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Genetic and clinical correlates of season of birth of schizophrenics

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Abstract The genetic and clinical characteristics of 55 patients with schizophrenia and 138 control patients (with major psychiatric disorders), were studied in relation to the season of birth. The morbid risk (MR) of schizophrenia was significantly higher among relatives of the schizophrenic probands born in Spring than among those of the psychiatric controls born in the same season. The MR of schizophrenia was also significantly higher among relatives of schizophrenic probands born in Winter or Spring (6.9%) than in those of schizophrenic probands born in Summer or Autumn (0%). Among the schizophrenic cases, Winter births were marginally related to the paranoid subtype, whereas other clinical variables showed no clear relationship with the season of birth.

Key words morbid risk, schizophrenia, subtype.

INTRODUCTION

An excess of winter births has been reported among schizophrenic patients when compared with normal controls.[1] This finding was also reported in the Southern hemisphere.[2] Shimura *et al.* was the first to report such a trend in Japan.[3] However, other studies have not always confirmed this finding, and may possibly contradict it when the 'age cohort' effect is considered.[4] Were schizophrenia a syndromal constellation of heterogeneous conditions, as was explicitly proposed when the term was coined,[5] it would be reasonable to speculate that the seasonality of schizophrenic births is related only to limited subgroups of patients. Hence, the season of birth hypothesis might be further supported if schizophrenics born in one particular season were proven to be clinically distinct from those born in other seasons.[6]

In some studies, demographic and clinical differences have emerged between schizophrenics with different seasons of birth.[6] The identification of clinical correlates that could distinguish patients born in different seasons might then provide an alternative way in which to recategorize those suffering from schizophrenia. For example, there have been intensive studies for possible relationship between genetic predisposition and schizophrenic births in any particular season. Some researchers have reported that winter births are related to a lower morbid risk (MR) of schizophrenia among the relatives of schizophrenic probands,[7–14] while other researchers have reported the opposite.[15–17]

This is a study of the comparative genetic and clinical characteristics of Japanese schizophrenic patients born in different seasons.

METHODS

We studied 193 inpatients consecutively admitted to one of the seven hospitals collaborating in a multi-center project on major psychiatric disorders.[18] All patients fulfilled the Research Diagnostic Criteria (RDC)[10] for schizophrenia, major depressive disorder, manic disorder, schizoaffective disorder or unspecified functional psychoses (UFP). Two patients with UFP who had no past history of any other major psychiatric disorders were included under the classification of schizophrenia. This led to a total of 55 cases. Because the lifetime diagnosis is more important than a current RDC diagnosis for a genetic study, we excluded one patient with episodes of schizophrenia and schizomania, four patients with episodes of UFP and major depressive disorder, and two patients with episodes of UFP and schizodepression from the rubric of schizophrenia. Consequently, the schizophrenic cases in the present study had no past affective episode. The remaining 138 patients were categorized using a pre-established recoding hierarchy of RDC diagnoses: affective unipolar disorder ($n = 70$), affective bi-

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polar disorder ($n = 29$), schizoaffective unipolar disorder ($n = 25$), and schizoaffective bipolar disorder ($n = 14$). These patients acted as the control group. Demographic and diagnostic data on the subjects have been reported fully elsewhere.[19] The sex ratio (male/female) showed no significant difference between the schizophrenic (23/32) and control (72/66) groups. The mean age (± s.d.) at entry was 29.0 (±8.9) for the schizophrenic group and 36.3 (±13.2) for the control group. The schizophrenics were significantly younger ($t = 4.43$, $P < 0.000$).

