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Adult Schizophrenia Following Prenatal Exposure to an Influenza Epidemic

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• **In the context of a Finnish birth cohort, we tested the hypothesis that viral infection during the latter two thirds of fetal development would increase the risk of adult schizophrenic outcome. Psychiatric hospital diagnoses were recorded for all individuals in greater Helsinki who were fetuses during the 1957 type A2 influenza epidemic. Those exposed to the viral epidemic during their second trimester of fetal development were at elevated risk of being admitted to a psychiatric hospital with a diagnosis of schizophrenia. This was true for both males and females and independently in several psychiatric hospitals. The second-trimester effect was seen in the elevated proportion of schizophrenics among those admitted to a psychiatric hospital and also in higher rates of schizophrenia per 1000 live births in the city of Helsinki. The study has several limitations: (1) We have no direct evidence that the subjects actually suffered a viral infection. (2) The psychiatric data were obtained only for subjects up to the age of 26 years, 56 days. (3) The findings are based on hospital diagnoses. (4) The determination of stage of gestation at time of exposure to the epidemic is based on date of birth. The viral infection might have occurred outside the official epidemic window; the infant may have had a preterm or postterm delivery. These sources of error, however, should not serve to enhance the findings. The observed viral effect is interpreted as being one of many potential perturbations of gestation. We suggest that it is less the type than the timing of the disturbance during fetal neural development that is critical in determining risk for schizophrenia.**

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In the context of a 24-year prospective study of Danish children at high genetic risk for schizophrenia, we have found perinatal disturbance to be a reliable precursor of enlarged brain ventricles[1] and adult schizophrenia.[2] The results of another high-risk study of Finnish children suggested to us that viral infection during fetal development might be one important basis for the observed perinatal disturbance.[3] In a subsequent study (suggested by the season of birth literature[4]) we noted that the Danish high-risk children who developed schizophrenia in adulthood, and had an excess of perinatal complications, tended markedly to have been born during periods of high prevalence of viral infection (January, February, and March) in a crowded urban area.[5] These findings led us to consider the possibility that fetal viral infection may be an etiological precursor of some subtype of adult schizophrenia.

An opportunity presented itself to test the fetal-viral hypothesis of the etiology of schizophrenia. From Oct 8 to Nov 14, 1957, the citizens of Helsinki experienced a severe type A2 influenza epidemic. The dates of the epidemic were defined by numbers missing work due to illness.[6] In 1984 we examined the psychiatric hospital diagnoses of the individuals born in Uusimaa County (which includes greater Helsinki) whose fetal development overlapped the period of the epidemic; we also studied controls. Hakosalo and Saxen[6] have previously reported that exposure to this particular epidemic in Helsinki during the first trimester of pregnancy (by exposure we mean living in Helsinki during the epidemic) was associated with a significant increase in central nervous system (CNS) anomalies observable at birth. (This result has recently been replicated for the 1968 Helsinki type A2 influenza epidemic. R. Pyhala, and L. Saxen [oral communication, April 1987] observed a significant excess of CNS birth anomalies [eg, anencephaly] associated with first-trimester exposure to the 1968 epidemic.) We hypothesized that later exposure, in the second or third trimester of fetal life, would be associated with more subtle CNS damage that would not be observable in the form of gross birth anomalies but would increase the risk of adult schizophrenia.

MATERIALS AND METHODS

The epidemic lasted from Oct 8 to Nov 14, 1957. The index year cohort consists of all children (1) born in Uusimaa (2) from Nov 15, 1957 to Aug 14, 1958 (3) who were admitted before the age of 26 years, 56 days as inpatients to one or more of the eight psychiatric hospitals serving the county of Uusimaa (Hesperia, Lapinlahti, Tammiharjo, Kellokoski, Nikkila, Paloniemi, Kevatkumpu, and Veikkola). The controls comprised all children (1) born

