Risk of leukaemia in children infected with enterovirus: a nationwide, retrospective, population-based, Taiwanese-registry, cohort study

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Summary

Background The association between enterovirus infections in children and risk of leukaemia is unclear. We aimed to assess the risk of leukaemia after enterovirus infection in children.

Methods We did a nationwide retrospective cohort study by analysing data from the National Health Insurance Research Database (NHIRD) in Taiwan. Children with enterovirus infections aged younger than 18 years were identified. With use of computer-generated random numbers, children not infected with enterovirus were randomly selected and frequency matched (1:1) with children infected with enterovirus by sex, age, urbanisation level, parental occupation, and index year of enterovirus infection. We only included children with complete baseline data for age and sex and who had at least three clinic visits with the diagnosis of enterovirus infection. The diagnosis date of the first clinic visit for the enterovirus infection was defined as the index date for initiation of follow-up person-year measurement and participants. All study patients were followed up until they developed leukaemia, were lost to follow-up, withdrew from the NHI programme, or until the end of the study without leukaemia (censored). Our primary endpoint was a diagnosis of leukaemia during follow-up.

Findings Insurance claims data for 3 054 336 children younger than 18 years were randomly selected from all insured children in the NHIRD. We identified 282 360 children infected with enterovirus and 282 355 children not infected with enterovirus between Jan 1, 2000, and Dec 31, 2007. The incidence density rates of leukaemia were 3·26 per 100 000 person-years for the enterovirus-infected and 5·84 per 100 000 person-years for the non-enterovirus-infected cohorts. The risk of leukaemia was significantly lower in the enterovirus-infected cohort than in the non-enterovirus-infected cohort (adjusted subhazard ratio [SHR] 0·44, 95% CI 0·31–0·60; p<0·0001). Children infected with enterovirus have a reduced risk of both lymphocytic leukaemia (adjusted SHR 0·44, 0·30–0·65; p<0·0001) and acute myeloid leukaemia (adjusted SHR 0·40, 0·17–0·97; p=0·04). Herpangina and hand-foot-and-mouth disease were the main diseases associated with the reduced risk of leukaemia.

Interpretation The association between enterovirus infection and the reduced risk of developing leukaemia supports Greaves' delayed infection hypothesis for the cause of childhood leukaemia.

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Introduction

Leukaemia is the most common cancer in children, accounting for more than a third of childhood malignancies.[1] Acute lymphoblastic leukaemia is the predominant leukaemia in children, accounting for 70–80% of cases, followed by acute myeloid leukaemia, which accounts for roughly 15–17%. Chronic myeloid leukaemia and other forms of myeloid leukaemia rarely exceed 4% of all types of leukaemia in children.[1–3] However, the causes of leukaemia remain unclear. Several studies[4,5] have proposed that genetic alterations in chromosomes and environmental factors are associated with leukaemia. Molecular genetic alterations might drive mutation, leading to childhood acute lymphoblastic leukaemia with racial and ethnic disparities. Genetic abnormalities have been associated with chromosomal translocations.[4] Mutations in the *IKZF1* gene and other genes encoding kinase-activating proteins are important contributors to acute lymphoblastic leukaemia.[4] Hispanic children are at a higher risk of developing acute lymphoblastic leukaemia but have poorer survival than children of non-Hispanic ethnic origin.[5] The chromosomal translocations known to be associated with acute lymphoblastic leukaemia include t(12;21)(p13;q22) with *ETV6-RUNX1* fusion, t(1;19)(q23;p13) with *TCF3-PBX1* fusion, t(9;22)(q34;q11) with *BCR-ABL1* fusion, t(4;11)(q21;q23) with *MLL-AF4* fusion, hyperdiploidy, or hypodiploidy.[4,5]

Viral infections have been regarded as a crucial environmental risk factor for leukaemia.[6–11] Greaves[12,13] proposed the delayed infection hypothesis in childhood leukaemia. According to this hypothesis, children who have a delayed exposure to common infections have a more vigorous immune response. Proliferative immunological cells frequently undergo a second mutation leading to the

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Research in context

Evidence before this study

Before the start of this study, on March 12, 2015, we searched PubMed with combinations of the terms "leukaemia" and "enterovirus" (as well as variations thereof) without language restrictions. Although enteroviruses are common, we identified no research to evaluate the association between enterovirus infection and leukaemia.

