14.9%) had DHS and TDS in both pair

TABLE I. Spearmen Rank Correlation Coefficient of Every Symptom Rating at Subsided Clinical State in Proband Group and the Coaffected Sib Group[a]

	Hallucination	Delusion	Unusual behavior	Thought disorder	Flat affect	Avolition	Alogia	Asociality	Global negative rating
Hallucination	1.00	0.69***	0.60***	0.04	−0.13	0.05	0.08	0.15	0.11
Delusion	0.49***	1.00	0.52***	0.20	0.07	0.05	0.19	0.14	0.19
Unusual behavior	0.29*	0.36**	1.00	0.28*	−0.20	0.01	0.06	0.21	0.15
Thought disorder	0.04	−0.05	0.45**	1.00	0.13	0.29*	0.29*	0.45**	0.37**
Flat affect	0.13	0.05	0.10	0.45**	1.00	0.71***	0.76***	0.60***	0.71***
Avolition	0.01	−0.05	0.17	0.28*	0.72***	1.00	0.73***	0.76***	0.81***
Alogia	−0.09	−0.16	0.10	0.31*	0.61***	0.78***	1.00	0.63***	0.87***
Asociality	0.07	−0.09	0.34*	0.35**	0.56***	0.69***	0.66***	1.00	0.99***
Global negative rating	0.07	−0.05	0.32*	0.26*	0.70***	0.86***	0.86***	0.64***	1.00

[a] Lower half of the matrix: proband group; upper half matrix: coaffected sib group.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

TABLE II. Concordance of Delusion–Hallucination Symptom (DHS), Thought Disorganization Symptom (TDS), Negative Symptom (NGS), and Severe Negative Symptom (SNGS) between Probands and Coaffected Sibs*

Proband	+	−	+	−	
Coaffected sib	+	−	−	+	Statistics
DHS	17	13	7	9	Kappa = 0.30 Random error = 0.30
TDS	7	23	9	7	Kappa = 0.21 Random error = 0.30
NGS	22	9	7	8	Kappa = 0.29 Random error = 0.35
SNGS	8	25	4	9	Kappa = 0.35 Random error = 0.43

* DHS, TDS, NGS, and SNGS as defined in the text.

members, respectively. By grouping the negative symptoms into severe (SNGS) (rating 4 and 5) and nonsevere categories (ratings 0, 1, 2, 3) (NSNGS), 8 pairs (17.4%) were found to have SNGS in both sib-pair members. There were 25 pairs who had NSNGS in both pair members. The analysis of concordance revealed a moderately high degree of concordance (kappa = 0.35, random error = 0.43).

Table II shows that 37 pairs (80.4%) were assumed to be included in the group with liability of NGS. Among these 37 pairs, 22 pairs (59.5%) had NGS in both pair members. In these 37 pairs, 28 pairs (75.7%) and 22 pairs (59.5%) were found to have DHS and TDS in any one member of the pairs, respectively. The remaining 9 pairs (19.6%) were free from liability of NGS. In this group, the prevalence rates of DHS and TDS were 55.6 and 11.1%, respectively. Table III shows that 7 pairs (77.8%) out of these 9 pairs were concordant in DHS. The values of kappa (0.5) and random error coefficient (0.56) were high in the analysis of concordance of DHS. A complete concordance (kappa = 1.00) of TDS in this group was found.

If NGS is classified into SNGS and NSNGS as stated above. Table II shows that there were 21 pairs (45.7%) having liability of SNGS. In these 21 pairs, 17 pairs (81.0%) and 12 pairs (57.1%) were found to have DHS and TDS in any one member of the pairs, respectively. The remaining 25 pairs (54.3%) out of 46 pairs were without liability of SNGS. Sixteen pairs (64.0%) and 11 pairs (44.0%) out of these 25 pairs were found to have DHS and TDS in any one member of the pairs, respectively. Table IV shows that the concordance of DHS was low, but the concordance of TDS was high in the 25 sib-pairs without liability of SNGS.

TABLE III. Concordance of Delusion–Hallucination Symptom (DHS) and Thought Disorganization Symptom (TDS) between Probands and Coaffected Sibs by Controlling the Presence of Negative Symptom*

Proband	+	−	+	−	
Coaffected sib	+	−	−	+	Statistics
DHS	3	4	1	1	Kappa = 0.55 Random error = 0.56
TDS	1	8	0	0	Kappa = 1.00 Random error = 1.00

* Using the pairs without negative symptom in any member for analysis.

TABLE IV. Concordance of Delusion–Hallucination Symptom (DHS) and Thought Disorganization Symptom (TDS) between Probands and Coaffected Sibs by Controlling the Presence of Severe Negative Symptom*

Proband	+	−	+	−	
Coaffected sib	+	−	−	+	Statistics
DHS	7	9	5	4	Kappa = 0.28 Random error = 0.28
TDS	5	14	4	2	Kappa = 0.45 Random error = 0.52

* Using these coaffected sib-pairs without severe negative symptom in any member for analysis.

DISCUSSION

This study design is unique in its use of coaffected schizophrenic sib pairs to tackle the heterogeneity issue by hypothesizing that there are three symptom dimensions of DHS, TDS, and NGS which have different genetic causes. Because the assessment of negative symptoms at a subsided state is more stable over time [Addington and Addington, 1991], it could be inferred that these symptoms in a subsided state might represent a stable or basic pathological state. It is therefore reasonable to study the negative and positive symptoms of the subsided state by coaffected sib-pair analysis to explore their possible discrete genetic contributions.

