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Schizophrenia Research 47 (2001) 159–165

SCHIZOPHRENIA RESEARCH

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Suspiciousness as a specific risk factor for major depressive episodes in schizophrenia

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Received 19 November 1999; accepted 24 January 2000

Abstract

Objective: Serious depression is a common and important complication of schizophrenia. In a prospective, population-based study, we tested the hypothesis that suspiciousness increases the risk for the later development of depression in schizophrenia. *Method*: Data came from the Epidemiological Catchment Area (ECA) study. Baseline clinical and demographic features were used to predict the onset of new episodes of depression at 1 year follow-up. As ECA diagnoses were based on lay interviews, which may have low sensitivity compared with clinical diagnoses, two overlapping groups of putative schizophrenia patients were defined. *Results*: Suspiciousness was associated with an increased risk of new episodes of depression in both patient groups, after accounting for demographic variables. There was no association between an increased risk of depression and either disorganization or hallucinations and delusions. *Conclusions*: Suspiciousness appears to be a specific risk factor for depression in psychotic groups. Interventions that decrease suspiciousness, or mitigate its isolating effects, might decrease the risk of serious depression and suicide.

Keywords: Depression; Risk factor; (Schizophrenia); Suspiciousness

1. Introduction

Serious depression is one of the many painful consequences of schizophrenia. Not only are depressive episodes common among people who suffer from schizophrenia, but these episodes probably make a major contribution to the high rate of suicide found in this group of patients (Wassink et al., 1999; Inskip et al., 1998; Hintikka et al., 1998), and depression may increase the risk of psychotic relapse (Mandel et al., 1982).

Many factors associated with schizophrenia probably contribute to the etiology of depression. Schizophrenic patients frequently have serious, chronic stresses, including problems in developing and maintaining relationships (Addington et al., 1998), as well as difficulties in functioning in other areas. It has also been proposed that abnormalities in brain dopaminergic systems play a more direct role in the etiology of depression in this group (Vijayakumar and Meti, 1999).

The variance in clinical features, long-term

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0920-9964/01/$ - see front matter
PII: S0920-9964(00)00030-X

course, and treatment response that is found in schizophrenia raises the question of whether a group of patients with specific clinical features is at particular risk for depression. Demographic features have been associated with suicide (Heila et al., 1997) in schizophrenia, as well as risk of depression in other populations (Bland, 1997). In a retrospective study, we found that suspiciousness was associated with a history of major depressive episodes in two groups of patients with schizophrenia, one consisting of outpatients and the other consisting largely of patients in an acute exacerbation (Kirkpatrick et al., 1996). In a further test of the hypothesis that suspiciousness is a risk factor for major depressive episodes in people with schizophrenia, we examined data from a prospective, population-based study. We also assessed the specificity of this relationship by considering demographic variables and other psychotic symptoms as risk factors for depression.

2. Methods

Data came from the five sites of the Epidemiological Catchment Area (ECA) study. At each site, some 3000 individuals were assessed initially (Regier et al., 1993). There were two 'waves' of interviews, separated by 1 year, between 1980 and 1984. Approximately 12% of the original respondents did not participate in the follow-up interview (Eaton and Kessler, 1985; Regier et al., 1993). Psychiatric symptoms were assessed in both waves with the National Institute of Mental Health Diagnostic Interview Schedule, or DIS (Robins et al., 1981), a structured interview that yielded DSM-III diagnoses. The DIS was administered by lay interviewers.

