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Original article

The role of maternal infectious diseases during pregnancy in the etiology of schizophrenia in offspring

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Summary – In 55 chronic schizophrenics, the occurrence of infectious diseases during their mothers' pregnancies was investigated. Different psychiatric diagnostic systems were compared. Infections were reported by the mothers of familial and sporadic DSM III-R schizophrenics in equal proportion. However, applying Leonhard's classification, the frequency of infections was found to be significantly increased in 'systematic' schizophrenia (mainly exogenously induced in the view of Leonhard) compared to 'unsystematic' schizophrenia (mainly genetically determined according to Leonhard's findings). Most of the infections occurred during the second trimester (nine out of 13). Thus, in the 'systematic' forms of schizophrenia (low genetic loading), maternal infections in this crucial period of neurodevelopment would appear to be important causative factors in the cytoarchitectural deviance detected in the central nervous system of schizophrenics.

maternal infection / pregnancy / schizophrenia / familial-sporadic concept / Leonhard classification

Introduction

Schizophrenia is postulated to be an etiologically heterogeneous disorder that emerges from an interaction of genetic and environmental factors (Wynne *et al*, 1978). The winterbirth seasonality which is often found in schizophrenics (Bradbury and Miller, 1985; Franzek and Beckmann, in press) draws attention to the seasonal prevalence of various bacterial and viral infectious diseases as presumed environmental factors (Watson *et al*, 1984; Torrey *et al*, 1988). Mednick *et al* (1988) were the first to find a strong relationship between the influenza A epidemic of 1957 and schizophrenia in adulthood. The offspring of women, exposed to this epidemic during the mid-trimester of gestation, subsequently had a higher risk of developing schizophrenia.

It is widely accepted that genes contribute to the etiology of schizophrenia (Gottesmann and Shields, 1982; Kringlen, 1990). However, the modes of transmission remain elusive, despite modern diagnostic criteria (WHO, 1979; APA, 1987). Within these classification systems, a positive family history of schizophrenia or related disorders in the pedigree, signifies high genetic risk with familial transmission (Tsuang *et al*, 1985). The absence of schizophrenia among relatives indicates the sporadic, mainly environmentally induced group (Kendler and Hays, 1982). This familial/sporadic distinction is assumed to be a useful strategy in schizophrenia research (Murray and Reveley, 1985; Lewis *et al*, 1987). Another approach in the classification of schizophrenia was advanced by Karl Leonhard (Fish, 1962; Hamilton, 1976; Astrup, 1979; Leonhard, 1979; Ban, 1982). Leonhard divided the entire disease into distinct subgroups, based on symptomatology, course and outcome. As an essential result of this approach he postulated two main categories: systematic and unsystematic forms. Subsequently, he investigated the inheritance of each of these categories. High family loading of psychoses was evident within the unsystematic forms. In contrast, almost no positive family history appeared in the systematic forms. Based on this significantly different heredity, Leonhard (1980) designated the unsystematic forms as being mainly genetically determined and the systematic forms as being sporadic, environmentally– induced forms.

Table I. Demographic and clinical characteristics of patients and age of their mothers at the time of the interview with regard to the various diagnostic groups. (Using *t*-test no significant differences were obvious between any of the diagnostic groups.)

		DSM III-R		*Leonhard criteria*	
	Total sample (n = 55)	*Familial* (n = 19)	*Sporadic* (n = 36)	*Unsystematic* (n = 32)	*Systematic* (n = 23)
Patients' age at study	35.8 ± 9.12	36.2 ± 9.72	35.6 ± 8.94	36.6 ± 8.82	34.8 ± 9.63
Age at first admission	22.2 ± 6.65	20.9 ± 8.35	22.9 ± 5.56	22.7 ± 5.97	21.5 ± 7.58
Duration of illness	17.8 ± 10.04	17.6 ± 10.59	17.9 ± 9.71	16.0 ± 8.72	20.2 ± 11.39
Sex (female/male)	13/42	6/13	7/29	8/24	5/18
Mothers' age at study	64.7 ± 9.27	63.5 ± 10.14	65.4 ± 8.83	64.4 ± 9.62	65.1 ± 8.95

The purpose of the present study was to investigate in retrospect the occurrence of infectious diseases during pregnancy by comparing the following diagnostic systems: the familial/sporadic strategy in DSM III-R and the unsystematic/systematic distinction according to Leonhard.

Subjects and methods

Starting in 1990, mothers of chronic schizophrenics were interviewed to investigate in retrospect various adverse events which had occurred during pregnancy, delivery, and the postnatal period and their relation to the development of schizophrenia. In this paper we report on the preliminary data about the occurrence of maternal infections during pregnancy.

