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

Hai-Gwo Hwu,1* Yuan-Ching Wu,4 Sandy F.-C. Lee,4 Ling-Ling Yeh,1 Shi-Chin Gwo,4 Hey-Chi Hsu,2 Ching-Jui Chang,1 and Wei J. Chen3

1Department of Psychiatry, College of Medicine, National Taiwan University, Taipei, Taiwan
2Department of Pathology, College of Medicine, National Taiwan University, Taipei, Taiwan
3Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan
4Provincial Taoyuan Psychiatric Center, Taipei, Taiwan

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. © 1997 Wiley-Liss, Inc.

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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
correlation was found only in a long-term chronic popu-
lation (>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
related with a family history of major psychiatric
disorders, but negatively with a family history of affec-
tive 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 ne-
gative symptom scores in the relatives of schizophrenic
cases were significantly higher than in the relatives of
depressive controls.

Twin study by Dwarkin and Lenzenweger [1984]
found an increased concordance rate for schizophrenia
in twins of probands with two or more negative sym-
tom items. This relationship was not found in positive
symptoms. It was also found that the negative symp-
tom level, but not the positive symptom level, was cor-
related significantly between pairs concordant for
schizophrenia. Corrigall and Murray [1994] found that
early onset psychosis, a disease with prominent nega-
tive symptoms, had an excessive probandwise concor-
dance 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 atten-
tion in planning further genetic validity studies of pos-
itive 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 fac-
tors [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 posi-
tive and negative symptoms may reveal 3 symptom di-
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 en-
dowment. Considering that negative symptom dimen-
sion 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
coeexistence 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
coaffect sib-pair members. Under this assumption,
the second hypothesis to be tested is that there is an-
other group of schizophrenic patients who has only li-
ability of positive symptoms, delusion-hallucination, or
thought disorganization, which will have high concor-
dance in coaffected sib-pairs. The positive symptom of
this group is independent from the liability of the neg-
ative 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 re-
cruited for study after informed consent was obtained.
These cases were personally interviewed by the au-
thors using the psychiatrist diagnostic assessment
schedule [Hwu, 1991]. Medical charts were reviewed.
These data were used together for diagnostic assess-
ment 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 ill-
ness of 9.0 ± 4.5) years and 10.0 ± 6.8) years, respec-
tively. 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 as-
essed using the Chinese positive and negative symp-
tom rating scale (PNSRS). The positive symptom items
in the PNSRS included hallucination, delusion, un-
usual behavior, and thought disorganization; the ne-
gative symptom items included flat affect, alogia, avoli-
tion, 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 corre-
lation 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 pre-
sence of a negative symptom of mild degree is relatively
unclear. For the definite presence of a negative symp-
tom, a score equal to or over 2 was considered to be ne-
necessary. Thus, to categorize symptom dimensions, each
positive symptom dimension was divided into an ab-
sent (rated 0) or present (rated 1, 2, 3, 4, and 5) cate-
gory, and each negative symptom dimension was di-
vided 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 coefficients 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 summarized 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%) discordant 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 members.
members, respectively. By grouping the negative symptoms into severe (SNGS) 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.

**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

| 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 |
| TDS | 7 | 23 | 9 | 7 | Kappa = 0.21 |
| NGS | 22 | 9 | 7 | 8 | Kappa = 0.29 |
| SNGS | 8 | 25 | 4 | 9 | Kappa = 0.35 |

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

| 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 |
| TDS | 1 | 8 | 0 | 0 | Kappa = 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 |
| TDS | 5 | 14 | 4 | 2 | Kappa = 0.45 |

* Using these coaffected sib-pairs without severe negative symptom in any member for analysis.
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 (95.5%) had TDS in any one member. The concordance 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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