Added value of this study

Our study showed a significantly reduced risk of leukaemia in children with enterovirus infection compared with those without infection. Herpangina and hand-foot-and-mouth disease were the major diseases associated with the reduced risk of leukaemia. To our knowledge, this study provides the first evidence to show a negative association between enterovirus infection and leukaemia risk.

Implications of all the available evidence

Findings from this study strongly support the epidemiological evidence for the role of viral infection in childhood leukaemia. Although this study does not show biological plausibility, experimental studies based on these findings to understand the pathogenesis of enteroviruses in leukaemia are suggested.

development of leukaemia in children. Conversely, exposure to common infections in early childhood is associated with a reduced risk of leukaemia.[12,13] Kinlen[14] proposed the population mixing hypothesis, suggesting that children might have an abnormal immune response to a common but unidentified infection; he suggested that when the infected population mixes with susceptible individuals, the risk of leukaemia increases.

Enteroviruses belong to the Picornaviridae family and include more than 90 distinct viral serotypes, such as polioviruses, coxsackieviruses, echoviruses, and numerically named enteroviruses.[15,16] Enterovirus infections are common in children and about 10–15 million children contract non-polio enterovirus infections in the USA every year.[17] Enterovirus infections are prevalent in children in Taiwan, as they are worldwide. Multiple clinical manifestations of enterovirus infections have been recognised in human beings, including herpangina, hand-foot-and-mouth disease, meningoencephalitis, acute flaccid paralysis, haemorrhagic conjunctivitis, respiratory tract infection, myocarditis, and pericarditis.[16]

Although enterovirus infections are common in children, the association between infection and leukaemia has not been assessed in a cohort study. We therefore aimed to establish whether the risk of developing leukaemia was greater in children infected with enteroviruses by analysing data from the National Health Insurance Research Database of Taiwan.

Methods

Study population and design

The National Health Insurance (NHI) programme was implemented in 1995 and has information about up to 99% of the 23·74 million people living in Taiwan.[18] We compiled data files for children (aged <18 years) from the NHI programme, which were established and maintained by the National Health Research Institutes (NHRI). The dataset consisted of a randomly selected sample of half of all children in Taiwan who were insured from 1996 to 2008. Randomisation was done with use of computer-generated random numbers assigned to individual data files from the NHRI. To protect patient privacy, the NHRI had encrypted all personal identification numbers into unique numbers before releasing the data files to the public for research purposes. The disease criteria were defined and classified according to the diagnostic codes of the International Classifications of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To ensure the accuracy of disease diagnosis, the Bureau of NHI randomly reviewed the medical charts of one in 100 ambulatory and one in 20 inpatient claims.

We identified children aged younger than 18 years with newly diagnosed enterovirus infections (ICD-9-CM codes 008.67, 047, 048, 074, 079.1, and 079.2) as the cohort infected with enteroviruses. To avoid coding errors in the claims data, we only included children who had at least three clinic visits with the diagnosis of enterovirus infection. The diagnosis date of the first clinic visit for the enterovirus infection was defined as the index date for initiation of follow-up person-year measurement. For each child with enterovirus infection, one child without enterovirus infection was randomly selected for the non-enterovirus-infected cohort with a frequency matching method to ensure both cohorts had the same distributions for strata of sex, age (every 1 year span), urbanisation level, parental occupation, and index year of enterovirus infection. Children with a history of cancer (ICD-9-CM codes 140–208) and with incomplete data for age or sex at baseline were excluded from both cohorts. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH-104-REC2-115 and CRREC-103-048).

The sociodemographic variables in this study were age, sex, urbanisation level, and parental occupation (office jobs, manual labour jobs, or other). The NHRI stratified all city districts and townships in Taiwan (based on national administrative zones demarcation) into seven urbanisation levels based on population density (people per km^2), proportion of residents with higher education, elderly and agricultural population, and the number of physicians per 100 000 people in each area.[19] Level 1