Using a Spearman rank correlation, these positive and negative symptom items could be classified into three dimensions of DHS, TDS, and NGS. Since the correlations between TDS and the negative symptom items ranged from mild to moderately, the degree of independence between TDS and NGS might only be of moderate degree. Delusion and hallucination were merged as one symptom dimension of DHS because of their high correlation. Behavior symptom dimension was considered to be a nonspecific positive symptom because of correlation with both DHS and TDS, and was therefore deleted from the concordance analysis.

These results substantiate the classification of these symptom dimensions into three dimensions for concordance study using coaffected schizophrenic sib-pairs. The results of concordance analysis show low kappa and random error coefficient values. The first hypothesis of this study which stated that DHS, TDS, and NGS dimensions are independent and have a high concordance of every symptom dimension between coaffected schizophrenic sibs, was thus not supported (Table II). The NGS was categorized into SNGS and NSNGS using a higher rating score of 4 or 5 for SNGS. The kappa and random error values of the concordance analysis on SNGS showed moderately high at 0.35 and 0.43, respectively. These results suggest that the negative symptom of severe degree (SNGS) will reveal a possible genetic etiological factor. This suggestion is consistent with the findings of previous genetic epidemiological

studies which found that NGS runs in families [Tsuang et al., 1991; Bassett et al., 1993, 1994] and that cases with NGS had higher genetic endowment [Dworkin and Lenzenweger, 1984; Sautter, 1987; Kay et al., 1986a,b].

Based on these previous genetic epidemiological findings, this study assumed that there was a liability of NGS in the coaffected sib-pair if NGS existed in any one member of the pair. Under this assumption, we found 37 (80.4%) out of 46 pairs had a liability of NGS. Of these 37 pairs, 28 pairs (75.5%) had DHS and 22 pairs (59.5%) had TDS in any one member. The prevalence figures of TDS in this group (59.5%) was higher than that in the group (11.1%) of 9 pairs without liability of NGS. But the prevalence rate of DHS was similar between these two groups (75.5 and 55.6%, respectively). In these 9 pairs, without liability of NGS, the concordance of TDS in coaffected pairs was complete (kappa = 1.00). The concordance of DHS in this group was also high (kappa = 0.55). These findings support the second hypothesis of this study that schizophrenia as defined by DSM-III-R criteria is composed of two discrete syndromes. The first syndrome has a liability of NGS and represents about 80% of all DSM-III-R schizophrenic cases. NGS and positive symptoms are dependent in this type of schizophrenia. The second syndrome has no liability of NGS, and only has liability of positive symptoms of either DHS or TDS. This syndrome represents about 20% of all schizophrenic cases.

If the NGS is divided into severe (SNGS) and not severe (NSNGS) groups, then 21 pairs (45.7%), about half of the study sample pairs, had liability of SNGS. The prevalence rates of DHS and TDS in the groups with SNGS and NSNGS were around 45–80%, and were comparable between these two groups though higher (81.0 versus 64.0% in TDS; 57.1 versus 44.0% in TDS) in the SNGS group. The concordance analysis shows (Table IV) high concordance of TDS between affected sib-pairs. But the concordance of DHS in the coaffected sib pairs was low.

These findings suggest that positive symptoms, frequently found in acute exacerbated conditions, have two different pathological meanings. One is related to a liability for NGS and another is independent from negative symptoms. This finding supports our previous hypothesis that positive and negative symptoms were as two axes of schizophrenic pathology with partial independence [Hwu et al., 1995]. The syndrome with liability of negative symptoms is associated with the concomitant epiphenomenon of positive symptoms, which are considered to be dependent on the pathophysiological process of liability of negative symptoms. Another schizophrenic syndrome has liability only of positive symptoms, and has no liability of negative symptoms. The epiphenomenological manifestations of positive symptoms are similar to that of the previous syndrome with liability of NGS. This theoretical formulation deserves further validity study. Although the theoretical basis is different, the statement of this hypothesis is similar to that presented by Corrigall and Murray [1994] in their examination of the validity of a novel classification of schizophrenia. They found a higher concordance rate in monozygotic than dizygotic twins in both of the two types of schizophrenia studied. The subtype with liability of NGS might be similar to the so called "congenital type" of psychosis, which has prominent negative symptoms and the subtype with positive symptoms only, without liability of NGS, might be similar to the so called "adult-onset type." The theoretical formulation proposed by the authors is consistent with one of the possible research models, the overlapping pathophysiological model with overlapping epiphenomenological manifestations, as proposed by Tsuang [1990] in his conceptual analysis of a research strategy for studying the heterogeneity of schizophrenia. The distinct causative etiological process for liability of negative symptoms will cause three pathophysiological processes of DHS, TDS, and NGS. On the other hand, the distinct causative etiological process of positive symptoms will cause two pathophysiological processes of DHS and TDS. These formulations offer a reasonable explanation for the discrepancy in results of clinical and genetic studies concerning negative and positive syndromes and may indicate the direction for biological studies including molecular genetic studies on the etiology of schizophrenia. Further study using a larger population will be worthwhile for replicating these findings.

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