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SPECIAL ISSUE

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Childhood central nervous system infections and risk for schizophrenia

Abstract Central nervous system (CNS) viral infections have been suggested to increase the risk of schizophrenia, although most of the evidence is indirect and comes from rather few studies on exposure to various infections in general. In the Northern Finland 1966 Birth Cohort the association between schizophrenia and other psychoses and childhood CNS infections has been analysed, and in this paper we present the follow-up results up to the end of 1994 and 1997.

Data regarding the infections were collected prospectively between 1966–1980 and data on psychoses from 1982. The registered psychiatric diagnoses were validated using the DSM-III-R classification. Out of the 11017 subjects (96% of all births in that year) 145 had suffered a CNS infection during childhood, which in 102 cases was a viral infection. In the follow-up to the end of 1994, 76 had schizophrenia, and their number increased to 100 to the end of 1997. In addition, up to the end of 1994, 52 patients had a non-schizophrenic psychosis.

Four cases in the schizophrenia patient group and none of the patients with other psychosis had suffered a viral CNS infection. None of the schizophrenia cases and two of the patients with other psychosis had had a bacterial infection. The adjusted odds ratio for schizophrenia after a viral CNS infection was 4.8 (95% confidence intervals [CI] 1.6–14.0) in the follow-up to the end of 1994 and 2.5 (0.9–7.0) in the follow-up to the end of 1997. The clinical course variables did not differ between the schizophrenia patients with or without CNS infection.

Our results suggest that viral CNS infections during childhood may have a role as a risk factor for schizophrenia. Their role may be modest at the population level due to their relative rareness.

Key words birth cohort · CNS infections · psychosis · schizophrenia · viral infection

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Introduction

There is an undoubted genetic element in the aetiology of schizophrenia, but twin and high-risk studies also indicate an environmental component (Cannon et al. 1998; Hodges et al. 1999). It is also probable that multiple genes and multiple environmental factors interact. In previous studies it has been shown that infections, such as prenatal exposure to influenza or polioviruses, may increase the risk of schizophrenia (O'Callaghan et al. 1994; Suvisaari et al. 1999a). Besides of intrauterine infections, exposure to early childhood infectious diseases may also be important (Westergaard et al. 1999).

In this paper we have three aims: 1) to review the existing epidemiological studies on the relation between infections in general and especially in the CNS and risk of psychosis; and 2) to clarify this association empirically by using the Northern Finland 1966 Birth Cohort. This is done by reviewing our (Rantakallio et al. 1997) earlier analysis until the end of 1994, and by updating and expanding it until the end of 1997. In addition, we have 3) a theoretical discussion on the possible mechanisms of this association.

Review of epidemiological studies

Viruses with an affinity for the CNS have been suggested to be involved in the etiology of schizophrenia (Murray et al. 2003). Second trimester respiratory infections have been observed to be associated with increased risk of schizophrenia and schizophrenia spectrum disorders in adulthood (O'Callaghan et al. 1994; Brown et al. 2000), although also negative results exist (Cannon et al. 1996; Westergaard et al. 1999). The reported increased frequency of schizophrenia in the offspring of women who were in their second trimester of pregnancy during influenza epidemic suggests that maternal virus infection may lead to aberrant neurodevelopment (Akil and Weinberger 2000). Mednick and coworkers interpreted their results from the Helsinki 1957 influenza study that viral infection occurring during the fast development of critical brain regions acted as a teratogen and increased the risk of schizophrenia (Mednick et al. 1998). Neurological soft signs often preceding adult-onset schizophrenia suggest a neurodevelopmental origin and could reflect physical illness, such as CNS infection, in childhood (Leask et al. 2002).

In the study of Westergaard et al. (1999) it was observed that an increased risk of schizophrenia was associated with having many siblings, which the authors found suggestive of environmental factors, such as exposure to infections in childhood, which, however, were not directly evaluated. In the study of Leask and coworkers (2002) no association between common childhood viral infections and schizophrenia was found. In their series information regarding the infections was gathered from the parents and no serological confirmation was used. Except of the series of Leask et al. (2002) and Rantakallio et al. (1997) there are no widespread studies on postnatal viral CNS infections and the risk of schizophrenia. Thus there is paucity in the available data and no replicating studies. The previous findings from the Northern Finland 1966 Birth Cohort project together with more indirect data from exposure to prenatal viral infections suggest that viral infections may affect the central nervous system and be an etiological factor for schizophrenia (Rantakallio et al. 1997).

Contribution of the Northern Finland 1966 Birth Cohort

Material and methods

The Northern Finland 1966 Birth Cohort is based upon 12058 live-born children in the provinces of Lapland and Oulu with an expected delivery date during 1966 (Rantakallio 1969). Data on biological, socioeconomic and health conditions, living habits and family characteristics were collected prospectively from pregnancy up to the age of 31. Until the age of 16, 284 had died and 757 emigrated, leaving 11017 eligible individuals in Finland. The research process and sample have been previously described by Isohanni et al. (2000).