In a study comparing the DIS diagnosis of schizophrenia with a clinical diagnosis, although the specificity was 99.4%, the sensitivity was 24% and the overall concordance for the diagnosis of schizophrenia was low, with a kappa of 0.19 (Anthony et al., 1985). Other studies have also suggested that the DIS, especially in the hands of lay interviewers, may result in diagnoses with low sensitivity but good specificity for schizophrenia (Pulver and Carpenter, 1983; Escobar et al., 1986). Because of the problems with the diagnosis of schizophrenia, we used two different definitions of a putative schizophrenia group, and conducted the same analysis in both. The first group was composed of subjects receiving a diagnosis of schizophrenia on the basis of the DIS interview. The second group consisted of subjects with four or more of the symptoms commonly found in schizophrenia. There were 15 such items: two for disorganization, three for suspiciousness, nine for other delusions and hallucinations, and one for blunted affect. The rationale for defining this second group came from comparisons of clinical diagnoses and diagnoses generated by lay interviewers using structured interviews (Pulver and Carpenter, 1983; Kendler et al., 1996), which suggested that an increasing number of psychotic symptoms on structured interview was associated with a diagnosis of schizophrenia on clinical examination. For both putative schizophrenia groups, we included in the analyses only those subjects with no previous history of a major depressive episode at the time of the first assessment.

o assess the risk for incident cases of major depression, we used a logistic regression model. The dependent variable was a DIS diagnosis of depression in wave 2 (DIS item D2SMDEP). One of the exclusion criteria for this diagnosis was the presence of a psychotic disorder, diagnosed using the DIS, or an organic mental disorder as defined by a Mini-mental Status Exam (MSE) score of less than 18 DIS items (ORGBRAIN). In order to include psychotic disorder subjects, subjects who met the criteria for a major depressive episode but also met this exclusion criterion were included, as were those meeting the usual criteria for a depressive episode. However, subjects with fewer than 18 items correct on the wave 2 MSE were excluded. The independent variables for the logistic regression analysis were gender, age, race (as a 0/1 variable, Caucasian versus other), suspiciousness, disorganization, and hallucinations and delusions other than suspiciousness. Multiple factor analysis studies of schizophrenia have usually found hallucinations and delusions loading on a single factor (Buchanan and Carpenter, 1994; Andreasen et al., 1995; Liddle et al., 1989), with disorganization as a separate factor. Disorganization was defined as the sum of the DIS neologism and formal thought disorder items (DIS 260 and 261), each as a 0/1 variable.

Table 1
Demographic features of the two schizophrenia groups

	ECA Schizophrenia ($n = 66$)	≥ 4 psychotic symptoms ($n = 65$)
Age (±S.D.)	33.5 (11.6)	40.9 (17)
% male	39.4	43.1
Education in years (±S.D.)	11.1 (2.8)	10.32 (3.2)
% Caucasian	50	47.7

Suspiciousness was the sum of the three DIS suspiciousness items, each coded as a 0/1 variable (see Appendix A). The measure for other or non-suspicious hallucinations and delusions was the sum of 10 items, each coded as a 0/1 variable (see Appendix A). The range of possible scores for disorganization was 0–2, for suspiciousness 0–3, and for other hallucinations and delusions 0–10. Only subjects with no data missing for any of the variables were included in the analysis.

There were 66 subjects in the group with a DIS diagnosis of schizophrenia, and 65 subjects who had four or more psychotic symptoms. Thirty patients were in both groups (kappa = 0.41, $P < 0.001$). The demographic characteristics of the two groups were similar (Table 1).

3. Results

The incidence of first episodes of depression at follow-up was 3.2% in the total sample (453 of 14 073), 28.8% in the group with a DIS diagnosis of schizophrenia (19 of 66), and 15.4% in the group with four or more psychotic symptoms (10 of 65). Suspiciousness had a low sensitivity and a high specificity in both groups (Table 2). In both psychotic groups, the severity of suspiciousness was associated with the appearance of a first episode of depression, but the other psychotic symptoms were not (Table 3). In both groups, female gender was also significantly associated with an increased risk of depression. For suspiciousness, the effect size — a measure of the amount of variance accounted for by suspiciousness — was similar to that of gender (for the schizophrenia group, 0.25 and 0.26 for suspiciousness and gender, respectively, and for the group with four psychotic symptoms, 0.26 and 0.32).