Schizophrenic patients whose mothers were alive and willing to be interviewed were drawn from patients at the Department of Psychiatry at Wuerzburg University and from the State Hospital Lohr/Main. The data of 55 chronic schizophrenics (12 women, 43 men) have so far been collected. The patients had to fulfil the diagnostic criteria of chronic schizophrenia according to DSM III-R and to the Leonhard classification. It should be emphasized here that Leonhard's criteria for inclusion are much more restrictive than those of DSM III-R. On the basis of all available data and of personal examination, patients were diagnosed by two psychiatrists (H Beckmann, E Franzek) working independently of each other. Both are experienced in DSM III-R and the Leonhard classification. In a recent study with chronic schizophrenics, they reached a coefficient of agreement (Cohen's kappa) of 0.88 within the Leonhard classification (Franzek and Beckmann, 1991). All the patients were clearly allocated to familial or sporadic cases (DSM III-R) and unsystematic or systematic forms (Leonhard). Table I shows important demographic and clinical data of the 55 patients as a whole and after separating into the diagnostic subsamples and the mean age of their mothers at the time of the interview.

Leonhard diagnoses (systematic *vs* unsystematic schizophrenia) were established by taking into account cross-sectional symptomatology, course and outcome. Family history was not considered. In the unsystematic schizophrenia, the acute symptomatology is usually polymorphous with a wide range of symptoms and remissions are the rule. They lead to residual states of varying degrees of severity after one or several attacks. In contrast, the systematic schizophrenias begin insidiously and take a chronic non-remitting course. They always lead to severe defective states and no marked change in the symptoms and signs takes place once the residual syndromes are established. The latter are meticulously elaborated by Leonhard and confirmed by others (Fish, 1962; Astrup, 1979; Ban, 1982; Franzek and Beckmann, in press). A familial form of schizophrenia (DSM III-R) was presumed when schizophrenia was present in first and/or second degree relatives. The family history data were taken from the hospital records of the patients containing information from their family doctors, reliable relatives, and acquaintances.

Familial/sporadic distinction according to DSM III-R

The 55 patients had a total of 38 relatives who had undergone psychiatric hospitalisation. Hospital records were available for all of these relatives. Twenty-six of them were diagnosed as schizophrenics and were related to 19 out of the 55 index patients. This results in 19 familial and 36 sporadic forms of DSM III-R schizophrenia.

Leonhard classification

Twenty-three systematic and 32 unsystematic forms (diagnosed independently of each other by E Franzek and H Beckmann).

Genetic risk supposed to be similar in both classification systems

Thirteen of the patients who were diagnosed as unsystematic schizophrenics (mainly genetically determined according to Leonhard) had a schizophrenic first or second degree relative (familial form according to DSM III-R). This subsample of patients was defined as the 'high genetic risk group'.

Seventeen of the patients without a schizophrenic relative (sporadic form) fulfilled the diagnostic criteria of systematic schizophrenia (mainly environmentally determined according to Leonhard). These patients formed a 'low genetic risk group'.

Wenar (1963), Joffe and Grisso (1985), and O'Callaghan *et al* (1990) likewise emphasized that mothers reliably and accurately recall the period of gestation and delivery and that passing of time does not diminish this reliability. Thus we felt sufficient justification to choose a retrospective study design.

We have developed a highly structured questionnaire (Stöber, in preparation). All questions concerning course of pregnancy, delivery and post-natal development were asked person-to-person and notable events were written down in detail. Great importance was placed on the occurrence of infectious diseases during pregnancy. In this context, the first question was: 'Did you suffer from any infectious diseases during pregnancy?' Then the interviewer regularly asked if the subject had suffered from the following:

nasal catarrh or cough lasting for at least 2 weeks; common cold; bronchitis; influenza; pneumonia; sinusitis; otitis media; tonsillitis; gastroenteritis; urinary infection (cystitis, pyelonephritis); localized pyogenic infections (abscess, phlegmone); salmonellosis; rubella; measles; mumps; varizella; (ictero-)hepatitis; herpes zoster; veneral diseases; osteomyelitis; meningitis; and sepsis.

If any of these infections were recalled, the interviewer (G Stöber) exactly noted its duration and when it occurred during the gestational period (month and trimester).

The questionnaire was carried out on 20 control mothers (mean age 65.7 years) with physically and mentally healthy children (mean age 32.4 years). In the controls, pregnancy, delivery, and post-natal development were vividly remembered.

The mothers of schizophrenic patients were contacted by letter and/or phone and the purpose of the study was pointed out to them. None of them refused a personal visit. Every interview took about 2 h.

The interviewer (G Stöber) was not aware of the differentiation of the diagnoses into familial/sporadic and unsystematic/systematic schizophrenia or family history. He was not permitted to ask a question about this issue during the interview. This rule was applied until all 55 mothers had been interviewed.

