

PAPERS AND ORIGINALS

Relation of antecedent illness to development of diabetes in children

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Summary and conclusions

Information was obtained by postal questionnaire in 1663 cases of childhood diabetes of recent onset about other illnesses for which the family doctor was consulted in the six months before onset. Consultation rates in each of these six months were compared with each other and with rates reported in a concurrent study of morbidity in general practices. There was a significant excess of consultations for mumps in the six months before onset of diabetes ($p < 0.001$), the greatest excess being in the month before onset.

These results support the suggestion that diabetes starting in childhood may result in a small proportion of cases from recent mumps infection.

Introduction

There is extensive evidence from animal studies that diabetes may follow virus infection,^{1 2} and a recent report of a case of childhood diabetes attributed to Coxsackie B4 virus infection now provides definitive evidence of viral diabetogenesis in man.³ It is not known, however, how often diabetes arises in this way, or which viruses can be responsible.

Diabetes has long been suspected as associated with antecedent mumps.⁴ Many cases of temporal association have been described both in individuals^{1 2} and in sibs,^{5 6} and outbreaks of diabetes a few months⁷ or years^{8 9} after outbreaks of mumps have been reported. Despite these persistent reports a causal association has not been established. The association of diabetes with an illness as common as mumps could occur fortuitously, and an increase in the incidence of mumps before the onset of diabetes has not been shown.

I report a study of consultation rates for mumps and other illnesses in the six months before the onset of childhood diabetes.

These rates were examined in relation to the date of onset of diabetic symptoms and compared with consultation rates reported in a concurrent study of morbidity statistics from general practice.¹⁰

Subjects and methods

In 1972 the British Diabetic Association began a register of new cases of childhood diabetes in Great Britain and Ireland.¹¹ Over 8000 patients have now been notified to the register, which provides a valuable basis for investigations of many aspects of the disease. In this study, notifying hospital doctors were asked to complete an epidemiological questionnaire in consultation with parents. From November 1972 to November 1974 doctors were asked: "Had the family doctor been consulted about any other illness in this child in the previous six months? If yes, please give brief details." From November 1974 to May 1977 a modified questionnaire was used that included the request: "If there are any other points of interest which may be related to this child's diabetes please give brief details. Examples might be a recent attack of mumps, pancreatitis, or some other illness, or the simultaneous onset of diabetes in another member of the family, or playmate, or a member of the same school." The data analysed included details of antecedent illnesses from 1663 questionnaires of the first type and details of antecedent mumps from 2180 modified questionnaires.

Episode rates of antecedent illnesses in patients with diabetes were compared with those reported in a study of morbidity statistics in general practice.¹⁰ In this study, from November 1970 to November 1971 53 practices in England and Wales collected data in a study population including 69 748 children aged 0-14 years; the study then continued on a reduced scale. For most illnesses, episode rates in patients with diabetes were compared with the published rates from the 1970-71 study,¹⁰ but for certain epidemic infections (mumps, rubella, varicella, and measles) the Office of Population Censuses and Surveys kindly provided unpublished episode rates for November 1972 to November 1974, based on a population including on average 25 493 children aged 0-14 years.

The study population of children with diabetes comprised 304 aged 0-4 and 1359 aged 5-15; as this included relatively more older children than the general population, episode rates were calculated separately for the two age groups and the combined significance of differences assessed using Cochran's test.¹² Expected numbers of episode rates in the diabetic population (see tables I and II) were obtained by adjusting the rates reported in the general practice study.

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Results

Completed questionnaires were received for about 70% of notified patients. Further inquiries about the remaining patients generally elicited information available from hospital records, and the main problem in completing the questionnaire appeared to be the need to interview parents. Data from questionnaires, therefore, probably did

TABLE I—Reported consultations for episodes of antecedent illness in 1663 patients between November 1972 and November 1974

ICD No	Disease or condition	No of episodes		Reported: expected ratio	Significance
		Reported	Expected		
072	Mumps	25	10.7	2.34	<0.001
785.5 Pt, 785.5 Rdr, 540-3	Abdominal pain	40	22.7	1.76	<0.001
493		Asthma	27	16.9	1.60
680, 685-6	Septic skin lesions	29	20.3	1.43	NS
056	Rubella	19	14.3	1.33	NS
052	Chickenpox	18	18.8	0.96	NS
788.2	Rash	22	24.3	0.91	NS
Group X	Genitourinary disease	21	25.0	0.84	NS
055	Measles	10	14.2	0.70	NS
033	Whooping cough	4	6.1	0.66	NS
507	Hay fever	8	13.5	0.59	NS
34, 381, 460 pt, 460 Rdr, 461-4, 466, 470-4	Acute respiratory illness	326	581.2	0.56	<0.001
783.3, 480-6		Diarrhoea, vomiting, or both	12	58.9	0.20
003-5, 007-9, 561	Prophylactic procedures	13	126.4	0.10	<0.001
784.1 pt		Accidents, poisoning, and violence	6	181.6	0.03
Group XVIII	All other diseases	78	335.1	0.23	<0.001
Group XVII					
Total		658	1470	0.45	

ICD = International Classification of Diseases, World Health Organisation (8th revision).

