Family transmission of positive and negative symptoms in familial and sporadic schizophrenia

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Transmisión familiar de los síntomas positivos y negativos en la esquizofrenia familiar y esporádica

Summary

Introduction. *A genetic component is recognized as a cardinal feature in the etiology of schizophrenia that is presently conceived as a complex disease. However, identifying its molecular bases has become a problem, mainly due to the difficulties that the schizophrenic phenotype presents. The aim of this study is to determine whether the positive and negative symptoms are differentiated from each other according to family history in a family study using familial/sporadic strategy.*

Methods. *601 subjects were studied (196 schizophrenics, 205 first degree relatives and 200 controls). A SCAN system and the diagnosis criteria of DSM IV were used. For the familial study the FIGS and PANSS scales were applied. Families were grouped into familial or sporadic groups according to family aggregation. Comparisons were made using the ANOVA.*

Results. *The groups of patients and the first degree relatives with familial schizophrenia showed significantly higher scores in the negative sub-scale than did the sporadic schizophrenia subjects. Behavior of the first degree relatives with sporadic schizophrenia was similar to the control group. Positive sub-scale scores and general psychopathology showed no differences in the patients and their relatives according to familiar aggregation.*

Conclusions. *This study confirms previous results that negative symptoms are more frequent in schizophrenics and their first degree relatives with familial schizophrenia. Therefore, it can be said that negative symptoms are a clinical phenotype more related to the genetic etiology.*

Key words: *Positive and negative symptoms. Familiar and sporadic schizophrenia.*

Resumen

Introducción. *Se reconoce un componente genético en la etiología de la esquizofrenia concebida en estos momentos como una enfermedad compleja. Identificar las bases moleculares de esta enfermedad se ha convertido en un problema por las dificultades del fenotipo esquizofrénico. El objetivo de esta investigación fue analizar si existen diferencias relacionadas con la presencia de los síntomas positivos y negativos en un estudio familiar utilizando la estrategia familiar/esporádica.*

Método. *Se estudiaron 601 sujetos (196 esquizofrénicos, 205 familiares de primer grado y 200 controles). Se utilizó el sistema SCAN y se usaron los criterios diagnósticos del DSM-IV. Para el estudio familiar se aplicó el FIGS y la Escala PANSS. La esquizofrenia se clasificó en familiar o esporádica de acuerdo al número de esquizofrénicos en la familia. La comparación entre los grupos se realizó con el test de análisis de varianza ANOVA.*

Resultados. *La esquizofrenia familiar presentó mayor puntuación en la subescala negativa en los pacientes y sus familiares de primer grado en relación con la esporádica. Los familiares esporádicos se comportaron de forma similar al grupo control. Los grupos familiar y esporádico se comportaron de forma similar en las subescalas positiva y de psicopatología general.*

Conclusiones. *Este estudio confirma resultados previos, donde se ha descrito que los síntomas negativos se presentan más en la esquizofrenia familiar, en los pacientes y en sus familiares. Por tanto pudiéramos decir que los síntomas negativos son un fenotipo clínico más relacionado con la etiología genética.*

Palabras clave: *Síntomas positivos y negativos. Esquizofrenia familiar y esporádica.*

INTRODUCTION

The results of family, adoption and twin studies have demonstrated a genetic component in the etiology of schizophrenia, presently conceived as a complex disease. In spite of the evidence, identifying the molecular bases of this disease has become a difficult problem to solve[1-9]. The problem not only occurs because this is a complex disease from the genetic point of view, but also due to the difficulties of the phenotype to be studied. The

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errors when obtaining results may be due to difficulties in the definition of a hereditary phenotype[10-12]. Classic strategies to study the phenotype, aimed at applying categorical clinical measurement instruments and the use of «schizophrenic spectrum», are not sufficient for this purpose.

The categorical clinical measurement basically focuses on the psychotic picture and psychosis is presently seen by many authors as something secondary, comparable with fever[13]. The dimensional clinical approach, study of more specific clinical symptoms and search for subclinical traits in first degree relatives may help in the search for the disease's genetic bases[14-18].