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in Uusimaa (2) from Nov 15, 1951 to Aug 14, 1957 (3) who were admitted before the age of 26 years, 56 days as inpatients to these same eight hospitals. The index year cohort and controls were paired by month of birth. Index year subjects born Nov 15, 1957, to Dec 14, 1957, were in their ninth month of fetal life during the epidemic exposure; their controls were born Nov 15 to Dec 14 in the years 1951 through 1956. Index year and control groups were paired in this manner for the nine months from Nov 15 to Aug 14. Those born Nov 15, 1957, to Feb 14, 1958, were defined as having been exposed to the epidemic in the third trimester of fetal development. Those born Feb 15 to May 14, 1958, were defined as having been exposed to the epidemic in the second trimester of fetal development. Those born May 15 to Aug 14, 1958, were defined as having been exposed to the epidemic in the first trimester of fetal development. Since the type A2/Singapore virus appeared for the first time in Europe in the fall of 1957, it is impossible for the controls to have suffered a type A2/Singapore viral infection during their fetal development.

For the period during which the index and control groups were "at risk" for a psychiatric disorder, Finnish psychiatrists employed an adaptation of the International Classification of Disease, versions 7 and 8, World Health Organization classification system.[7] For each admission of a member of the index or control group to one of the eight listed psychiatric hospitals, we recorded all primary and up to three additional diagnoses, dates of admission and discharge, place of birth, and sex. The data were recorded by clerical and administrative personnel of the eight hospitals who were not aware of the hypotheses of the study. Individuals with at least one hospital diagnosis of schizophrenia were considered to be schizophrenic for purposes of this study.

The youngest subjects in the study were born on Aug 14, 1958. At the time of the check of the psychiatric hospitals, individuals born on that day were 26 years, 56 days of age. To equate the entire study population for period of risk for psychiatric admission, admissions beginning after a subject reached the age of 26 years, 56 days were not considered in the analyses.

RESULTS

A total of 1781 individuals born in the index and control periods experienced 6035 admissions to psychiatric hospitals. Of these, 695 had only one admission; 1086 had two or more admissions. The Table gives the percent of psychiatric cases who were diagnosed schizophrenic for the index subjects and controls as a function of fetal trimester of exposure to the epidemic. The differences between the index and control groups are not significantly different for the first and third trimesters. The index group exposed in the second trimester evidences a significantly higher rate of admissions for schizophrenia than does the control group. Within the index group, the second-trimester–exposed subjects evidence a significantly higher proportion of schizophrenia diagnoses (among hospital diagnoses) than do the pooled first- and third-trimester–exposed subjects ($\chi^2[1]=3.93$, $P<.05$). (The first- and third-trimester–exposed index groups do not differ significantly in proportion of schizophrenia diagnoses.) The hypothesis is partially supported; psychiatric patients were more likely to be diagnosed schizophrenic if their second trimester of fetal life overlapped the 1957 epidemic. No significant effects are seen for the first or third trimesters.

Reliability of Findings

The reliability of the findings may be examined by analyzing the results separately by psychiatric hospital. For purposes of this analysis, each patient was assigned to only one hospital, the one to which she or he was first admitted. Hesperia Hospital is the primary Helsinki facility for treatment of acute psychiatric problems most common for a young population. It maintains a 24-hour psychiatric emergency service. The elevated risk of schizophrenia diagnosis (in comparison with controls) is seen in the index year second-trimester–exposed subjects in Hesperia ($\chi^2[1]=7.75$, $P<.005$). Tammiharjo Hospital and Kellokoski Hospital are acute-treatment facilities that are similar to Hesperia but serve the northeast and western sections of greater Helsinki. Due to small numbers of index schizophrenics, the results for these two hospitals were combined. The second-trimester–exposed subjects evidence an elevated proportion of schizophrenia diagnoses ($\chi^2[1]=3.94$, $P<.05$). For Lapinlahti Hospital the index group did not differ significantly from controls in any of the trimesters. Lapinlahti differs from Hesperia, Tammiharjo, and Kellokoski in that these other three hospitals are acute-admission centers with 24-hour psychiatric emergency services; Lapinlahti is a psychodynamically oriented treatment center. Too few second-trimester–exposed index schizophrenics were found in the other hospitals to permit meaningful analyses (Nikkila, two; Paloniemi, none; Kevatkumpu, none; and Viekkola, none).

