ORIGINAL ARTICLE

Maternal Infections and Subsequent Psychosis Among Offspring

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Background: We tested the hypothesis that maternal infections during pregnancy are associated with the subsequent development of schizophrenia and other psychoses in adulthood.

Methods: We conducted a nested case-control study of 27 adults with schizophrenia and other psychotic illnesses and 54 matched unaffected control subjects (matched for sex, ethnicity, and date of birth) from the Providence, RI, cohort of the Collaborative Perinatal Project. We retrieved stored blood samples that had been obtained from these mothers at the end of pregnancy. These samples were analyzed for total class-specific immunoglobulins and for specific antibodies directed at recognized perinatal pathogens capable of affecting brain development.

Results: Maternal levels of IgG and IgM class immunoglobulins before the mothers were delivered of their neonates were significantly elevated among the case series ($t=3.06$, $P=.003$; $t=2.93$, $P=.004$, respectively, for IgG and IgM immunoglobulin-albumin ratios). Secondary analyses indicated a significant association between maternal antibodies to herpes simplex virus type 2 glycoprotein gG2 and subsequent psychotic illness (matched t test $=2.43$, $P=.02$). We did not find significant differences between case and control mothers in the serum levels of IgA class immunoglobulins, or in specific IgG antibodies to herpes simplex virus type 1, cytomegalovirus, *Toxoplasma gondii*, rubella virus, human parvovirus B19, *Chlamydia trachomatis*, or human papillomavirus type 16.

Conclusions: The offspring of mothers with elevated levels of total IgG and IgM immunoglobulins and antibodies to herpes simplex virus type 2 are at increased risk for the development of schizophrenia and other psychotic illnesses in adulthood.

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SCHIZOPHRENIA AND related psychotic illnesses are a class of pervasive neuropsychiatric disorders of uncertain origin. Family, twin, and adoption studies have identified a genetic component to schizophrenia and other psychotic illnesses. However, specific genes have not as yet been identified.[1-5] Epidemiological studies have identified several environmental factors associated with these illnesses, many related to events that occur during pregnancy or during the birth process. These include winter and spring birth, birth in an urban area, prematurity, complications during labor and delivery, and extreme famine during pregnancy.[6-10] Studies have also suggested an association between exposure to infectious agents during pregnancy and the subsequent development of schizophrenia,[11-13] although findings in this area are equivocal[14,15] and with the occurrence of infections in early infancy.[16,17] This body of research suggests that prenatal and perinatal infections and other environmental insults that adversely affect infant brain development may result in schizophrenia in later life, most likely in genetically susceptible individuals.[4,18-20]

The Collaborative Perinatal Project (CPP) was a prospective cohort study directed at the identification of perinatal factors with adverse effects on infant and child development. This study monitored more than 55 000 pregnancies in 12 study sites in the United States between 1959 and 1966. Cohort mothers were intensively studied during pregnancy and their infants were evaluated for physical and intellectual development during the first 7 years of life.[21,22] In addition to detailed clinical evaluations, blood samples were obtained from the mothers and stored in a repository for further analyses.[23] Data generated by the CPP study have led to the increased understanding of the effect of infections, nutrition, and other perinatal factors on childhood neurologic, cognitive, and physical development.[24-29] This ar-

SUBJECTS AND METHODS

The study sample was drawn from the Providence, RI, cohort of the CPP. Pregnant women were enrolled during clinical visits and selected to be representative of patients receiving prenatal care at each of the 12 study sites. The Providence cohort includes 3804 surviving offspring of a sample of 3078 pregnant women.[30] Data from examinations and interviews were recorded by trained staff beginning at the time of registration for prenatal care, using standardized protocols. Maternal blood samples were collected at registration, approximately every 2 months after registration, and when the mother was delivered of the neonate. The samples were stored at National Institutes of Health repositories at −20°C.