Results

Thirteen out of 55 (24%) mothers of adult schizophrenics recalled an infectious disease during pregnancy, compared to four out of 20 control mothers (20%). In comparison to trimesters I and III, the frequency of maternal infectious diseases was significantly increased in trimester II in the patients' group ($\chi^2 = 7.54$, df = 2, $P < 0.05$). Not less than 46% of the infections occurred during the fifth month of gestation. This was also statistically significant ($\chi^2 = 19.55$, df = 8, $P < 0.02$, fig 1).

Table II. Types of maternal infections ($n = 13$) and their allocation to the three trimesters of gestation in the entire sample.

Type of infection	*Trimester of gestation* I	II	III
Influenza	1	4	0
Cold with fever	0	2	0
Pyonephritis	0	1	1
Otitis media	0	1	0
Sinusitis	1	0	0
Tonsillititis	0	1	0
Sepsis	0	0	1

As shown in table II, most of the infections were of the respiratory tract. Six out of the 13 mothers (46%) remembering an infectious disease reported influenza or the common cold with fever at midgestation.

In the total sample, there were no substantial differences in the frequency of maternal infections between the familial and sporadic forms of DSM III-R schizophrenia (fig 2A). In contrast, taking the Leonhard classification as a diagnostic basis, highly significant differences occurred (fig 2B). Only 6.3% of the unsystematic forms, but 47.8% of the systematic forms were associated with maternal infection ($\chi^2 = 15.2$, df = 1, $P < 0.001$).

Figure 3 shows the subsample of patients (n = 30) which was supposed to be at equal genetic risk in both classification systems. In the high-genetic risk group (*ie* diagnosis of unsystematic schizophrenia and of familial schizophrenia) mothers did not report any infection during pregnancy. In contrast, 41% of mothers in the low-genetic risk group (*ie* diagnosis of systematic and sporadic schizophrenia) recalled an infection during pregnancy. This difference was also significant ($\chi^2 = 4.87$, df = 1, $P < 0.05$).

Discussion

The relationship of maternal infectious diseases during pregnancy to the development of schizophrenia

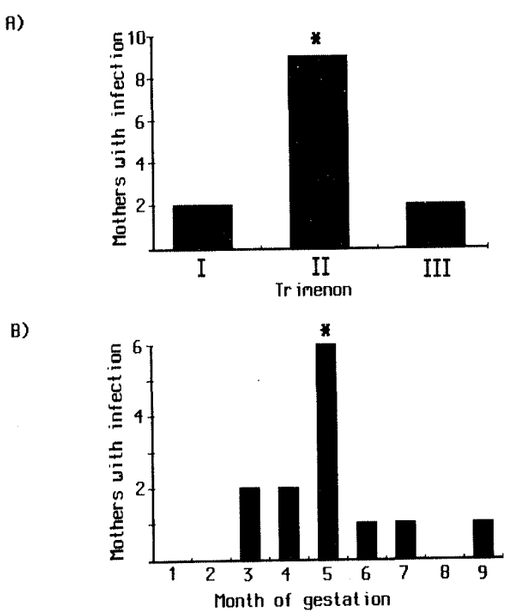

Fig 1. Number of infections in the total sample (n = 13) and their distribution between trimester (**A**) and between month of gestation (**B**). In trimester II, maternal infectious diseases were significantly higher than in trimester I and III ($P < 0.05$, df = 2, $\chi^2 = 7.54$). With respect to months of gestation, there was a significantly higher number of maternal infections in the fifth month ($P < 0.02$, df = 8, $\chi^2 = 19.55$) compared to the other months.

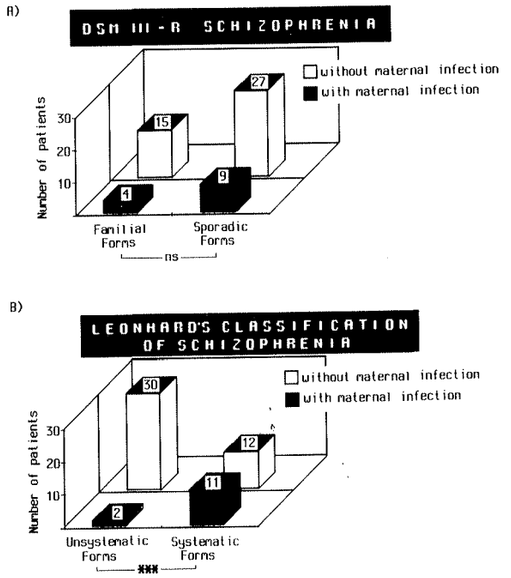

Fig 2. Maternal infections co-varied with familial/sporadic distinction in DSM III-R (**A**) and with Leonhard's main categories (**B**) of schizophrenia. No substantial difference was found in the familial/sporadic distinction (**A**: ns, df = 1, $\chi^2 = 0.437$). In contrast, the difference between unsystematic schizophrenia in the Leonhard classification was highly significant (**B**: $P < 0.001$, df = 1, $\chi^2 = 15.2$). Here, maternal infections mostly occurred in the systematic schizophrenias.

