Childhood Central Nervous System Viral Infections and Adult Schizophrenia

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Objective: An earlier Finnish cohort study suggested that childhood viral CNS infections are associated with a fivefold increased odds of developing schizophrenia in adulthood. The authors sought to replicate this finding.

Method: From the archives of the Department of Virology of the National Public Health Institute in Finland, 320 individuals born between 1960 and 1976 who had suffered virologically confirmed CNS infections before their 15th birthdays were identified. Of the infections, 202 had been caused by enteroviruses. The sample was followed up in the 1969–2000 records of the National Hospital Discharge Register of Finland to identify all cases of schizophrenia that emerged.

Results: The cumulative incidence of schizophrenia was 0.94% in the whole sample and 0.99% among individuals who had suffered enteroviral infections. These rates are comparable to that found in the general population.

Conclusions: Childhood viral CNS infections were not associated with increased risk of schizophrenia.

Viral infections are suspected of playing a role in the etiology of schizophrenia (1). The North Finland 1966 Birth Cohort study indicated that childhood viral CNS infections were associated with an almost fivefold increased odds of developing schizophrenia in adulthood (2). Two of the four individuals who had suffered childhood viral CNS infections and developed schizophrenia in adulthood had had infections caused by coxsackievirus B5 (CBV-5), an enterovirus, giving an incidence of schizophrenia of 12.5% among those with neonatal meningitis caused by CBV-5 (2). Our previous study (3) showing an association between prenatal exposure to poliovirus epidemics and later development of schizophrenia also suggested that enteroviruses are involved in the etiology of schizophrenia. In the present study we sought to verify the findings from the North Finland 1966 Birth Cohort in a sample of 320 individuals with virologically confirmed childhood CNS infections.

Method

The Department of Virology at the National Public Health Institute, founded in 1953, was the first viral laboratory in Finland. During the 1960s and 1970s, it analyzed clinical samples sent from hospitals throughout Finland. One branch of the laboratory specialized in enteroviral infections. Samples from individuals with suspected enteroviral diseases were therefore particularly often sent to be investigated in our laboratory.

Results of all virological analyses from each individual patient were stored on a card that also contained the patient’s name, date of birth or social security number, and clinical diagnosis; it often also provided a brief description of the presenting symptoms, treating hospital, date when the samples had been taken, and the type of samples (blood, fecal, cerebrospinal fluid). These cards were scrutinized to identify all individuals born from 1960 to 1976.
who had suffered virologically confirmed CNS infections before their 15th birthdays. The names and birth dates of those with missing social security numbers were linked with information from the Population Register Center to obtain their social security numbers.

The social security numbers were then matched with National Hospital Discharge Register data to obtain information on all hospital treatments from 1969 to 2000. Schizophrenia was defined as a 295 diagnosis according to ICD-8 and ICD-9 diagnostic systems, used between 1969 and 1995, or an F20 diagnosis according to ICD-10, used since 1996. These codes comprise schizophrenia, schizophreniform disorder, and schizoaffective disorder. Cumulative incidence was calculated by dividing the number of individuals who developed schizophrenia by the number of individuals in the sample. We calculated the exact 95% confidence intervals (CIs) by using the Bayesian method.

The study was approved by the institutional review boards of the National Public Health Institute and of the National Research and Development Centre for Welfare and Health, which maintains the National Hospital Discharge Register.

**Results**

The sample consisted of 370 individuals. The social security number for 47 of them could not be found. One subject had to be excluded because two different viruses had been identified, and it was thus unclear which had caused the infection. Two subjects were excluded because of missing clinical diagnoses. Therefore, the final sample contained 320 individuals. Almost all had been treated in public hospitals, and the samples came evenly from different parts of Finland. Their clinical diagnoses were encephalitis (N=28), meningitis (N=256), meningoencephalitis (N=17), and “seizures” (N=19). The infections had been caused by adenoviruses in 30 cases, by mumps in 84 cases, by enteroviruses in 202 cases—including 40 caused by CBV-5—and by other viruses in four cases. The mean age when the infection occurred was 3.8 years (SD=3.0, range=0.0–11.6), and the mean age at the end of the follow-up was 32.0 years (SD=4.5, range=23.3–41.0).

Of the subjects with childhood viral CNS infections, three developed schizophrenia during the follow-up. Two of them had suffered enteroviral infections (one caused by CBV-5) at the ages of 42 and 25 months, respectively; the clinical diagnoses were encephalitis in the former case and seizures in the latter case. The ages at onset of schizophrenia for these two subjects were 21 years and 16 years, respectively. The third individual to develop schizophrenia had had adenovirus meningitis at the age of 27 months and developed schizophrenia at the age of 23 years. In addition, there was one subject with more than 30 admissions as an adult because of substance abuse and borderline personality disorder who had received a diagnosis of psychotic disorder not otherwise specified at the age of 37 years and who had suffered an enteroviral encephalitis at the age of 66 months. The cumulative incidence of schizophrenia was 0.94% (95% CI=0.00%–2.72%) among those with any CNS infection and 0.99% (95% CI=0.00%–3.53%) among those with enteroviral CNS infections. The risk of schizophrenia did not differ among those with enterovirus infections and those with other types of infections (odds ratio=1.16, 95% CI=0.10%–12.87%).

**Discussion**

The observed cumulative incidences of 0.94% in the total sample and 0.99% among those who suffered enteroviral CNS infections are similar to the register-based cumulative incidence of schizophrenia of 0.74% until 1995 in Finnish birth cohorts born from 1960 to 1969, a figure we calculated by using our register-based data (see reference 3) and the cumulative incidence of 0.91% observed in the North Finland 1966 Birth Cohort (4). Compared with the study by Rantakallio et al. (2), our investigation tracked a sample that was three times larger and benefited from knowledge of the causative virus in each case. The main limitation was that the diagnosis of schizophrenia was based on register data rather than on face-to-face assessment. However, the reliability of register diagnoses of schizophrenia in the National Hospital Discharge Register has been found to be good, and the kappa value for the agreement between register- and interview-based diagnoses was 0.84 in a cohort study (5).

Our data provide no support for the hypothesis that childhood viral CNS infections, or enteroviral CNS infections in particular, are associated with a markedly increased risk of developing schizophrenia. However, our sample size was still inadequate for examining whether a CNS infection caused by CBV-5 in particular would increase the risk of adult-onset schizophrenia. It also is possible that individuals who have suffered viral encephalitis are at increased risk of developing schizophrenia. There were 28 individuals whose clinical diagnosis was encephalitis, and two of them developed schizophrenia in adulthood. Since we have no information on the reliability of differentiation between viral meningitis and encephalitis in clinical work back in the 1960s and 1970s, we are cautious in drawing any conclusions based on our study sample. Instead, we suggest that the possible role of viral encephalitis in the etiology of schizophrenia should be studied further.

References


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