Positive and negative dimensions measured by the positive and negative symptoms scale (Scale for the Positive and Negative Syndrome of Schizophrenia, PANSS; Kay et al., 1987) have been analyzed in several family studies. The result found was that schizophrenic patients with several affected relatives have a greater magnitude of negative symptoms and greater resistance to treatment[19-21]. Negative symptoms have also been reported in first degree relatives of schizophrenic patients[20,21]. Studies of twins show that the negative symptoms have a greater agreement than the positive ones[20-27]. Index cases with negative symptoms predict more schizotypal factors in relatives[25]. Some studies have reported a modest agreement with negative symptoms among twins (Hwu et al. 1997[23], using the PANSS's Chinese version). Cardno, 1999[28], reported family aggregation of negative symptoms in 89 schizophrenic couples as non-significant[28]. Baron et al., 1992[29] studied 65 chronic schizophrenics and reported that the negative symptoms had a low genetic component.

Presence of symptoms in first degree relatives has been mentioned by many authors as a risk factor of suffering the disease. Tsuang[20] includes the presence of negative symptoms in first degree relatives as a criterion to consider for the diagnosis of schizotaxia, a term used to refer to first degree relatives who have disease trait markers and who do not have a psychotic picture. More investigations are required to retort the presence of these disorders in the relatives and validate this term.

The search for which symptoms are more inheritable and their manifestation in first degree relatives in the familial schizophrenia is one of the strategies of psychiatric genetics to validate phenotypes that have more relationship with genetic etiological bases[30-33]. This investigation aimed to analyze if there are differences related with the presence of positive and negative symptoms in a familial study using the «familial/sporadic» strategy.

METHODS

Sample

A total of 601 subjects were studied; 196 were out-patient schizophrenic patients in two communities, one in the City of La Havana and the other in the providence of Sancti Spíritus. The patients were interviewed using the SCAN system (Schedules for Clinical Assessment in Neuropsychiatry)[34]. The DSM-IV criteria[35] were used for the diagnosis. In addition, 205 first degree relatives of the index cases (parents, siblings and children of the index cases) and 200 normal subjects without personal or family background of psychiatric diseases were studied. All accepted and signed the terms of the consent to perform the study.

Family study

The FIGS (Family Interviews for Genetic Studies), (NIMH-Molecular Genetics Initiative, 1991) was used for the family study. The interview for genetic studies (FIGS) is a guideline to gather diagnostic information on the relatives of patients with schizophrenia and bipolar disorders. A genealogical tree is elaborated to apply this instrument and it is reviewed with the informer. General screening questions are made regarding all the known relatives and the profile sheets and symptom lists (depression, mania, alcohol, and other drug abuses, psychosis, schizoid/paranoid /schizotypal personality disorders) are administered based on the responses. These specific lists of symptoms are applied if, based on the informer's responses to the general screening questions, the interviewer suspects that the psychopathology evaluated in each specific list reflects symptoms present in the subject. The interview was applied to at least two family informers. The interviewers were psychiatrists previously trained in the use of the instrument.

Schizophrenics and first degree relatives were divided into two groups according to the presence of one or more schizophrenics in the families studied, in addition to the index case (familial aggregation). If there were more schizophrenics, it was considered as a familial schizophrenia and, on the contrary, as sporadic schizophrenia.

Evaluation of the symptoms

The Spanish version[36] of the Positive and Negative Syndrome Scale of Schizophrenia (PANSS) (Kay et al., 1987) was used for the evaluation of psychopathology. The schizophrenic syndrome was evaluated from the dimensional perspective that measured the seriousness of the positive, negative and general psychopathology syndrome. It is made up of a positive and negative subscale that includes seven items each and a third 16 item general psychopathology subscale. Each item is scored according to a Likert scale having 7 intensity or seriousness grades that go from 1 (absence of symptom) to 7 (extreme seriousness of symptom). The scale was also administered to first degree relatives and normal subjects.

Statistical analysis

For the global comparison of the PANSS results in the index cases, first degree relatives and controls, the analysis of variance test (ANOVA) was used. The sum of the items of each subscale of the PANSS was used as dependent variable.

To compare the groups divided according to familial aggregation, the LSD *pos-hoc comparison* test of ANOVA was used. The tests were calculated for a 95 % significance index.

RESULTS

A total of 156 (79.5 %) of the sample of 196 schizophrenics diagnosed had the paranoid clinical form, 27 (13.7 %) responded to residual schizophrenia, 9 (4.5 %) to undifferentiated schizophrenia and 4 (2.0 %) to disorganized schizophrenia. The index cases studied came from a community sample of chronic patients, so that the disease course time was 22.15 ± 12 years, the disease onset age was 22.32 ± 6.3 years (tabla 1).

According to the familial aggregation type, 62 (41.33 %) were classified as familial schizophrenia and 88 (58.67 %) as sporadic schizophrenia.