Data concerning CNS infections up to the age of 14 were collected in several ways between 1966 and 1980. The most important sources were records of admissions to the four children's hospitals in the area from 1966 to 1972 and Finnish Hospital Discharge Register (FHDR) thereafter until 1980. The nation-wide Finnish Hospital Discharge Register covers all hospitals. An additional 12% of the cases were identified from other sources, mainly the records of neurological outpatient clinics.

The psychiatric outcome (hospital-treated mental disorders) was followed up in two phases: to the end of 1994 and 1997. All cohort members over 16 appearing on the FHDR until the end of 1994 and 1997 for any mental disorder (i. e. ICD-8 diagnoses 290–309, DSM-III-R diagnoses 290–316, and ICD-10 diagnoses F00-F69, F99) were identified. All case records were scrutinized and diagnoses were checked against the DSM-III-R (Isohanni et al. 1997; Moilanen et al. 2003).

The age of onset of schizophrenia was identified from the first psychotic symptoms appearing in case notes. Comorbid diagnoses of substance use disorder (DSM-III-R codes 303.9 and 305) and mental retardation (including borderline intellectual functioning (IQ 50–84; DSM-III-R codes 317.00 and V40.00) were also recorded. The use of inpatient care was evaluated as a proxy measure for the severity of clinical symptomatology by recording the number of hospital treatment periods and length of stay in hospital. This latter measure was assessed in three ways: cumulative number of treatment days, proportion of days stayed at the hospital after the onset of psychosis, and the longest treatment period. As mediating and confounding factors father's social class, perinatal brain damage, mental retardation, childhood epilepsy were also recorded. Children were considered to have perinatal brain damage if they had an Apgar score of zero at one minute or less than five at 15 minutes, convulsions during the neonatal period, or a diagnosis of asphyxia, brain injury, or intraventricular haemorrhage at discharge, but did not have CNS malformation, chromosomal aberrations, or hereditary CNS degeneration.

Statistics

The risk of schizophrenia was expressed in terms of cumulative incidence ratio with 95% confidence intervals (CI). Multiple logistic regression analysis was used to examine the association between CNS infection and schizophrenia, when the confounding factors were adjusted. Population attributable risk and its 95% confidence interval were calculated according to Leung-Kupper methods (Lachin 2000).

Results

There were 145 verified CNS infections in the study population, and 102 of them had a viral infection. The 1994 diagnostic validation identified 76 patients (51 males) with schizophrenia, four of them having had CNS viral infection. Until the end of 1997 the total number of schizophrenia had increased to 100 cases (65 males), but none of the new cases had a history of CNS infection. In addition, until 1994 there were 52 cases of other psychosis, which increased to 55 at the end of 1997.

The cumulative incidence of schizophrenia in the 1994 follow-up was 0.7 % (72/10872), and in the 1997 follow-up 0.9 % (96/10791) among those not exposed in childhood to CNS infections. The cumulative risk for the exposed until the end of 1994 was 2.8 % (4/145), which remained the same up to the end of 1997. Thus the relative risk for schizophrenia was 4.2 (95 % CI 1.5–11.3) in the 1994 follow-up, and somewhat smaller in the more prolonged 1997 follow-up, i. e. 3.2 (1.2–8.4). The population attributable risks for schizophrenia following CNS infection were 4 % (95 % CI 1.9–4.8) and 2.7 % (0.7–10.6) respectively.

Four cases of schizophrenia and none of the patients with other psychosis had suffered a viral CNS infection. None of the schizophrenia cases and two of the patients with other psychosis had had a bacterial infection. In schizophrenia patients two cases had Coxsackie B5 infection, while adenovirus 7 and mumps were recorded in one case each. Only one of these four cases of CNS infection was a female. Thus the cumulative incidence ratio of schizophrenia was even higher among those with a past viral CNS infection; 4.5 (95 % CI 1.6–12.6). The clinical course variables of schizophrenia did not differ between the schizophrenia patient groups with or without a previous CNS infection (Table 1).

Table 2 shows the association (adjusted odds ratios [OR]) between schizophrenia and viral CNS infection during childhood as well as other risk factors. For comparison, Table 2 contains also the 1994 follow-up results. The complete results are described by Rantakallio et al. (1997).

Table 2 Adjusted odds ratios (OR) and their 95 % confidence intervals (CI) for the association between various exposures and schizophrenia estimated by the multiple logistic regression model in the Northern Finland 1966 Birth Cohort, 1994 and 1997 follow-up data

Variables	1994 OR (95 % CI)	1997 OR (95 % CI)
Paternal social class		
– I + II	1.06 (0.58–1.93)	1.12 (0.66–1.90)
– IV	0.93 (0.51–1.70)	1.18 (0.71–1.97)
– farmers	0.93 (0.47–1.82)	0.79 (0.42–1.49)
male sex	1.83 (1.13–2.97)	1.71 (1.13–2.58)
viral CNS infections	4.80 (1.65–14.0)	2.48 (0.88–7.0)
IQ < 85	4.77 (10.3)	3.48 (1.65–7.35)
perinatal brain damage	4.55 (1.72–12.1)	3.84 (1.52–9.72)
cerebral palsy	0.64 (0.11–3.77)	0.74 (0.12–4.12)
childhood epilepsy	1.13 (0.33–3.82)	1.05 (0.33–3.38)

Discussion

The purpose of this part of the Northern Finland 1966 Birth Cohort study was to investigate the possibility of an association between childhood CNS infection and adult onset psychosis. In the CNS infection group schizophrenia was more common as compared to the non-exposed group. Age at onset, the number and total length of the psychiatric hospitalisation did not, however, differ between the two groups indicating that the psychosis was not more severe in the CNS infection group.