Table 2
Suspiciousness and depression in schizophrenia[a]

	Suspiciousness	
	Yes	No
≥ 4 psychotic symptoms		
Depression		
Yes	10	0
No	43	12
Sensitivity = 10/10 + 43 = 19%		
Specificity = 12/0 + 12 = 100%		
ECA Schizophrenia diagnosis		
Depression		
Yes	15	4
No	30	17
Sensitivity = 15/15 + 36 = 33%		
Specificity = 17/4 + 17 = 81%		

[a] In contrast to the results in Table 3, these data are not corrected for demographic variables or other covariates. The groups in which suspiciousness are coded as 'yes' include subjects with a score of 1, 2, or 3.

4. Discussion

In a large population-based sample, we found that suspiciousness and female gender were associated with an increased risk for a new episode of depression in the subsequent year in two putative schizophrenia groups. In contrast, neither disorganization, nor hallucinations and delusions that were not suspicious, were associated with an increased risk of subsequent depression. The per cent of the variance accounted for by suspiciousness was similar to that of gender, and represents a 'medium' effect size (Cohen, 1988).

An important limitation of the study is that the diagnoses were based on lay interviews and patient recall. Information from other sources of information was not available, and clinical judgment could not be used to minimize false-positive and false-negative diagnoses. Previous research has documented problems with the psychiatric diagnoses in epidemiological studies, including the diagnosis of schizophrenia, although the ECA diagnoses of schizophrenia appear to have

Table 3
Relationship of baseline variables and the appearance of depression at follow-up

Group	Variable	Wald χ^2	df	*R*	*P* value
ECA Schizophrenia diagnosis	Gender	7.02	1	0.25	< 0.01
	Age	0.35	1	< 0.01	0.55
	Race	0.40	1	< 0.01	0.52
	Disorganization	1.26	1	< 0.01	0.26
	Other hallucinations and delusions	2.78	1	0.09	0.09
	Suspiciousness	**6.92**	**1**	**0.24**	**< 0.01**
≥ 4 Psychotic symptoms	Gender	8.04	1	0.32	< 0.01
	Age	3.33	1	0.15	0.60
	Race	1.79	1	< 0.01	0.18
	Disorganization	0.01	1	< 0.01	0.90
	Other hallucinations and delusions	2.53	1	0.09	0.11
	Suspiciousness	**5.22**	**1**	**0.24**	**< 0.03**

good specificity (Pulver and Carpenter, 1983; Anthony et al., 1985; Escobar et al., 1986). As a consequence, our groups may be closer to a nonaffective psychosis group than schizophrenia narrowly defined. However, the pattern of results did not change when we used another definition of a putative schizophrenia group, suggesting that suspiciousness is a risk factor within narrowly defined schizophrenia. The diagnoses of depression that we used may also have been liable to miscategorizations.

Other limitations relate to the scaling of the DIS, as the clinical variables did not all have the same possible range of scores, and the reliability may have differed among them. However, studies using other instruments have also suggested that the severity of disorganization is not correlated with the severity of dysphoric symptoms (Serretti et al., 1996; Kay and Murrill, 1990; Sham et al., 1996), and have also found a relationship between suspiciousness and depression (see below).

Twelve per cent of the original respondents did not participate in the follow-up interview, raising the possibility that our results were distorted by bias. Those who could not be located at follow-up were more often young, male, unmarried and Hispanic than the rest of the ECA sample, while the group refusing participation at follow up was on average older, married and uneducated (Eaton et al., 1992). However, we co-varied for demographic variables, and the specificity of the relationship with suspiciousness, but not with other psychotic symptoms, also suggests that bias was not the cause of the relationship that we found.

In this dataset it was not possible to determine whether suspiciousness preceded the onset of depression, or was an early manifestation of an emerging depressive episode. Suspiciousness would be a risk factor in either case, but the specificity of the relationship between depression and suspiciousness (but not other psychotic symptoms) suggests that the former was not an early symptom of the latter.