CASE SERIES

Members of this cohort with psychotic illness were identified through a 2-stage diagnostic assessment procedure. In stage 1 subjects with possible psychotic illness were identified through (1) personal interviews and/or (2) record linkage with psychiatric treatment facilities. In a first interview study, as described previously,[30] 928 subjects were selected for follow-up and 693 interviewed (75%) using the *Diagnostic Interview Schedule Version III*.[31] In a second study,[32] we selected an additional 775 subjects for follow-up and interviewed 574 (74%). A total of 1267 follow-up interviews were completed; 29 of these subjects reported clinically relevant psychotic symptoms. Record linkage efforts identified an additional 14 subjects with a history of psychiatric treatment for a psychotic illness. For the second stage, subjects were contacted again and interviewed by a trained diagnostic interviewer using the *Structured Clinical Interview for DSM-IV*.[33] Trained diagnosticians (2 clinical psychologists, 2 adult psychiatrists) then completed best-estimate consensus diagnoses according to the *DSM-IV* criteria, based on interview data and medical record review. Diagnostic interviews were completed for 34 subjects; medical records alone were available for the remaining 9 subjects.

Of the 43 potential subjects with psychosis, 16 were evaluated as being nonpsychotic, with diagnoses including mild mental retardation, major depressive disorder (without psychosis), posttraumatic stress disorder, substance abuse, and obsessive-compulsive disorder. The remaining 27 subjects were determined to have a major psychotic disorder, including schizophrenia (n=13), schizophreniform disorder (n=1), bipolar disorder with psychotic features (n=2), brief psychosis (n=3), and psychosis not otherwise specified (n=8). These diagnostic procedures were completed prior to and independent of the analysis of maternal serum samples.

CONTROL SERIES

For each of the 27 subjects with psychosis, 2 healthy matched controls were selected, matched for sex, ethnicity, and date of birth. Controls were selected from an unaffected subset of 137 of the 693 subjects assessed in the first interview study, who received no Axis I psychiatric diagnoses. Cases and controls were stratified into 4 sex and ethnic groups (white or African American), and within strata sorted by month of birth. The 2 closest controls within each stratum were selected. In 4 instances there were no remaining control subjects available within the stratum, resulting in 1 instance in which a female control was selected for a male case, and 3 instances in which white controls were selected for African American cases. Month of birth for controls was within 2 months of the matched case for 76% of the controls (n=41) and within 3 months for 89% of the controls (n=48). Human subjects approval was

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ticle is a report of the findings from a follow-up study in adulthood of offspring who had been enrolled in the CPP cohort, to test the hypothesis that maternal infections during pregnancy are associated with the development of schizophrenia and other psychoses in adult life.

RESULTS

There are no significant differences between the 27 subjects with psychosis (cases) and 54 matched controls for any of the sample characteristics examined (**Table 1**). Compared with the entire surviving cohort of 3804 subjects from which the current sample was drawn, the case series includes a higher proportion of males (77.8%), with a comparable proportion among controls, as a result of matching. Rates of all other demographic, family, and perinatal variables for the case and control series were comparable to the larger cohort from which they were sampled.

We considered several potential risk factors that might occur more commonly among the pregnancies and births of case subjects and might confound any noted association between signs of prenatal infection and psychosis. There were no significant differences between the case and control groups relating to season of birth, late prenatal care, or maternal age or education. Family SES (a composite index of maternal and paternal income, educational level, and occupation at birth)[40] and maternal smoking during pregnancy were lower and weight gain during pregnancy greater among the case sample but these differences were not statistically significant. These differences remained nonsignificant when subjected to the matched-set analyses described earlier.

Levels of total maternal IgG and IgM , but not IgA, class immunoglobulins were significantly elevated among the case series (**Table 2**). Differences in the IgG-albumin and IgM-albumin ratios were particularly pronounced, with differences at the $P=.002$ level for both ratios. The groups did not differ in terms of IgA-albumin ratios.

To explore the potential source of these elevated levels of total maternal IgG class immunoglobulins, we conducted assays for IgG antibodies to infectious agents of known neuropathologic potential. As summarized in **Table 3**, we did not observe a significant association between psychosis and IgG antibodies to *T gondii*, rubella, cytomegalovirus, or HSV-1. However, as given in Table 3 and shown in the **Figure**, there was a significant and graded association between maternal antibod-

granted by human studies review groups at Harvard University, Boston, Mass, the National Institute of Child Health and Human Development, Rockville, Md, and local psychiatric facilities. Written consent was obtained from all interviewed study participants.