The impact of the various non-genetic or environmental risk factors (e. g. obstetric complications; Jones et al. 1998; Cannon et al. 2002) on later schizophrenia is generally small. The same was found in our study as the earlier follow-up resulted moderate risk levels (Rantakallio et al. 1997), which, however, diluted during the more prolonged follow-up as all schizophrenia patients with previous CNS infection belonged to the early-onset schizophrenia group. The size of the group of other psychoses was smaller and did not contain enough patients with previous CNS infection to be statistically assessed.

Theoretical discussion

There are several hypotheses how infections may cause schizophrenia. It could be a direct result of an active in-

Table 1 Some clinical course variables in patients with CNS infection and schizophrenia cases without CNS infection

	Age at onset	Cumulative days in hospital	Proportion of days stayed at hospital after onset (%)	Number of hospitalisations	Longest hospital period (days)
Case1	20	180	3.8	4	143
Case2	20	470	12.7	8	124
Case3	21	955	25.6	20	198
Case4	27	17	1.4	1	17
	Median	Median	Median	Median	Median
Schizophrenia patients without CNS infection	22	227	10.2	5	120

fection, which disrupts cellular and molecular functioning. A viral infection may also act in a more subtle way, for example by mimicking CNS neurotransmitters and receptors. Schizophrenia could also be caused by a latent virus, which is periodically reactivated, or by retroviral genomic material integrated into host-cell DNA. Finally, it has been suggested that it is the immune response, rather than the infection itself, that is responsible for the development of schizophrenia. Although most attention has focused on the prenatal exposure to infection as a risk factor for schizophrenia, the timing of the infections may vary from the prenatal period to the onset of psychosis (Kirch 1993).

The association of CNS infections in childhood and increased risk of schizophrenia in adults may be related to abnormalities in immune mediators, such as cytokines and chemokines or raised antibodies, triggered by a postnatal viral infection (Katila et al. 1999). Viral meningoencephalitis, and bacterial meningitis, tuberculosis and more rarely mumps can lead to a more direct central nervous system involvement. For common viral infections, autoimmune responses to the CNS can be triggered by chicken pox, measles, scarlet fever and rheumatic fever. Whooping cough can lead to punctuate haemorrhages in the brain following explosive coughing leading to neurological soft signs, which may also be caused by meningitis and tuberculosis (Leask et al. 2002). In some studies common childhood infections have not been associated with adult psychotic illness, although findings remain vulnerable to selection and recall bias (Leask et al. 2002).

The model of McGlashan and Hoffman (2000) suggests that schizophrenia arises from critically reduced synaptic connectedness as a result of developmental disturbances during gestation and early childhood and/or synaptic pruning during adolescence. Postnatal mammalian CNS development is characterized by synaptogenic overelaboration in the cortex followed by a gradual reduction. In humans this process is largely complete by age of 2 years in sensory areas but not complete until midadolescence in prefrontal and association areas, which are centrally affected in schizophrenia. Thus, in addition to other environmental stressors, such as famine, malnutrition, Rhesus incompatibility and severe environmental stress, the CNS infections in early childhood may adversely affect the developing brain and result a non-specific developmental delay acting as a risk factor for schizophrenia (Beckmann 1999; Goldfield and Wolff 2002; Hollis 2003). Differences in the rates of CNS infections may also contribute in the observed variation of incidence changes of schizophrenia (Suvisaari et al. 1999b; Boydell et al. 2003).

Conclusions

Our results from a large, general population birth cohort with laboratory confirmation of infection and validation of individual psychiatric diagnoses showed a higher rate of schizophrenia in patients with a previous viral CNS infection during childhood supporting the connection. The observed association may be due to a more widespread vulnerability of maturing brain to various adverse environmental factors. In the 1997 follow-up the risk level was lower than reported from the previous follow-up (see also Rantakallio et al. 1997) suggesting that multiple factors interact in the genesis of schizophrenia and only modest contributions of single individual factors. In addition, there was a Coxsackie epidemic, which may have increased association by period effect (Rantakallio et al. 1970). The rather small number of cases should also be viewed with caution owing to the danger of type II statistical errors. As far as we know there are no other studies demonstrating association between CNS viral infections and increased risk of schizophrenia. In the future the replication and verification of our finding with a more extensive study population is needed.

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