TABLE II—Relation of antecedent illnesses to onset of diabetes

Disease	No of episodes									
	Reported					Expected				
	Months before onset					Not known	Total	per 6 months		per month
	0-	1-	2-	3-	4-			5-	per 6 months	
Mumps ..	10	6	4	2	1	1	1	25	10.7	1.8
Chickenpox ..	6	5	2	2	1	1	1	18	18.8	3.1
Rubella ..	4	1	3	1	2	3	5	19	14.3	2.4
Measles ..	3	2	1	2	1	-	1	10	14.2	2.4
Acute respiratory illness ..	96	26	18	9	3	2	172	326	581.2	96.9
All other diseases and conditions* ..	27	16	9	8	10	9	134	213	787.8	131.3
Total ..	146	56	37	24	18	16	314	611	1427.0	237.8

*Except diabetes and conditions that may be associated with its onset, such as enuresis, pruritis vulvae, balanitis, septic skin lesions, and abdominal pains.

not reflect a biased sample for antecedent illness. In comparison with consultation rates in general practice, ascertainment of illness was clearly incomplete but reporting was selective (table I). Doctors were aware of the special interest in infective illness, which presumably accounts for underreporting of conditions included in "all other diseases," most of which were non-infective. Prophylactic procedures and trauma were rarely reported, probably because they were not regarded as illnesses. Underreporting of "diarrhoea and/or vomiting" may have been due to their triviality, or in some cases to a non-infective origin.

Reports of acute infections were generally within or above the expected ranges, except for acute respiratory illness. Apart from abdominal pain, which may be symptomatic of diabetes, only mumps and asthma were reported in significant excess; of these, mumps showed the more striking excess of 2.3 times the expected number of episodes in the six months before the onset of diabetes ($p < 0.001$).

The incidence of reported antecedent illness was greatest in the month before the onset of diabetic symptoms, decreasing progressively in earlier months (table II). This distribution would occur if illnesses were associated with onset of diabetes, but other factors might also be

responsible. The pattern was most apparent in acute respiratory illness, but since the highest consultation rate in the month before onset of diabetes did not exceed the expected rate the much lower rate in earlier months may have been due to underreporting. Moreover, more than one respiratory infection would be expected in many children in the six months before onset of diabetes but only the most recent episode would have been reported.

A similar pattern, however, was found in some illnesses for which there was no evidence of underreporting. There were over five times the expected number of reported episodes of mumps in the month before onset of diabetes, compared with the 2.3-fold excess in the six months before onset. Because of the importance of this observation 2180 modified questionnaires were examined; 36 episodes of mumps were reported with a similar association with onset of diabetes to that found in the first series (table III).

TABLE III—Relation of antecedent mumps to onset of childhood diabetes, shown as number of episodes in months before onset

Period of study	Months before onset					
	0-	1-	2-	3-	4-	5-
November 1972–November 1974 (1663 patients)	10	6	4	2	1	1
November 1974–November 1977 (2180 patients)	19	7	5	1	3	1

There were relatively few reported episodes of chickenpox, rubella, and measles; there was no evidence of an excess over the expected incidences in the six months before onset of diabetes, but in the months immediately preceding onset the incidence of chickenpox particularly was higher than expected.

Discussion

These results suggest an association between diabetes and antecedent mumps, but caution is necessary in comparing

results from different investigations. Apart from the substantial excess of episodes of mumps and a small excess of asthma in patients with diabetes, however, the differences between the results of the two investigations can be plausibly explained. Moreover, data from this study independently show a highly significant association of mumps with onset of diabetes in the distribution of episodes in the six months before onset (table III). If the 10 episodes reported in the 1663 patients in the month before onset of diabetes reflected the normal consultation rate this would imply that all children would be seen by their doctor with clinical mumps by the age of 13.8 years. Only about 90% of unvaccinated subjects acquire infection in childhood, however, and about 40% of infections are subclinical.^{13 14} In many mild cases of clinical mumps moreover a doctor is not consulted. The number of reported episodes of mumps, therefore, was probably not due to chance association with onset of diabetes.