These findings are consistent with results from our retrospective study of two other patient groups (Kirkpatrick et al., 1996), as well as some other research. In the Chestnut Lodge study, a historical cohort study, both suspiciousness and delusions of all kinds (including suspiciousness) were more severe among schizophrenia-spectrum patients who committed suicide (Fenton et al., 1997). However, another study showed that suspiciousness was negatively correlated with depressive mood during the acute phase, although at the post-acute phase or at the residual phase no significant correlation existed between depressive and any positive symptoms (Dollfus et al., 1993). Two studies of the families of depressed probands have also shown a higher prevalence of paranoid personality or suspiciousness than in the families of control probands (Maier et al., 1994; Squires-Wheeler et al., 1989).

It would be interesting to know whether

more sensitive instruments would reveal a relationship between depression and suspiciousness of a nonpsychotic severity. The two family studies of depression mentioned above (Maier et al., 1994; Squires-Wheeler et al., 1989) suggest that a relationship between suspiciousness of a lesser severity and depression may exist outside of schizophrenia or nonaffective psychosis.

The suspicious person is concerned in a particular way about his or her relationships. Some other risk factors for depressive episodes also involve relationships, including the loss of a parent in childhood (Patten, 1991; Breier et al., 1988), loss of social support (Paykel, 1994; Brown, 1988), and living in an environment with high 'expressed emotion,', i.e. critical and intrusive relationships (Okasha et al., 1994). Primate models of depression are also based on isolating highly social monkeys (Katz, 1981). At the other end of the spectrum, patients with the deficit syndrome of schizophrenia, who as a group are defined in part by a loss of interest in relationships, may have a decreased risk of depressive episodes (Kirkpatrick et al., 1996), and are also characterized by less severe suspiciousness than are other patients with schizophrenia (Kirkpatrick et al., 1996).

Although it is not clear from our data that suspiciousness actually contributes to the etiology of depression, confirmation that it is a specific risk factor would have clinical implications, as the identification of suspicious patients would also be the identification of people at higher risk of depression and suicide. Closer monitoring and interventions to ameliorate the isolating effects of suspiciousness might help decrease the risk of depression in these patients.

Acknowledgements

Supported in part by PHS grant MH 40279.

Appendix A

Diagnostic Interview Schedule items used to define the severity of disorganization, suspiciousness and other hallucinations and delusions

Disorganization

1. *DIS 260*: Neologism (use of made-up or meaningless words).
2. *DIS 261*: Thought disorder (verbal production that makes communication difficult because of a lack of logical or understandable organization).

Suspiciousness

1. *DIS 118*: Have you ever believed people were watching you or spying on you?
2. *DIS 119*: Was there ever a time when you believed people were following you?
3. *DIS 120*: Have you ever believed that someone was plotting against you or trying to hurt you or poison you?

Other hallucinations and delusions

1. *DIS 121*: Have you ever believed that someone was reading your mind?
2. *DIS 122:* Have you ever believed you could actually hear what another person was thinking, even though he was not speaking, or believed that others could hear your thoughts?
3. *DIS 123:* Have you ever believed that others were controlling how you moved or what you thought against your will?
4. *DIS 124*: Have you ever felt that someone or something could put strange thoughts directly into your mind or could take or steal your thoughts out of your mind?
5. *DIS 125*: Have you ever believed that you were being sent special messages through television or the radio?
6. *DIS 126*: Any volunteered delusions
7. *DIS 129*: Have you ever had the experience of seeing something or someone that others who were present could not see — that is, had a vision when you were completely awake?
8. *DIS 130*: Have you more than once had the experience of hearing things other people couldn't hear, such as a voice?
9. *DIS 131*: Have you ever been bothered by strange smells around you that nobody else seemed to be able to smell perhaps even odors coming from your own body?

10. *DIS 132*: Have you ever had unusual feelings inside or on your body — like being touched when nothing was there or feeling something moving inside your body?

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