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Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis

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Abstract

Objectives: To monitor incidence of insulin dependent diabetes in children in Oxford health region since 1985, and to look for any evidence of disproportionate increase in children aged under 5.
Design: Primary ascertainment of cases of childhood diabetes was by prospective registration of all patients with insulin dependent diabetes diagnosed before age 15 years between 1985 and 1996 and resident in Oxford region at time of diagnosis. This was supplemented by examination of centralised hospital discharge records and death certificates. Secondary case ascertainment was by postal surveys of general practitioners in 1987 and 1996.
Setting: Area formerly administered by Oxford Regional Health Authority.
Subjects: 1037 children presenting with insulin dependent diabetes under age of 15 years.
Main outcome measures: Incidence of insulin dependent diabetes in children aged 0-4, 5-9, and 10-14 years during 1985-95.
Results: Overall incidence of diabetes in children aged 0-15 was 18.6 cases/100 000/year and showed an annual increase of 4% from 1985 to 1996. This was mainly due to a rapid increase in children aged 0-4 years, in whom there was an annual increase of 11% (95% confidence interval 6% to 15%, $P < 0.0001$), while the annual increase in those aged 5-9 was 4% (0 to 7%, $P = 0.05$) and in those aged 10-14 was 1% (−2% to 4%, $P = 0.55$).
Conclusions: Incidence of insulin dependent diabetes in children aged under 5 years has risen markedly in the Oxford region over the past decade. The cause of the increase is unknown, but environmental influences encountered before birth or in early postnatal life are likely to be responsible.

Introduction

The incidence of childhood diabetes has increased in Europe and many other parts of the world over the past 20-30 years.[1,2] One of the best documented long term surveys has been in Finland, which showed a 57% increase between 1965 and 1984 in children aged under 15 years, equivalent to an annual increase of 2.4%.[3] In England there has been particular concern about the rising incidence in children aged under 5 years, with a reported increase from 4.2 to 9.9/100 000/year between 1973-4 and 1988.[4] Rapid changes such as this in populations that are for the most part genetically stable would, if confirmed, imply

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a major role for environmental factors encountered early in life.

The Bart's-Oxford Study Group surveyed the incidence of childhood insulin dependent diabetes in the Oxford health region in 1985-6 and has monitored incidence continuously since then in an area with a population of 2.6 million. Some 90% of families of affected children participate in a prospective family study. We now report the changes in incidence in children, particularly those aged under 5, over the past 11 years.

Patients and methods

This study was undertaken in the course of the Bart's-Oxford study of childhood diabetes, established in 1985 in collaboration with all paediatricians and physicians with a specialist interest in diabetes in the area formerly administered by Oxford Regional Health Authority. This region is divided into eight health districts, each containing one or more general hospitals. The area is 8107 km^2 and in 1991 had a population of 2.6 million, of whom 512 500 were aged under 15 years (264 000 boys, 248 000 girls). Of these, 178 700 were aged under 5. The population is 95% white European, and the remainder originate mainly from the Indian subcontinent (data from Office of Population Censuses and Surveys for 1991).

Children with insulin dependent diabetes diagnosed before their 15th birthday between 1 January 1985 and 31 December 1995 and resident in the Oxford region at the time of diagnosis were included in the study. Eligible patients were notified to the study by the local clinicians and diabetes specialist nurses. Diagnosis of diabetes was based on the World Health Organisation's criteria and a clinical requirement for insulin treatment. We identified cases of secondary diabetes treated with insulin or maturity onset diabetes of the young (MODY) by examination of case records, or from a clinical history taken by one of our field workers, and excluded these from the analysis. We used data from the hospital inpatient activity analysis as a supplementary ascertainment source for 1985-6[5] to ensure that cases were not missed while the reporting system was established and validated.

Primary methods of case ascertainment were validated twice during the study by means of questionnaires sent to all general practitioners in the region in 1987 and 1996. Details were requested of any eligible patients on the general practitioner's list in whom insulin dependent diabetes had been diagnosed in the previous year. Further information to confirm eligibility was then sought on patients not already known to the study.