The comparison of the positive, negative and general PANSS subscales in patients and first degree relatives divided according to the familial aggregation grade and control group is shown in our results. There are differences between the three subscales according to familial or sporadic behavior.

Schizophrenics with familial schizophrenia had a higher score in the negative subscale ($p = 0.01$) in relationship to the sporadic ones. In the familial group, those who belonged to familial schizophrenia were significantly different from the familial ones with sporadic schizophrenia ($p = 0.027$) and the control group ($p = 0.00$). The familial ones without history of familial aggregation behaved in a similar way to the control group ($p = 0.25$) (fig. 1).

When the LSD pos-hoc comparison test of the ANOVA test was performed, no significant difference was obtained in the positive subscale according to familial aggregation type in the patient group and familial one ($p = 0.79$ and $p = 0.72$, respectively) (fig. 2).

The general psychopathology subscale acts as a positive subscale, differentiating between patients, relatives and controls but not in regards to familial or sporadic aggregation ($p = 0.06$ and $p = 0.18$, respectively) (fig. 3).

TABLE 1. Sample characteristics

	Patients	*First degree relatives*	*Normal subjects*
N	196	205	200
Age	45.4 ± 12.1	53.34 ± 18.2	50.05 ±16.19
Gender (male)	96 (49%)	78 (38%)	78 (39%)
Skin color			
White	150 (76.5%)	161 (78.5%)	144 (72.0%)
Racially mixed	23 (11.7%)	24 (11.7%)	27 (13.5%)
Black	23 (11.7%)	20 (9.7%)	29 (14.5%)
Onset age	22.32 ± 6.3	—	—
Course time	22.15 ± 12.1	—	—

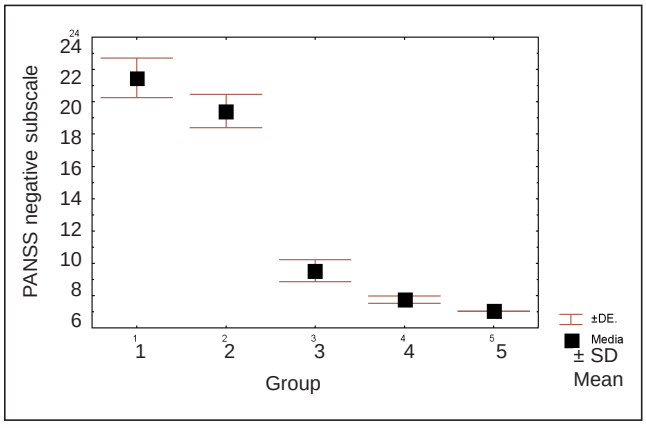

Figure 1. Comparison of the negative subscale total score according to presence of familial or sporadic schizophrenia in index cases and their first degree relatives. 1: familial schizophrenia. Patients. 2: sporadic schizophrenia. Patients. 3: familial schizophrenia. 1st degree relatives. 4: sporadic schizophrenia. 1st degree relatives. 5: control: control group.

CONCLUSIONS

Our results show that the groups studied behave differently in regards to PANSS scale measurements, suggesting that the negative symptoms have a close relationship with the disease's familial background. The pa-

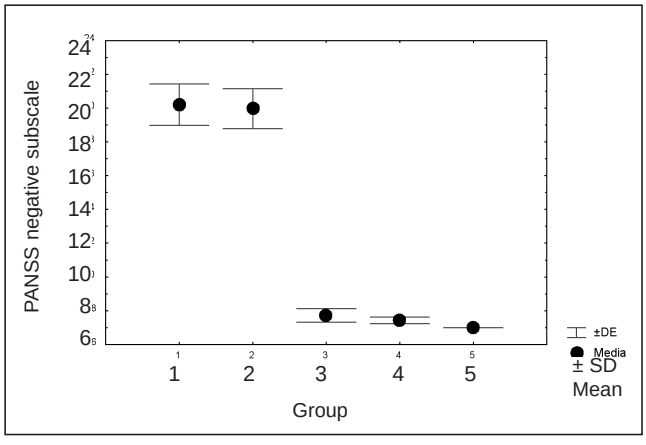

Figure 2. Comparison of the positive subscale total score according to presence of familial or sporadic schizophrenia in index cases and their first degree relatives. 1: familial schizophrenia. Patients. 2: sporadic schizophrenia. Patients. 3: familial schizophrenia. 1st degree relatives. 4: sporadic schizophrenia. 1st degree relatives. 5: control: control group.

