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Hospital admission for selected single virus infections prior to diabetes mellitus

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Abstract

Aims: To determine whether hospital admission for a range of specified virus infections was followed by a raised admission rate for diabetes mellitus; and, if raised, whether the increase is compatible with the hypothesis that virus infection is a cause of diabetes.
Methods: Analysis of a database of hospital statistics including admissions for people with diabetes mellitus before the age of 30 years.
Results: There was no evidence of excess risk of diabetes after measles, mumps, rubella, infectious mononucleosis, influenza, infectious hepatitis, varicella and herpes zoster, herpes simplex, aseptic meningitis or bronchiolitis. For example, of 1433 patients admitted for measles, 6 were later admitted with diabetes (risk ratio 1.32; 95% confidence interval 0.5–2.9); of 866 patients admitted for mumps, 2 were later admitted for diabetes (risk ratio 0.74; 0.1–2.7). Numbers of people with diabetes subsequent to infection were too few, however, to rule out the possibility of small effects.
Conclusions: Our findings do not support the hypothesis that any of these virus infections initiate the processes that lead to the development of diabetes, or that these infections act as a trigger to precipitate active disease in those whose diabetes is already present but latent.

Keywords: Diabetes mellitus; Virus infection; Mumps; Measles; Infectious mononucleosis

1. Introduction

Type 1 diabetes mellitus results from immunologically mediated damage to the beta cells in the pancreas [1]. Its causes are largely unknown but it is thought that pancreatic damage follows an autoimmune response either to infection or to a non-infectious stimulus. It is likely that there are initiating events in its aetiology, followed by a long and probably variable latent period prior to the onset of disease, and precipitating events for the eventual manifestation of clinical disease. Accordingly, observations about infection close to the time of clinical

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disease are unlikely to reveal useful information about an initiating role of infectious pathogens [1]. Similarly, seroepidemiological studies cannot generally distinguish between initiation and a precipitating trigger. Interview-based case-control studies, asking about infections that may have occurred years ago, may be subject to recall bias. Independently of the possible role of viruses in initiating aetiological processes, virus infection might sometimes have a role in precipitating the onset of clinical disease in people whose diabetes has developed but not yet manifested itself. For these reasons we undertook a record-linkage cohort study of people admitted to hospital for selected virus infections, and sought information about subsequent diabetes mellitus.

2. Methods

2.1. Population and data

We used data from the Oxford Record Linkage Study (ORLS). The ORLS includes brief statistical abstracts of records of all hospital admissions (including day cases) in National Health Service (NHS) hospitals, and all deaths regardless of where they occurred, in defined populations within the former Oxford NHS region, from 1 January 1963 to 31 March 1999. The hospital data were collected routinely in the NHS as the Oxford Regional Health Authority's hospital discharge statistics. The death data derived from death certificates. Data collection covered part of one health district from 1963 (population 350,000), two health districts from 1965 (population 850,000), six districts from 1975 (population 1.9 million) and all eight districts of the region from 1987 (population 2.5 million). The data for each individual were linked together, as they accrued, as part of the region's health information system. They are anonymised and archived.

The 'exposure' cohorts of people with the viruses of interest were obtained by selecting records with an admission for measles, mumps, rubella, infectious mononucleosis and a number of other specific virus infections. A reference cohort was constructed by similarly selecting records of individuals admitted for various medical and surgical conditions. This is our standard comparison group of patients that has been used in other studies of inter-relationships between diseases [2,3]. We considered that rates of diabetes mellitus in the reference cohort would approximate to those in the general population of the region while allowing for migration from it (data on migration of individuals were not available). We identified any subsequent record for diabetes mellitus in the cohorts of people with each individual virus infection and in the reference cohort. Type 1 and type 2 diabetes were not generally coded as such in the dataset; and, although the dates of each admission were recorded, the date when the diagnosis was first made was not. Accordingly, people with a first record of admission over the age of 30 years may have either had type 1 or type 2 diabetes. The great majority admitted under the age of 30 years, however, will have had type 1 diabetes. For this reason, we confined this study to diabetes mellitus in people admitted under the age of 30 years. We excluded from the analysis all people in the virus and reference cohorts who had a previous record of diabetes or who had diabetes on the record of admission for the virus infection or reference condition. We present findings here on infections for which there were more than 300 cases in the database, and which had at least one 'observed' and at least one 'expected' case of subsequent diabetes, diagnosed under the age of 30.

We analysed time intervals from first admission with each virus or reference disease to the first recorded admission for diabetes, in time periods of less than one year, 1–4 years, 5–9 years and 10 years and over.

2.2. Statistical methods

We calculated rates of diabetes after each virus infection based on person-years at risk. We took ''date of entry'' into each cohort as date of admission for the exposure disease, e.g. measles, mumps, rubella, infectious mononucleosis, or reference condition, and ''date of exit'' from each cohort as the date of first admission for diabetes (if it occurred), death, their 30th birthday or 31 March 1999, whichever was the earliest. In comparing each virus cohort with the reference cohort, we first calculated rates, standardised by age (in 5-year age groups), sex, calendar year of first recorded admission, and district of residence, taking the combined individual virus and reference