PROCESSING OF SERUM SAMPLES AND IMMUNOGLOBULIN MEASUREMENTS

For each study participant, a maternal blood sample was obtained from the National Institutes of Health repository for the last collection obtained during pregnancy (usually when the mother was delivered of the neonate). Levels of total IgG, IgM, IgA, and albumin were measured by laser rate nephelometry.[34] For each sample, the level of immunoglobulin was analyzed in terms of absolute concentrations (measured in milligrams per deciliter) as well as a ratio of the concentration of immunoglobulin to the concentration of albumin (immunoglobulin-albumin ratio) to control for individual differences related to hemodilution that can occur during pregnancy[35] or differential evaporation that might occur during sample storage.

Levels of specific IgG class antibodies to cytomegalovirus, rubella virus, *Toxoplasma gondii*, human parvovirus B19, herpes simplex virus type 1, herpes simplex virus type 2 (HSV-2) virion antigen (HSV-1) and *Chlamydia trachomatis* were measured by solid-phase enzyme immunoassay.[36] A typical protocol is as follows: wells of microtiter plates coated with target antigens (obtained from KMI Diagnostics Inc, Minneapolis, Minn) were reacted with test serum diluted 1:100 in phosphate-buffered saline solution at pH 7.4 containing 0.1% polysorbate (Tween) 20. Following incubation for 2 hours at 37°C, the plates were washed 5 times with phosphate-buffered saline solution containing 0.1% polysorbate 20, and incubated with peroxidase-labeled anti–human IgG. Following incubation for 1 hour at 37°C, the plates were washed 5 times and incubated with 2-2′-azino-*bis*[3-ethylbenzthiazoline-6-sulfonic acid]–hydrogen peroxide peroxidase substrate. Followingreaction for 30 minutes, the amount of color generated by reaction between the antigen-bound enzyme and the soluble substrate was quantitated by means of a microplate colorimeter at a wavelength of 450 nm. Assays for the same analyte performed using different microtiter plates were standardized by the use of standard curves generated from standard samples run on each assay plate. Solid-phase enzyme immunoassays were performed for the measurement of IgG antibodies to HSV-2 type-specific glycoprotein gG2[36] and converted to log values to generate a scale equivalent to that of the optical density results.[37] Immunoassays were performed for the measurement of antibodies to human papillomavirus type 16 using solid-phase viral-like particles cloned and expressed in baculovirus.[38] All samples were analyzed under code, with the laboratory performing the studies being unaware of the clinical status of the study individuals.

STATISTICAL ANALYSIS

Demographic, familial, and perinatal characteristics of the case and control groups were compared using the χ^2 and *t* tests (2-tailed). To test our primary study hypothesis, we conducted analyses that considered the matching of 2 controls per case to test for differences in maternal immunoglobulin levels between the case and control groups. For each triplet, we calculated the difference between the case value and the average for the 2 controls and computed a single sample *t* test on these differences. Similar analyses were conducted to test secondary hypotheses regarding IgG antibodies to specific pathogens. As noted earlier, 4 cases and controls were imperfectly matched. Two sets of analyses were conducted, including and excluding these control subjects.[39] We conducted a series of restricted analyses to further address potential confounding by maternal mental illness, family socioeconomic status (SES), and other factors.

ies to HSV-2 and adult psychosis. Subjects whose maternal antibodies to HSV-2 exceeded the 75th percentile of the control sample had an odds ratio of 3.4 for psychosis; those whose maternal antibodies exceeded the 90th percentile had an odds ratio of 4.4. Since antibodies to the virion-derived antigens used in standard solid-phase immunoassays can bind to cross-reactive herpesvirus epitopes,[41] we confirmed the specificity of this association by the measurement of antibodies to HSV-2 type-specific glycoproteins gG1 and gG2.[42] The positive finding for HSV-2 antibodies was confirmed using this more precise measure ($t = 2.43$, $P = .02$). All of the analyses noted earlier were recalculated dropping the 4 imperfectly matched controls; the results were unchanged.