Statistical analysis

We calculated the incidence of diabetes using the registrar general's mid-year estimates (unpublished data from Office of Population Censuses and Surveys) and determined confidence intervals assuming a Poisson distribution. We standardised the incidences for age by fitting Poisson regression models to the number of cases, with the resident population being the normalising constant. The models were fitted using STATA statistical software (release 4.0, Stata Corp, College Station, Texas). We performed the analysis for the age groups 0-4, 5-9, and 10-14 years. The Poisson regression models fitted adequately, allowing comparison of trends in incidence within and between each age group. We also investigated differences in trends between boys and girls.

Table 1 Yearly incidence (No of cases/100 000) of insulin dependent diabetes in children aged under 15 years in Oxford region during 1985-95

Year	No of cases	Incidence (95% confidence interval)
1985	82	16.7 (13.3 to 20.9)
1986	88	18.0 (14.4 to 22.5)
1987	77	15.6 (12.3 to 19.8)
1988	76	15.3 (12.0 to 19.4)
1989	88	17.6 (14.1 to 22.1)
1990	84	16.5 (13.2 to 20.7)
1991	91	17.8 (14.4 to 22.0)
1992	102	19.6 (16.0 to 23.9)
1993	99	18.9 (15.3 to 23.4)
1994	114	21.7 (17.7 to 26.5)
1995	136	25.9 (21.5 to 30.6)
1985-95	1037	18.6 (17.4 to 19.8)

Results

A total of 1037 eligible patients (572 boys, 465 girls) were notified to our study. A further four were excluded (two with cystic fibrosis, one with maturity onset diabetes of the young, and one receiving steroid therapy). Three children (two aged 2 years and one aged 4) died in hospital shortly after admission in diabetic ketoacidosis, with a clinical diagnosis of cerebral oedema.

The overall incidence of insulin dependent diabetes throughout the 11 year study was 18.6 cases/100 000/year (95% confidence interval 17.4 to 19.8). Subdivided by age, there were 12.7 cases/100 000/year (11.0 to 14.6) in children aged 0-4 years, 17.5 cases/100 000/year (15.6 to 19.7) in those aged 5-9, and 25.9 cases/100 000/year (23.6 to 28.4) in those aged 10-14. Table 1 shows the annual incidence of insulin dependent diabetes from 1985 to 1996.

During the study the overall incidence of diabetes increased by 4% a year (95% confidence interval 2% to 6%, $P < 0.001$). This increase occurred predominantly in the youngest age group (fig 1). The incidence in children aged under 5 increased by 11% (6% to 15%) per year ($P < 0.0001$), while the increase in those aged 5-9 was 4% (0 to 7%, $P = 0.05$), and in those aged 10-14 was 1% (– 2% to 4%, $P = 0.55$)

There was a first degree family history of insulin dependent diabetes in 12.8% of the children; the relative affected was the father in 4.5%, the mother in 2%, and a sibling in 4.5%. In 10 cases more than one first degree relative was affected, and six of these cases had been diagnosed before the age of 5.

The overall incidence of diabetes was higher in boys than in girls (19.9 cases/100 000/year (18.3 to 21.5) *v* 17.2 cases/100 000/year (15.6 to 18.7), ratio 1.16 (1.04 to 1.28)), but the incidence did not differ under the age of 5. The rate of increase in incidence was similar in boys and girls, both overall ($P = 0.08$) and when subdivided according to age (see table 2).

Validation of ascertainment

Of the 1276 general practitioners contacted in 1987, 990 returned the questionnaire. They reported a total of

117 eligible cases, of which 112 had already been registered in the study. In 1996, 919 of the 1443 general practitioners contacted (64%) returned the second questionnaire, and they reported 147 eligible patients diagnosed in 1994-5, of whom 142 were already known to the study. The overall levels of case ascertainment were therefore 95.7% for cases diagnosed in 1985-6 and 96.6% for those diagnosed in 1994-5.