We diagnosed the patients according to the RDC using an *ad hoc* structured interview guide, and completed the Oxford version[20] of the Brief Psychiatric Rating Scale (BPRS)[21] and the Global Assessment Scale (GAS).[22] A factor analytic study of the BPRS among Japanese psychiatric patients yielded four major factors: positive, negative, manic and dysphoric symptoms.[23] In the present study, four BPRS subscales were calculated accordingly. Family history of the psychiatric diagnosis was collected using the Family History-Research Diagnostic Criteria (FH-RDC) for first-degree relatives of probands.[24] The MR was calculated using Weinberg's abridged method,[25] with the age-at-risk for FH-RDC schizophrenia, UFP, alcoholism of 15 to 39 years and the age-at-risk for depression, other psychiatric disorders (OPD) and suicide of 15 to 59 years.

Fifteen of the schizophrenic patients (27.3%) were born in Winter (January to March), nine (16.4%) in Spring (April to June), 16 (29.1%) in Summer (July to September) and 15 (27.3%) in Autumn (October to December). The corresponding numbers for the psychiatric controls were 40 (29.0%), 29 (21.0%), 33 (23.9%) and 36 (26.1%), respectively. No difference was found between the two groups in relation to the seasonal distribution of their births ($\chi^2 = 0.909$, d.f. = 3, NS). Season of birth information on the relatives was not available.

The MR of each FH-RDC diagnosis was then compared between the relatives of schizophrenic probands and those of the control patients who were born in different seasons, using the Chi-squared test (d.f. = 3). The MR of FH-RDC schizophrenia among the relatives was then compared between the schizophrenic patients of different seasons of birth. The schizophrenic patients of different seasons of birth were compared in relation to sex ratio, age, duration of the present episode, clinical subtypes, total and subscale totals of the BPRS and GAS scores of three time periods, using the Chi-squared test or one-way analysis of variance (ANOVA) as appropriate. The SPSS-X program was used for most of the statistical analyses.[30]

RESULTS

The relatives of the Spring-born schizophrenic probands had a significantly higher MR for FH-RDC schizophrenia than those of the Spring-born probands with other disorders ($\chi^2 = 4.558$, d.f. = 1, $P < 0.05$). The relatives of the Winter-born schizophrenic probands had a higher MR for schizophrenia than those of the Winter-born probands with other disorders, but this did not reach statistical significance (Table 1). The relatives of the Summer-born schizophrenic probands had higher, although not significant, MR for UFP and OPD.

When the schizophrenic probands were dichotomized into Winter/Spring- and Summer/Autumn-born groups, the MR of FH-RDC schizophrenia was found to be significantly higher among the relatives of the former group (MR, 6.9%) than among those of the latter group (MR, 0.0%) ($\chi^2 = 4.733$, d.f. = 1, $P < 0.05$).

We then attempted to identify demographic and clinical correlates which could distinguish schizophrenics of different birth season. The male:female sex ratio was highest among the Autumn-born schizophrenic patients (10/15, 67%), followed by Summer-born (6/16, 38%), Winter-born (5/15, 33%), and Spring-born (2/9, 22%) patients. This difference was not statistically significant ($\chi^2 = 5.79$, d.f. = 3, $P < 0.2$). The mean age (±s.d.) was 28.8 (±8.0) for Winter-born, 28.0 (±11.3) for the Spring-born, 30.6 (±6.4) for the Summer-born and 28.1 (±10.9) for the Autumn-born patients. There was no statistically significant difference among the four groups ($F_{3,51} = 0.242$, $P < 0.9$).

The mean duration (±s.d.) of the present episode in weeks was shorter in the Winter-born group (81.0, s.d. = 113.4) than in the other three groups (Spring-born, mean = 233.8, s.d. = 270.6; Summer-born, mean = 197.4, s.d. = 189.3; Autumn-born, mean = 133.5, s.d. = 124.0). There was, however, no statistically significant difference among ($F_{3,49} = 1.896$, $P < 0.2$) between the four groups in this respect.

A cross-tabulation of the subtypes of schizophrenia by season of birth showed that there were more Winter-born cases (47%) of the paranoia subtype than in any other season; Spring-born (11%), Summer-born (25%) and Autumn-born (13%). Nevertheless, the ratio of the paranoid subtype to any other subtypes over the four seasons of birth groups was not statistically significant ($\chi^2 = 4.87$, d.f. = 3, $P < 0.2$; Table 2).