Apart from a causal association between mumps and diabetes,

other explanations for the excess of episodes of mumps must be considered. In a retrospective inquiry, failure to recall more remote events would lead to underreporting of earlier illnesses and to a spurious relative excess of episodes in the more recent months; but if mumps were underreported its association with diabetes would be even stronger than that suggested by these results. There may be an increased susceptibility to infection or a diminished threshold at which a doctor is consulted in the period before onset of diabetes, but it is unlikely that these would increase the consultation rate for mumps more than for other diseases. There may have been a tendency for doctors or parents to underestimate the interval between mumps and onset of diabetes or to misdiagnose other illnesses as mumps, or even to invent episodes of mumps. These seem rather remote possibilities, and though such personal bias cannot be excluded it is unlikely to have contributed substantially to the large excess found. The reliability of the dates of episodes of mumps is uncertain, but questionnaires generally indicated either the week or month of episodes and errors of four or five months seemed unlikely.

A more serious difficulty is that notifying doctors may have reported episodes of mumps for which general practitioners were not consulted, and if this occurred it might have doubled the number of episodes reported. It is unlikely that all of these parents would have recognised mumps or that they would all be recorded as having consulted their doctor. Even if they were, although this might account for the overall 2-3-fold excess of episodes of mumps, it would not account for the uneven distribution of these episodes in the period before onset of diabetes. The absence of any comparable excess of other infections such as chickenpox also suggests that this was not a major factor. The seasonality of onset of diabetes would imply a seasonal bias in the illnesses reported in the six months before onset. The aggregated periods in which the patients studied were at risk in the six months before onset showed only a small autumn bias, however, which did not coincide with the seasonal (winter-spring) prevalence of the illnesses seen in table I.

A causative association of antecedent mumps with childhood diabetes seems the most probable explanation of these results, but although the alternative explanations considered seem individually implausible the possibility that several sources of bias might collectively be responsible cannot be dismissed. Further studies are needed to solve this problem, and an important factor in their design is the probable rarity of cases of diabetes associated with antecedent mumps. In this study the excess of children reported as having had mumps consists of only 15 of the 1663 patients; cases of diabetes associated with mumps in which a doctor was not consulted, or with subclinical disease, would probably not greatly increase this proportion. Mumps immediately preceding onset could therefore be responsible for only a small proportion of all cases of diabetes.

There were too few episodes of infections other than mumps to support any firm conclusions but their distribution in relation to the onset of diabetes, particularly in the case of chickenpox

(table II), suggests the need for further investigation. Incomplete ascertainment of less recent episodes could account for this distribution, but there was no evidence of underreporting of chickenpox.

Infection might contribute to the development of diabetes either by specifically damaging the islets of Langerhans or by precipitating the disease in patients about to develop diabetes caused in some other way. In the second case the onset would be associated with many different infections, and the results do not exclude this possibility. On the other hand, if mumps infection is specifically associated with diabetes there is no obvious reason why it should precipitate it more often than other infections, and it may therefore start islet-cell damage. This would be in keeping with earlier suggestions of this association, with the known ability of mumps virus to invade the human pancreas, and with the observation that it can infect and destroy human and rhesus beta-cells in vitro.¹⁵

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ONE HUNDRED YEARS AGO A singular case came before the Gloucester County Court on Monday. Mr Walter Brown, house-surgeon at the County Infirmary, was sued by a labourer named Cuff, who claimed £2 damages for a *post mortem* examination of his wife, which was made without his knowledge or consent. Cuff's wife was admitted into the infirmary in April with an internal complaint, and she died about a month afterwards. After her death a pathological examination was made to discover the seat of the disease, and it was found that she died from peritonitis, the disease for which she had been treated. The plaintiff admitted that he had not suffered any pecuniary loss, but alleged that the examination had hurt his feelings, and that portions of the body had been taken away. For the defence medical evidence was called to show that the examination made was not in any sense of an anatomical character, that it was important in the interests of medical science, and that it was usual in certain cases. The allegation that any of the organs of the body were taken away was

denied. The judge gave a verdict for the defendant. Oddly enough, a similar case was lately commenced in Cincinnati by Ann Farley, a widow, against Dr William Carson, a leading physician, to recover five thousand dollars for injuries alleged to have been caused to her feelings by reason of a *post mortem* examination made on her husband by the defendant. In her complaint, she alleged that her husband went to the Cincinnati Hospital to be treated for injuries which, resulting in an abscess of the liver, caused his death. The defendant, Dr Carson, made the *post mortem* examination without her knowledge or consent, by reason of which she claimed to have been injured to the extent of five thousand dollars. The court held that, as a question of law, no property right in the dead is injured by a *post mortem* examination, and that there is no case in which mere injured feelings will give a right of action. The case was taken from the jury and judgment rendered for the defendant. (*British Medical Journal*, 1880.)