Percent of Schizophrenics Among Hospital Admissions for Index and Control Groups*

	Trimester of Gestation		
	1	2	3
	Total Sample Admitted		
Index	20.0 **(70)**	34.6 **(81)**	24.6 **(65)**
Controls	19.6 **(494)**	20.8 **(558)**†	24.4 **(513)**
	Sex		
Male			
Index	17.9 (39)	34.0 (50)	22.9 (35)
Controls	21.7 (309)	21.3 (315)‡	27.3 (315)
Female			
Index	22.6 (31)	35.5 (31)	26.7 (30)
Controls	16.2 (185)	20.2 (243)§	19.7 (198)
	No. of Psychiatric Admissions		
One‖			
Index	8.0 (25)	15.6 (32)	12.5 (24)
Controls	7.8 (193)	10.5 (228)	9.8 (193)
Two or more			
Index	26.7 (45)	46.9 (49)	31.7 (41)
Controls	27.2 (301)	27.9 (330)¶	33.1 (320)

*Values are the percent of psychiatric patients with schizophrenia. Figures in parentheses are the total number of psychiatric patients in that cell. Except as noted, no difference was statistically significant.
†$\chi^2(1)=7.69$, $P<.01$.
‡$\chi^2(1)=3.96$, $P<.05$.
§$\chi^2(1)=3.77$, $P<.052$.
‖Fisher's exact test, not significant.
¶$\chi^2(1)=7.3$, $P<.01$.

The Table gives the data separately for males and females. The higher proportion of schizophrenia diagnoses for the second-trimester–exposed index subjects is repeated for both sexes. No significant differences are observed for either sex for trimesters 1 and 3. These findings for the two sexes are another form of replication of the second-trimester findings.

Population-Based Rates

We were able to identify the index schizophrenics born in the city of Helsinki by postal code of area of birth. By reference to published birth rates, we determined the number of people born in the City of Helsinki for each of the relevant months in 1957 and 1958. The tabled figures refer to the number born from the first to last day of each month. Since our research project months begin on the 15th day of the month, we interpolated to estimate the number born in Helsinki in each of the research months. Population-based schizophrenia rates were obtained by dividing the number of schizophrenics by the numbers obtained by interpolation. The rate of schizophrenia diagnoses for those exposed to the epidemic in the second trimester of fetal development was 11.6/1000. The rates for the first and third trimesters were 5.8/1000 and 6.2/1000, respectively. The rate of schizophrenia diagnoses for second-trimester–exposed individuals is significantly higher than the combined first- and third-trimester rates ($\chi^2[1]=4.82$, $P<.05$).

Diagnoses

These analyses utilize hospital diagnoses produced for purposes of patient care. Despite the fact that Finnish pyschiatric hospital diagnostic procedures are relatively conservative, the reliability

and validity of these diagnoses and their equivalence to current diagnostic practice might be questioned. One way to approach the problems of the reliability and the validity of the hospital diagnoses of schizophrenia is to choose subjects who have been observed for longer periods by more diagnosticians. We accomplished this by reanalyzing the data considering only cases with two or more admissions. As can be seen in the Table, for those with two or more admissions, the difference in proportion of schizophrenia diagnoses for the second-trimester–exposed index and control groups remains significant. No significant differences are observed in any of the three trimesters for those with only one admission.

Trend Analysis

Since we compare the 1957-1958 cohort with individuals from the previous six years, it could be argued that the 1957-1958 results might represent the end point of a tendency for an increasing proportion of schizophrenia admissions over these years. Three considerations argue against this interpretation. First, it is difficult to imagine why such a trend would confine itself to those individuals whose second trimester of fetal development coincided with the epidemic. Second, statistically significant second-trimester–exposed findings are observed *within* the index year. Third, we subjected the data to a log-linear analysis, testing whether there was a progression in the proportion of schizophrenia diagnoses from 1951 to 1956 that could predict the 1957-1958 index schizophrenia proportions. A log-linear model with a linear component was fit to the data. A test for deviation from nonlinearity indicated that no higher-order polynomials were significant (Pearson $\chi^2[5] = 5.82$), suggesting that the data best fit a *linear* model. The proportion of schizophrenia for the second-trimester–exposed index year subjects deviated significantly from predictions based on a linear combination of the control years (Pearson $\chi^2[1] = 7.43$, $P < .007$).