Table 2 Yearly incidence (No of cases/100 000) of insulin dependent diabetes in children aged under 15 years in Oxford region during 1985-95, stratified by age and sex

	Boys		Girls	
Age group (years)	No of cases	Incidence (95% confidence interval)	No of cases	Incidence (95% confidence interval)
0-4	128	12.9 (10.7 to 15.1)	117	12.5 (10.3 to 14.8)
5-9	182	19.1 (16.3 to 21.9)	143	15.9 (13.3 to 18.5)
10-14	262	28.2 (24.8 to 31.3)	205	23.4 (20.2 to 26.7)
0-14	572	19.9 (18.3 to 21.5)	465	17.2 (15.6 to 18.7)

Discussion

Our prospective study has shown a rapid increase in the incidence of diabetes in young children over the past decade. This increase was largely confined to those aged under 5 years, with an 11% annual increase (95% confidence interval 6% to 15%, $P < 0.0001$) over the 11 year period. In contrast, the increase in children aged 5-9 was 4% (0 to 7%, $P = 0.05$), just reaching statistical significance, and there was no change in those aged 10-14. The study was designed to monitor the incidence of insulin dependent diabetes prospectively, and potential bias due to variation in ascertainment has been minimised.

Undiagnosed diabetes is a fatal condition, and increased diagnostic vigilance is unlikely to have been a factor; deaths at diagnosis were identified by our survey. The primary ascertainment method was unchanged, and independent validation of case ascertainment by questionnaires to general practitioners was carried out twice during the study with very similar results. The questionnaires showed no major change in referral patterns during the study, and children referred into the region from outside were excluded from the analysis. Although more than 20% of patients started to receive insulin at diagnosis as outpatients in 1985-6[6]—a proportion that seems to have risen—our procedure for case ascertainment was based on the diabetes nurse specialists who start insulin treatment in such patients and seems to have been effective. Some 90% of families—a constant proportion over the years—have participated in the prospective family study, so that ascertainment has involved direct contact and confirmation of details of diagnosis in the great majority of cases.

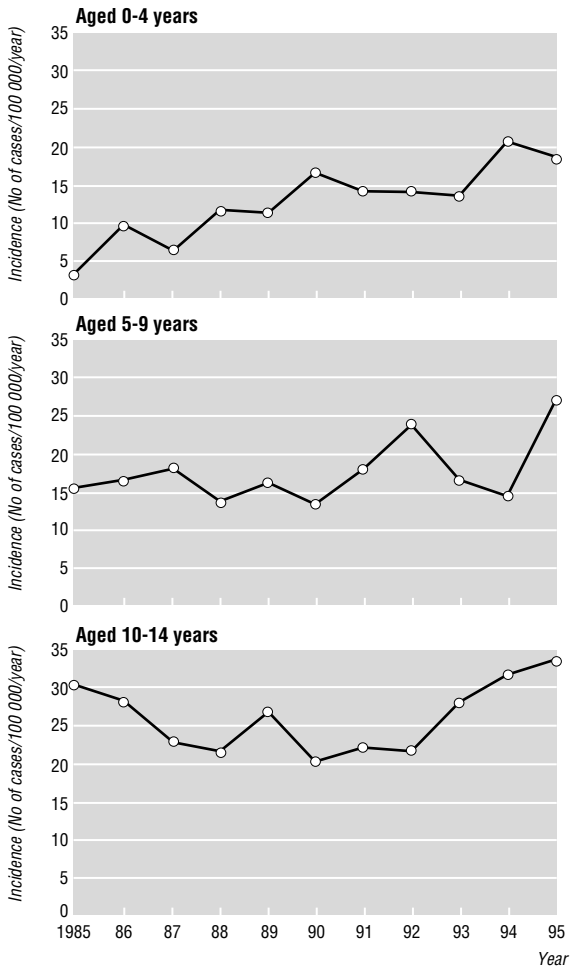

Fig 1 Incidence of insulin dependent diabetes in children aged 0-4, 5-9, and 10-14 years in Oxford region during 1985-95

Is this increase an aberration—a local epidemic of insulin dependent diabetes—or is it a continuation of an underlying time trend? In 1944 R D Lawrence wrote that "diabetes . . . is very rare under 6 years of age," and a survey of school medical officers and hospitals in selected areas of Britain in 1948 identified 183 children under the age of 16 with diabetes from a childhood population of 1 307 000; of these, only three were currently aged under 5 years.[7] In 1995 the Oxford region contained 600 children aged under 15 with insulin dependent diabetes, including 61 aged under 5, from a background population of 525 800. In 1948 one child in 180 000 aged under 5 was known to have diabetes; in 1995 the figure was close to 1 in 3000. Although the earlier survey might have underestimated the true incidence of insulin dependent diabetes because of incomplete ascertainment and death from undiagnosed diabetes, the comparison suggests the likely scale of the increase that has occurred.