We conducted a series of restricted analyses to address potential residual confounding by maternal mental illness, weight gain, smoking during pregnancy, and family SES. We dropped the following: (1) the lowest SES quartile, (2) the highest weight gain quartile, (3) nonsmokers, (4) heavy smokers (> one-half pack per day during pregnancy), and (5) offspring of women with any indication of psychiatric treatment; and reran all of the above analyses. The results were unchanged; all of the associations reported earlier remained statistically significant at the $P < .05$ level. The elevated antibody values among the psychotic sample do not result from a subset of cases of lower SES, maternal history of psychiatric treatment, greater weight gain, or high or low levels of cigarette smoking.

We performed additional analyses to determine if the case and control mothers differed in terms of exposure to sexually transmitted pathogens other than HSV-2. We found that the groups did not differ in terms of antibodies to *C trachomatis* or to the E6 and E7 proteins of human papillomavirus type 16.

COMMENT

The study results indicate a significant association between increased levels of maternal serum IgG and IgM class immunoglobulins at delivery and the subsequent development of psychosis in offspring. IgG and IgM class antibodies are both generated in response to infection; IgM immunoglobulins are generally generated within a few days following systemic infection and are detect-

Table 1. Demographic and Clinical Characteristics of Case and Control Subjects*

Characteristic	No. (%) of Cases (n = 27)	No. (%) of Controls (n = 54)	χ^2_1 Test Value	*P* Value	Total Sample, % (n = 3804)
Demographics of offspring					
Male	21 (77.8)	41 (75.9)	0.03	.85	49.7
White	19 (70.4)	41 (75.9)	0.29	.59	77.3
Winter-spring (December-April) birth	8 (29.6)	19 (35.2)	0.25	.62	31.0
Urban residence at birth	26 (96.3)	47 (90.4)	0.89	.35	88.7
Maternal					
Married	20 (74.1)	42 (77.8)	0.14	.71	76.1
History of psychiatric treatment (reported during pregnancy)†	1 (3.7)	1 (2.0)	0.22	.64	3.1
No/late prenatal care (no prenatal care or first visit during third trimester)	9 (34.6)	16 (29.6)	0.20	.65	30.6
	Cases, Mean (SD) (n = 27)	**Controls, Mean (SD) (n = 54)**	***t* Test Value**	***P* Value**	**Total Sample, Mean (SD) (n = 3804)**
Age when delivered of neonate, y	23.9 (6.2)	25.4 (6.9)	1.00	.32	24.3 (6.2)
Educational level at neonate's birth, y completed	9.6 (2.6)	9.8 (2.2)	0.31	.76	10.2 (2.4)
Family socioeconomic index (0 = low, 99 = high)	39.6 (19.0)	46.7 (20.9)	1.49	.14	45.0 (20.3)
Cigarettes smoked third trimester, No./d	9.8 (12.9)	15.3 (12.9)	1.74	.09	10.7 (12.2)
Weight gain during pregnancy, lb‡	24.4 (11.1)	20.2 (11.0)	–1.59	.12	21.9 (10.9)

*Categorical variables analyzed by χ^2 test, quantitative variables analyzed by *t* test. Total sample refers to the rates, means (SDs) of study variables for the entire surviving Providence, RI, cohort of the Collaborative Perinatal Project.

†Positive response during pregnancy to the question: "Have you ever had any nervous problem which required hospital care or psychiatric treatment?"

‡To convert pounds to kilograms, multiply by 0.45.