in adulthood is a matter of controversy. Based on population data, several research groups drew attention to the fact that the risk of schizophrenia is higher for those who were in mid-gestation during the influenza A epidemic of 1957 (Mednick *et al*, 1988; Barr *et al*, 1990; O'Callaghan *et al*, 1991). However, none of the studies on pregnancy and birth complications had ever demonstrated an increased frequency of prenatal infections among mothers of a representative sample of schizophrenics (McNeil, 1987). With respect to maternal infectious diseases during pregnancy, 55 mothers of adult chronic schizophrenics were interviewed using a highly structured questionnaire. Twenty-four percent of the mothers reported an infection during pregnancy and in most cases the infection was of the respiratory tract. Contrary to Watson *et al* (1984) and Torrey *et al* (1988), we did not find any case of diphtheria, scarlet fever, rubella, varicella

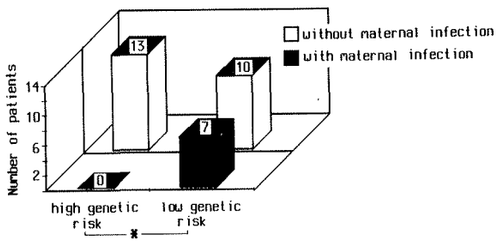

Fig 3. Subsample of patients (n = 30) that had an equal genetic risk in both DSM III-R and Leonard's classification. The high risk group represents patients who fulfel not only the criteria of familial schizophrenia in DSM III-R but also those of Leonhard's unsystematic schizophrenia. No mother out of this group (n = 13) had suffered from an infectious disease. The low risk group comprises patients (n = 17) who fitted the definition of sporadic schizophrenia in DSM III-R and Leonhard's systematic forms. With respect to the occurrence of maternal infectious diseases during pregnancy, there was a significant difference between the low risk and the high risk group ($P < 0.05$, df = 1, $\chi^2 = 4.87$).

or measles (table II). Sepsis as a very serious illness occurred in only one case (1.8%) which is in accordance with the findings of DeLisi *et al* (1988). In corroboration with the findings of Barr *et al* (1990) and O'Callaghan *et al* (1991), we found a significantly increased number of maternal infections in mid-trimester and in particular in the fifth month of gestation in the total sample.

Using the familial/sporadic concept of Lewis *et al* (1987), an equal proportion of infections occurred in both groups. Within the Leonhard classification, however, maternal infections were rarely found in patients with unsystematic schizophrenia which is mainly transmitted genetically, according to Leonhard's findings. On the contrary, they were highly significantly associated with the systematic (*ie* nongenetic) schizophrenics. This significant association persisted in a distinct subsample of patients, labeled as 'low-genetic risk group' (fig 3), *ie* fulfilling the definition of sporadic schizophrenia (Lewis *et al*, 1987) and systematic schizophrenia (Leonhard, 1980). Interestingly, in the 'high-genetic risk group', *ie* patients not only with familial but also unsystematic schizophrenia, maternal infections were not traceable at all. This indicates that maternal infections did not substantially contribute to the etiology of genetically vulnerable forms of schizophrenia. However, in the 'low-genetic risk group' (not only systematic but also sporadic schizophrenia, fig 3) and in particular in Leonard's systematic schizophrenics (fig 2B), maternal infections during gestation seem to be of great etiological importance. Nearly 50% of the mothers in these groups unequivocally recalled an infectious disease during pregnancy. This stresses that there is a link between disturbances of prenatal brain maturation and the development of schizophrenia in adulthood (Jakob and Beckmann, 1986; Falkai *et al*, 1988; Arnold *et al*, 1991; Beckmann and Jakob, 1991). Jakob and Beckmann (1986) reported definite cytoarchitectural deviance in the rostral entorhinal region of the parahippocampal gyrus in postmortem studies of schizophrenics. This was explained by a disruption of neuronal migration. In particular during the second trimester of gestation, neurons migrate from the ventricular zone to their predetermined positions within the central nervous system (Rakic, 1978, 1988). For this reason, our results suggest that maternal infection during this period is an important etiological factor in the disturbance of neurodevelopment and that there is a positive correlation only to forms with low genetic loading and in particular to the systematic forms of schizophrenia in Leonhard's concept.

The findings shed new light on the heterogenous etiology of schizophrenic syndromes and on the validity of different diagnostic and nosological systems.

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