Comparison with other studies

Several studies have reported time trends in incidence of childhood diabetes in England. In Leicester the overall incidence in children aged under 15 rose from 3.8 to 10.6 cases/100 000/year between 1951 and 1980, with an increase from 1.8 to 6.3/100 000/year in the under 5 year olds over the same period.[8] Metcalfe et al[4] compared the findings of a British Diabetic Association survey carried out in 1973-4[9] with a national survey carried out in 1988 and found that the incidence in under 5 year olds had risen from 4.2/100 000/year to 9.9/100 000/year between the two studies, although no further increase was noted when the national survey was repeated in 1992.[10] In Yorkshire the incidence in children aged 0-4 years was 9.7/100 000/year during 1978-90, with a minor upward drift (estimated at 1.75% a year) over this period.[11] The rates from the Yorkshire register and from the national survey of 1988 are similar to our own over the first half of this study. Although the Yorkshire

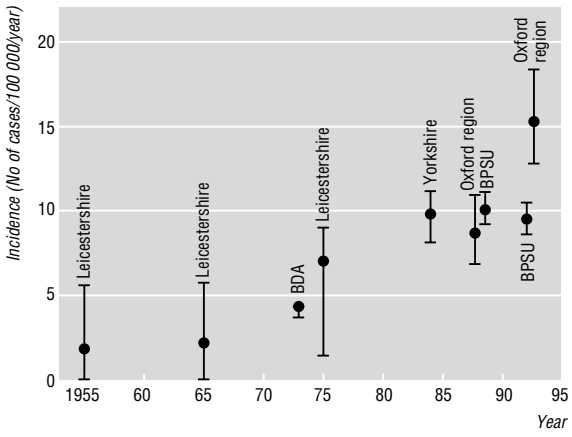

Fig 2 Estimates of the incidence of insulin dependent diabetes in children aged under 5 years in England since 1950. The Leicestershire results are summarised as mean incidence for each decade (1951-60, 1961-70, and 1971-80)[8]; the British Diabetic Association (BDA) figure for Great Britain in 1973-4 was based on questionnaire data[9]; the Yorkshire register covered the period 1978 to 1990[11]; and the British Paediatric Surveillance Unit (BPSU) questionnaires were used to calculate incidence figures for 1988 and 1992.[10] (Error bars show 95% confidence intervals)

study found little change, and the national surveys found no difference between 1988 and 1992, an overview of all these surveys is consistent with the view that the incidence of insulin dependent diabetes in children aged under 5 has been increasing for the past 30 years (see fig 2).

The difference between the rate of increase in those aged under 5 and in older children is perhaps the most unusual feature of our report. Studies across Europe found that the proportion of children with diabetes in the age bands 0-4, 5-9, and 10-14 years was remarkably similar,[12 13] and it has been remarked that "the most constant feature of insulin dependent diabetes incidence in different populations is its age distribution."[14] Most studies have shown a parallel increase within each age band,[15] although Finland, with the highest incidence in the world, has seen a steep increase in children aged under 5 since the mid-1980s.[16] In Finland, as in the Oxford region, the difference in incidence between childhood age bands has virtually disappeared.

Key messages

- The incidence of childhood diabetes has increased in Europe and many other parts of the world over the past 20-30 years
- In the Oxford region we found that the incidence of childhood insulin dependent diabetes increased by 4% per year during 1985-95
- Most of this increase was due to an increase of 11% a year in children aged under 5 years, in whom incidence doubled over the study period
- Environmental factors encountered very early in life are likely to have been responsible for this increase, but the nature of such factors is unknown
- Attempts at preventing disease should be directed towards intrauterine or early postnatal life

Reasons for increased incidence

Why is the incidence of insulin dependent diabetes in young children increasing? The rate of increase is too rapid to be caused by shifts in the population gene pool due to improved survival of people with insulin dependent diabetes, and it is therefore usually attributed to a change in the environment. Insulin dependent diabetes is heterogeneous with age, and we therefore need to consider disease characteristics that might result in a selective increase in young children.