Table 2. Total Class-Specific Immunoglobulins and Albumin Measured in the Serum Samples of Case and Control Mothers When Delivered of the Neonates*

	Cases (n = 27)	Controls (n = 54)	Difference	t_{26} Test	*P* Value
Total IgG level, mg/dL	1030 (250)	897 (257)	133 (293)	2.35	.03
Total IgM level, mg/dL	220 (91)	162 (93)	58 (87)	3.46	.002
Total IgA level, mg/dL	184 (70)	186 (115)	–2 (99)	–0.09	.93
Albumin level, mg/dL	2968 (327)	3056 (440)	–88 (364)	–1.26	.22
IgG-albumin ratio	0.35 (0.07)	0.29 (0.07)	0.05 (0.08)	3.35	.002
IgM-albumin ratio	0.07 (0.03)	0.05 (0.03)	0.02 (0.03)	4.04	<.001
IgA-albumin ratio	0.06 (0.02)	0.06 (0.04)	0.001 (0.03)	0.20	.84

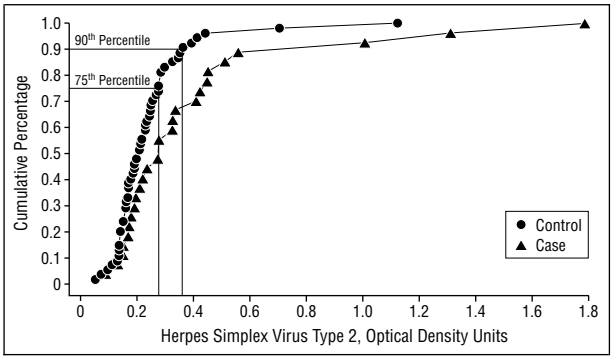
*All values are given as means (SDs). Immunoglobulins and albumin were measured by laser rate nephelometry as described in the "Processing of Serum Samples and Immunoglobulin Measurements" subsection of the "Subjects and Methods" section.

Table 3. IgG Antibodies to Microbial Pathogens Measured in the Serum Samples of Case and Control Mothers When Delivered of the Neonates*

IgG Antibody	Cases (n = 27)	Controls (n = 54)	Difference	*t* Test[1]	*P* Value
Toxoplasma gondii	0.22 (0.18)	0.20 (0.18)	0.02 (0.12)	0.51	.61
Human parvovirus B19	0.22 (0.12)	0.19 (0.14)	0.03 (0.14)	1.10	.28
Rubella virus	0.58 (0.26)	0.51 (0.23)	0.08 (0.31)	1.30	.20
Cytomegalovirus	0.45 (0.36)	0.50 (0.41)	–0.04 (0.55)	–0.42	.68
Herpes simplex virus type 1	0.94 (0.70)	1.03 (0.70)	–0.09 (0.81)	–0.57	.57
Herpes simplex virus type 2 (virion antigen)	0.40 (0.39)	0.24 (0.16)	0.16 (0.39)	2.11	.04
Herpes simplex virus type 2 (gG2 glycoprotein)	0.70 (0.51)	0.44 (0.32)	0.25 (0.54)	2.43	.02

*All values are given as means (SDs). Antibodies were measured by immunoassay methods as described in the "Processing of Serum Samples and Immunoglobulin Measurements" subsection of the "Subjects and Methods" section. All of the values are optical density except for the gG2 glycoprotein, which is expressed as the $\log_{10}$ of standard units.[37]

able for several months while IgG immunoglobulins are generated 1 to 3 weeks after initial infection and are detectable for several years. There were no differences in maternal levels of serum IgA class antibodies, indicating that the results were related largely to a systemic, as opposed to a mucosal, immune response. The differences were apparent when the IgG or IgM levels were expressed as concentrations per milliliter of serum or as im-



Cumulative percentage of herpes simplex virus type 2 antibody levels for controls and cases showing the 75th and 90th deciles for the control sample.

munoglobulin-albumin ratios. These findings indicate that the differences were unlikely to be explained on the basis of differential hemodilution or evaporation of the samples.[35] The association of elevated levels of total immunoglobulins and subsequent psychosis thus provides objective confirmation of previous studies that have documented a correlation between the history of clinical signs of infection during pregnancy and the development of schizophrenia in the offspring.