COMMENT

We have noted an increased rate of hospital diagnoses of schizophrenia among individuals exposed to a large type A2 influenza epidemic in their second trimester of fetal development. This second-trimester effect was observed for both males and females and independently in several greater Helsinki mental hospitals.

Limitations of Study

This study has several limitations: (1) We have no direct evidence that the pregnant women actually suffered a viral infection during the epidemic. We do not have viral antibody titers on either the mother or the offspring. We only know that in the epidemic period 38% of the population experienced a clinical viral infection. It is estimated that another 30% were infected subclinically.[6] (2) The findings should be generalized with caution since at this stage of the project we have not examined admissions for individuals beyond 26 years, 56 days of age. (3) The diagnoses are Finnish hospital psychiatric diagnoses. On the whole, Finnish psychiatric diagnoses are conservative. The next step in our research project will involve evaluation of these diagnoses by interviews and in-depth review of the hospital records. It is difficult to assess the role of possible misdiagnoses on the reported results. However, it is hard to imagine a reason misdiagnoses would be restricted to those whose second trimester of fetal development coincided with the epidemic window. In addition, when we examined those with two or more hospital admissions the pattern of results did not change. (4) Some of the epidemic-related viral infections in the pregnant women must have occurred outside the epidemic window. Also, some small percentage of the children had preterm or postterm deliveries. The calculation of trimester of exposure assumed full-term delivery and that the viral exposure occurred at the end of the epidemic period. Both of these factors would serve to add error to our data and reduce the statistical significance of the reported findings.

Specificity of Viral Second-Trimester Effect

One may ask if type A2 fetal influenza infection is the only type of second-trimester disturbance that can increase the risk of adult schizophrenia. Logic and sparse evidence suggest a negative answer. Huttunen and Niskanen[8] observed psychiatric outcomes for fetuses whose mothers learned of their fathers' death during the fetus' gestation. When the pregnant women were informed of the father's death during the second trimester of fetal development, the offspring later evidenced an elevation in psychotic disorders, including schizophrenia. Jacob and Beckmann[9] studied postmortem brains of chronic schizophrenics and controls. They noted cytoarchitectonic deviations of the entorhinal region, which they ascribe to genetic or environmental disturbances in fetal brain development occurring in the second trimester. Kovelman and Scheibel[10] observed disarray in the orientation of the pyramidal cells of the hippocampus in schizophrenics. The disarray noted is likely due to disruptions in brain development early in the second trimester. Torrey et al[11] report that in comparison with controls, the pregnancy that produces autistic children is characterized by excessive maternal bleeding in the second trimester. Otake and Schull[12] note that Hiroshima survivors who were second-trimester fetuses when the atomic bomb exploded later evidenced increased levels of mental disturbance (chiefly mental retardation). It seems likely that a variety of illnesses or physical or psychological stresses at this critical point in gestation can have related effects on brain development. Though the second-trimester data for the index group are in general agreement with the results of these five studies, there is a difference; we only observe an increase in proportion of *schizophrenia* diagnoses. No increase is noted for any other diagnosis. When individuals with schizophrenia diagnoses are removed from the index and control populations, all differences between these groups disappear. Our findings seem to be specific for schizophrenia.

Can these results be specifically attributed to the type A2 influenza infection process? As noted by Hakosalo and Saxen,[6] during the epidemic Helsinki pharmacists enjoyed record sales of over-the-counter and prescription drugs. It is conceivable that one or more of these drugs or the severity of clinical symptoms (such as high fever) impinging on the fetus in the second trimester might have had long-term, teratogenic effects.

There are other considerations that might absolve type A2 influenza from being a unique schizophrenogenic agent. As mentioned, during the epidemic, over 38% of Helsinki pregnant women suffered clinical viral symptoms and an unknown number (estimated as an additional 30%) suffered subclinical infection.[6] Not all the fetuses affected by the influenza virus in the second trimester became schizophrenic. In a previous publication from the Danish High-Risk Project, Machon et al[5] have suggested that the viral infection may increase the risk of schizophrenia only in those genetically predisposed.