Children with diabetes of early onset are more likely to have a diabetic relative, have a higher prevalence of HLA susceptibility alleles and autoantibodies to pancreatic islet cells at diagnosis[17 18] and more rapid progression to failure of β cells. Equal numbers of boys and girls are affected, and many studies including our own (data not shown) have found that the seasonal pattern of onset typical of older children is absent under the age of 5. Explanations such as selective interaction of an environmental risk factor with high risk HLA alleles might therefore need to be considered. A number of environmental influences encountered early in life could be relevant. Infection with rubella[19] and Coxsackie virus[20] during gestation can affect subsequent development of insulin dependent diabetes, as may early exposure to cow's milk products.[21] Changes in incidence might be linked to patterns of childhood immunisation, but this has yet to be confirmed.[22]

These possibilities need to be explored, but it is difficult to explain the apparently remorseless increase in incidence over three decades on any of these grounds.

Conclusion

The continued rise in the incidence of insulin dependent diabetes is cause for serious concern, since the overall effect of the increase in the younger age group upon cumulative incidence by age 15 in the Oxford region is considerable. Thus, the estimated cumulative incidence of insulin dependent diabetes by age 15 was 2.5 children per 1000 in 1985 and 3.8 per 1000 in 1995.

Diabetes in early childhood has a considerably greater impact on children and their family than it does in later years. A survey of children with newly diagnosed diabetes from the early years of the study found that diabetes of early onset was associated with a much higher frequency of ketoacidosis, severe hypoglycaemia, and hospital admission.[6] Further, four of the 245 children with diabetes diagnosed under the age of 5 in our region have died, three from ketoacidosis at presentation while the other, diagnosed at age 4, died in her sleep at the age of 7.

The long term prognosis is also worse in early onset diabetes, with increased relative mortality[23] and a higher risk of nephropathy.[24] Lifetime insulin therapy is demanding, expensive, and offers incomplete protection against disabling late complications. At present, the best hope of reversing this trend would seem to lie in identifying and eliminating environmental trigger factors or, failing this, in strategies of inducing tolerance or vaccination targeted at the neonatal population.

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Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts

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Abstract

Objective: To investigate whether changes in certain perinatal and social factors explain the increased prevalence of hay fever and eczema among British adolescents between 1974 and 1986.

Design: Two prospective birth cohort studies.

Setting: England, Wales, and Scotland.

Subjects: 11 195 children born 3-9 March 1958 and 9387 born 5-11 April 1970.

Main outcome measures: Parental reports of eczematous rashes and of hay fever or allergic rhinitis in the previous 12 months at age 16.

Results: The prevalence of the conditions over the 12 month period increased between 1974 and 1986 from 3.1% to 6.4% (prevalence ratio 2.04 (95% confidence interval 1.79 to 2.32)) for eczema and from 12.0% to 23.3% (prevalence ratio 1.93 (1.82 to 2.06)) for hay fever. Both conditions were more commonly reported among children of higher birth order and those who were breast fed for longer than 1 month. Eczema was more commonly reported among girls and hay fever among boys. The prevalence of hay fever decreased sharply between social classes I and V, increased with maternal age up to the early 30s, and was lower in children whose mothers smoked during pregnancy. Neither condition varied significantly with birth weight. When adjusted for these factors, the relative odds of hay fever (1986 *v* 1974) increased from 2.23 (2.05 to 2.43) to 2.40 (2.19 to 2.63). Similarly, the relative odds of eczema rose from 2.02 (1.73 to 2.36) to 2.14 (1.81 to 2.52).

Conclusions: Taken together, changes between cohorts in sex, birth weight, birth order, maternal age, breast feeding, maternal smoking during pregnancy, and father's social class at birth did not seem to explain any of the observed rise in the prevalence of hay fever and eczema. However, correlates of these factors which have changed over time may still underlie recent increases in allergic disease.

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