Further, we observed a statistically significant and graded association between maternal levels of IgG antibodies to HSV-2 and the subsequent development of psychosis in the offspring, in both the virion antigen and gG2 HSV-2 assays. Previous studies have documented a strong association between antibodies to HSV-2 gG2 glycoprotein and anogenital herpesvirus infections.[43-45] These type-specific assays confirmed the presence of increased levels of antibodies to HSV-2 in the mothers of offspring who developed psychosis later in life. Not all of the increased immunoglobulin levels in the case series can be attributed to HSV-2 infection. Of the 13 cases who had elevated levels of total IgG antibodies (defined as >1 SD above the mean for the control sample), 5 (38%) also had elevated HSV-2 antibody levels. The relationship between elevated levels of immunoglobulins and increased levels of antibodies to HSV-2 should be addressed in studies of additional populations.

A limitation of this study is the size and heterogeneity of the sample of 27 psychotic subjects, which include diagnoses of schizophrenia, affective psychoses, and other psychotic conditions. While this sample is adequate to detect moderate effect sizes (ie, ≥0.67) for the continuous measures of immunoglobulins, power for smaller effects and for categorical exposures is limited. We found nonsignificant positive associations between adult psychosis and increased levels of maternal antibodies to rubella and other known perinatal pathogens that might have reached statistical significance in a larger sample. We were unable to estimate the relative risk of psychosis for dichotomous cutoff points of antibody levels indicating maternal infection. Owing to the limited sample size, we were also unable to determine whether the findings are specific to schizophrenia, nonaffective psychoses, or other specific classes of psychosis, all limitations that will be addressed through our ongoing work with the larger Boston cohort of the CPP.

The 27 psychotic offspring represent 0.71% of the eligible cohort (n=3804) and are presumably a subsample of all affected subjects. Case ascertainment involved both personal screening interviews for approximately half of the cohort and record linkage with state treatment facilities for the entire sample. Loss to follow-up in the interview component was marginally elevated for males and subjects of lower SES. However, owing to changes in maiden names and our focus on publicly funded psychiatric hospitals, males and lower SES subjects are somewhat overrepresented in the linkage sample. The net effect, as reflected by the sociodemographic characteristics of the psychotic sample compared with the entire cohort (ie, slightly lower SES, greater proportion of males), indicates that the case series reflects a reasonably representative subset of the psychotic subjects among this cohort, supporting the generalizability of the study results.

There are several possible pathophysiological mechanisms by which maternal infection with viruses such as HSV-2 might lead to the subsequent development of psychosis in their offspring. It is possible that some of the infants were directly infected with HSV-2 as a result of maternal viral shedding during pregnancy or delivery. Since viral cultures were not collected, the rate and timing of viral shedding cannot be precisely determined.[46,47] However, the potential relationship between HSV-2 infection and subsequent psychosis is plausible in light of the tropism of HSV-2 for the infant central nervous system[48,49] and of case reports of the onset of psychosis following documented cases of HSV encephalitis.[50,51] It is also possible that some of the HSV-2 seropositive mothers infected their children after birth; however, this possibility is rendered unlikely in light of the low incidence of postnatal infection of HSV-2 that occurs during childhood.[52] The possibility that the presence of antibodies to HSV-2 is a marker for increased sexual exposure or another sexually transmitted disease that could adversely affect the fetus is rendered unlikely by the lack of association with antibodies to other sexually transmitted pathogens such as *C trachomatis* or human papillomavirus.[53] However, direct studies of HSV-2 infection and other sexually transmitted pathogens will be required to define the relationship between HSV-2 infection and the development of psychosis. In addition, the possible effects of changing levels of HSV-2 prevalence on the epidemiology of psychosis should be the subject of future studies.

None of the infants who developed psychosis as adults had evidence of encephalitis or other major neurologic abnormalities apparent at birth. This finding is consistent with that of Brown et al,[47] who found no cases of clinically apparent HSV-2 infection in infants of mothers who acquired antibodies to HSV-2 prior to the onset of labor. However, HSV-2–infected infants who are asymptomatic at birth have not been systematically studied in follow-up for extensive periods. The long-term follow-up of infants with documented perinatal exposure to HSV-2 will be required to completely define the potential effects of maternal HSV-2 infection on the developing central nervous system and to define the relationship between perinatal HSV-2 infection and adult neurologic or psychiatric diseases.

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