We should also point out that schizophrenia was known in Helsinki even before the 1957 advent of the type A2 virus. Thus, it is clear that other factors can increase vulnerability to schizophrenia. If fetal *viral* infection is a critical factor in the etiology of schizophrenia, then a broad spectrum of virus types must be involved. Other types of viruses have received attention in epidemiological and laboratory studies.[13,14]

Significance of Second-Trimester Timing of Stress

All of these considerations suggest to us that it is not so much the type of stress as the timing of stress during gestation that is critical in determining risk for schizophrenia. What is the importance of the second trimester of fetal development? By the fifth month of gestation almost all neurons slated to compose the human neocortex have been generated, but many have not yet migrated to their target structures and become positioned and synaptically connected.[15] A viral infection occurring in the second trimester may (1) interfere with the generation of late-developing cortical neurons, (2) destroy already existing neurons, and/or (3) disrupt the migration to the neocortex of the young postmitotic neurons from the ventricular zone in which they proliferate. Jacob and Beckmann[16(p1183)] suggest that the deviation in cytoarchitectonics they observed in schizophrenics "may indicate an abnormal ontogenetic development of the entorhinal region towards the end of the migration of the cerebral cortex, during the fourth to fifth fetal months." In any case the timing of the viral influence suggests disruption of cortical development.

What might be responsible for these defects of fetal neural development? There are three possibilities: (1) genetic predisposition; (2) pathogenic environmental factors; and/or (3) the interaction of these two factors. Genetic factors have been found to be quite potent in producing defective neuron migration in laboratory animals.[17] There is no reason to suspect that genetic factors are not also responsible for some cases of migratory defects seen in humans. Defective migration of critical neuron systems could conceivably be a pivotal component of the genetic liability for some types of schizophrenia.

We will attempt to organize these statements in the form of hypotheses.

1. Distortions in the organization of specific (but as yet unspecified) critical brain structures or systems will predispose an individual to schizophrenia (or a type of schizophrenia). Genetic factors can distort the organization of cortical brain structures or systems by producing second-trimester perturbations in the generation or migration of late-developing cortex-bound young neurons. Individuals experiencing such perturbation during the development of these critical brain systems will be at heightened risk for schizophrenia.

2. The critical cortical brain structures, whose inappropriate development may produce a specific predisposition to schizophrenia, are formed by the migration of young neurons from the ventricular zone to the neocortex in the period around the 16th to 24th weeks of gestation. The processes of generation, migration, and organization can be perturbed by genetic factors and/or by environmental factors, such as a fetal viral infection, occurring at this critical time. The specific neural and/or behavioral consequences of genetic and viral perturbation will not necessarily be equivalent. Consequently, genetic influences and teratogenic disturbances of neural development (or the combination of these two factors) may produce characteristic and different clinical syndromes that currently are subsumed under the "schizophrenia" diagnostic umbrella.

3. Individuals will be at markedly increased risk of developing schizophrenia if they experience *both* a viral infection during the critical period and also have a genetic predisposition for defective generation and/or migration of young neurons of the schizophrenia-critical brain structures.

4. We cannot emphasize too strongly that the fetal neuron growth factors will interact with other personal characteristics and life experiences to help determine the likelihood that the individual will develop schizophrenia.

A viral hypothesis of the origin of schizophrenia must address the fact that suspected viruses are ubiquitous, yet the lifetime prevalence of schizophrenia is less than 1%. Several explanations (individually and in combination) are possible: (1) We have already suggested that the virus will only lead to schizophrenic outcome in those genetically predisposed. (2) The viral infection may only lead to schizophrenia in individuals who later experience severe life stress. (3) It is also possible that the window of vulnerability during fetal brain development is very narrow, perhaps just a matter of days. That is, the critical period of vulnerability may involve the few days it takes to develop a specific delimited brain structure. The results of this study are compatible with all of these interpretations. The third has special interest because of its implications for preventive intervention.

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