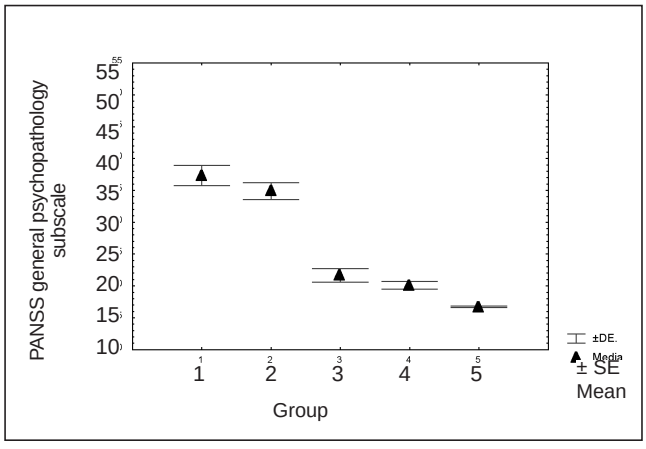

Figure 3. Comparison of the total score of the general psychopathology subscale according to the presence of familial or sporadic schizophrenia in index cases and their first degree relatives. 1: familial schizophrenia. Patients. 2: sporadic schizophrenia. Patients. 3: familial schizophrenia. 1st degree relatives. 4: sporadic schizophrenia. 1st degree relatives. 5: control: control group.

tients who have a higher score in the negative symptoms belong to familial schizophrenia. Presence of negative symptoms in the first degree relatives where there is familial aggregation suggests that the negative symptoms can be inherited.

These findings suggest a strong genetic component of the negative symptoms, demonstrated in other familial and twin studies[20-24].

This independence of positive and negative symptoms gives the idea of different domains of the disease, from the neurobiological point of view and perhaps the relationship with different cognitive functions and neural zones, so that there could be differences in the genetic etiological factors. From Bleuler up to date, the question of whether the schizophrenic syndrome is etiologically homogeneous has gone unanswered. The genetic approach to the disease could help to answer this[22].

Considering the above, the dimensional approach and study of individual symptoms that are more related with inheritance may provide more useful models for genetic investigation[14].

Familial-sporadic distinction has been reported as having low power and little sensitivity by Kendler (1987), who explains that genetic background would be better explained by familial schizophrenias, however, families with few generations studied, non-dominant models and incomplete penetrance could be reported as sporadic. Other authors report that sporadic schizophrenia may be phenocopies of genetic phenomena, the environmental factors acting more directly here than the perinatal events[30]. Our study observes a clear distinction between familial-sporadic in the PANSS scale measured symptoms. The negative symptoms have been reported with a high genetic relationship, not only in familial studies but also in studies of twins. Average subjects per families were 20 and more than three generations were reported in the genealogical trees. Thus, we consider that the sporadic report was not influenced by the families' size and structure in our investigation.

One of the limitations of this study is that it was performed with a community sample formed by chronic patients with a mean disease course of 22.15 ± 12.10 years. Some authors suggest that the long course with the use of typical neuroleptics could be influencing the presence of negative symptoms, while other evidence shows that the negative symptoms are primary and independent of evolution time and that they are found in the first degree relatives. The relatives studied present negative symptoms significantly in the familial schizophrenia and we believe that this finding has no direct relationship with disease course time in the patients. We suggest future studies to answer the investigation in first episode psychotic patients to measure the presence of these symptoms at the disease's onset, according to familial background.

The presence of negative symptoms in first degree relatives and their relationship with familial schizophrenia supports that reported on the «schizotaxia» concept, that includes the presence of negative symptoms in first degree relatives as a criterion to consider for the use of this term[20]. Genetic predisposition as risk factor to present the disease, combined with environmental factors, seem to support the diathesis-stress model, that postulates a biological type (genetic) vulnerability in which one or two environment factors would be added up (biological or psychological), precipitating the schizophrenia due to the sum of both factors. The finding of sub-clinical characteristics related with first degree relative disease is important both for genetic studies as well as for the detection of persons at risk of suffering it.

In conclusion, we could say that this study verifies previous results, in which it has been described that negative symptoms occur more in familial schizophrenia in both the patients as well as their first degree relatives. Given that the negative symptoms are a clinical phenotype that is more related with genetic etiology, we propose that the measurement of these symptoms should be considered for these genetic studies in both the patients as well as their first degree relatives.

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