The four BPRS subscales scores (positive, negative, manic and dysphoric symptoms) all showed no difference between the four season-of-birth groups (Table 3).

The GAS scores for three different time periods [i.e. (i) an average week before the present episode (the average of functioning during the period prior to the present episode), (ii) the worst week of the present episode (the worst functioning observed at any week during the course of the present episode), and (iii) the last week] all demonstrated no differences between the four season-of-birth groups. The GAS scores (±s.d.) for the first time period were 66.2 (±15.1), 61.9 (±19.2), 63.1 (±14.1) and 61.5 (±16.6) for the Winter-, Spring-, Summer and autumn-born, respectively. The GAS scores for the second time period were 25.3 (±6.6), 25.1 (±8.4), 25.2 (±10.1) and 24.1 (±6.2), respectively. The GAS scores for the third time period were 33.0 (±11.3), 33.6 (±15.2), 34.0 (±11.9), and 31.5 (±6.1), respectively.

Table 1. Morbid risks of Family History-Research Diagnostic Criteria (FH-RDC) diagnoses among the relatives of the probands with schizophrenia and other psychiatric disorders by season of birth. Note: read, for example, that the MR of schizophrenia among relatives of Winter-born schizophrenic probands was derived by dividing the number of relatives diagnosed as schizophrenic ($n = 3$) by the BZ 15–39 ($n = 43.5$).

Relatives' FH-RDC diagnosis		Season of birth			
		Winter	Spring	Summer	Autumn
Schizophrenic probands					
n		59	41	64	66
BZ 15–39		43.5	28	47	49.5
BZ 15–59		32.5	23	38	38
Schizophrenia	*n*	3	2	0	0
	MR (%)	6.9	7.1	0.0	0.0
Depression	*n*	1	0	3	1
	MR (%)	3.1	0.0	7.9	2.6
UFP	*n*	0	0	2	0
	MR (%)	0.0	0.0	4.3	0.0
Alcoholism	*n*	0	0	0	2
	MR (%)	0.0	0.0	0.0	4.0
OPD	*n*	2	0	2	4
	MR (%)	6.2	0.0	5.3	10.5
Suicide	*n*	1	0	1	0
	MR (%)	3.1	0.0	2.6	0.0
Other psychiatric probands					
n		229	168	179	180
BZ 15–39		164.5	130	127	137.5
BZ 15–59		125.5	99.5	96	102.5
Schizophrenia	*n*	2	0	0	1
	MR (%)	1.2	0.0	0.0	0.7
Depression	*n*	10	0	3	4
	MR (%)	8.0	0.0	3.1	3.9
UFP	*n*	2	0	0	0
	MR (%)	1.2	0.0	0.0	0.0
Alcholism	*n*	3	1	4	1
	MR (%)	1.8	0.8	3.1	0.7
OPD	*n*	4	2	0	5
	MR (%)	3.2	2.0	0.0	4.9
Suicide	*n*	2	0	1	1
	MR (%)	1.6	0.0	1.0	1.0
Schizophrenic vs. other psychiatric probands					
Schizophrenia	χ^2	2.583	4.558	—	0.282
	P	< 0.2	< 0.05		
Depression	χ^2	0.364	—	0.548	0.024
	P				
UFP	χ^2	0.019	—	3.085	—
	P			< 0.1	
Alcoholism	χ^2	0.035	0.719	0.437	0.001
	P				
OPD	χ^2	0.068	0.053	2.174	0.696
	P			< 0.2	
Suicide	χ^2	0.031	—	0.011	0.272
	P				

BZ, Bezugsziffer (age-corrected number of relatives); UFP, unspecified functional psychoses; OPD, other psychiatric disorders; MR, morbid risk.

Table 2. Subtypes of schizophrenia by the season of birth

Subtypes	Season of birth				Total
	Winter (%)	Spring (%)	Summer (%)	Autumn (%)	
Paranoid	7 (47)	1 (11)	4 (25)	2 (13)	14 (26)
Disorganized	2 (13)	2 (22)	4 (25)	1 (7)	9 (16)
Catatonic	0 (0)	1 (11)	0 (0)	2 (13)	3 (6)
Undifferentiated	4 (27)	3 (33)	2 (13)	4 (27)	13 (24)
Residual	1 (7)	1 (11)	6 (38)	5 (33)	13 (24)
Other	1 (7)	1 (11)	0 (0)	1 (7)	3 (6)
Total	15	9	16	15	55

DISCUSSION

This study has demonstrated that the MR of schizophrenia is higher in the relatives of schizophrenic probands born in Winter or Spring than in the relatives of non-schizophrenic psychiatric probands born in the same seasons and also than among the relatives of schizophrenics born in Summer or Autumn.

In many studies the relationship between season of birth and family history of schizophrenia was considered by comparing the seasonal or monthly birth rate of schizophrenic probands with and without such a family history, respectively.[7–9,12,15,17,27] However, results from classifying patients into familial and non-familial groups should be interpreted with caution. The findings may be distorted by unequal numbers of relatives in both groups. Morbid risk studies are usually considered more robust. Only two studies have applied the MR method to study the relationship between season of birth and family history of schizophrenia.[12,16] Baron and Gruen studied the MR of schizophrenia and schizophrenia-related disorders among relatives of probands with DSM-III schizophrenia.[12] They found that the MR was higher among the relatives of schizophrenic probands born in Winter or Spring than among those of schizophrenic probands born in Summer or Autumn. Sacchetti *et al.*, on the other hand, studied 187 DSM-III-R schizophrenic cases and found that the MR of schizophrenia was lower among the relatives of schizophrenic probands born in Winter or Spring. Our results are in accordance with those of Baron and Gruen and in dispute with those of Sacchetti *et al.* This discrepancy in findings is difficult to explain.

One may speculate that in addition to differences in the characteristics of the sample populations and in the assessment methods employed, the association between schizophrenic genetic loadings and season of birth is spurious, and mediated by a third factor. For example, Machon *et al.* suggested that a higher rate of schizophrenic cases among winter-born individuals is observed only for those born in urban areas, but not for those in non-urban areas.[28] They postulated that viral infection was a mediating factor.

In our sample, as an alternative approach the paranoid subtype was marginally related to Winter birth. This is consistent with the finding of Michitsuji *et al.* They found that the excess of Winter-born schizophrenic cases reached statistical significance among the paranoid subtype of schizophrenia but not among other subtypes. Thus, the paranoid *vs* non-paranoid subcategories might be another mediating factor in the genetic seasonality association. It is relevant that in a family study of schizophrenia, the MR of schizophrenia was higher among the relatives of schizophrenic probands with positive symptoms than among those of schizophrenic probands with negative features.[29] In order to explore this association further, the range of variables needs to be expanded and to be examined among a much larger sample of patients.

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Table 3. Brief Psychiatric Rating Scale (BPRS) subscales and season of birth

BPRS subscales	Season of birth				$F_{3,5}$	P
	Winter (±s.d.)	Spring (±s.d.)	Summer (±s.d.)	Autumn (±s.d.)		
Positive symptoms	10.9 (5.3)	9.8 (7.0)	8.9 (6.0)	9.7 (3.9)	0.366	0.778
Negative symptoms	5.1 (4.1)	6.6 (4.9)	4.9 (2.8)	7.8 (4.1)	1.750	0.169
Manic symptoms	1.3 (2.0)	0.9 (1.7)	0.1 (0.3)	0.7 (1.3)	1.692	0.180
Dysphoric symptoms	5.1 (3.1)	4.0 (3.1)	3.7 (3.5)	4.2 (3.0)	0.513	0.675
Total score	25.2 (11.0)	22.2 (12.6)	19.2 (9.0)	25.1 (7.2)	1.317	0.279

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