Family characteristics and insulin dependent diabetes

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Abstract

During the calendar year of 1988 a survey of new cases of insulin dependent diabetes mellitus (IDDM) in children under the age of 15 years in the British Isles was conducted. After cases had been confirmed and permission obtained to contact the families, postal questionnaires were sent to the parents of children diagnosed in England, Wales, Northern Ireland, and the Republic of Ireland.

Children who developed diabetes were significantly more likely to be heavier at birth in comparison with national reference data. The diabetic children were less likely to have been breast fed, and there were more children than expected whose fathers were in non-manual occupations. Where there was a first degree relative with IDDM there were positive correlations between the age at diagnosis of the index cases and that of their diabetic fathers and their diabetic siblings, but not their diabetic mothers. A higher proportion of children than expected who were diagnosed under the age of 5 years had fathers with IDDM.

Characteristics of family members associated with IDDM in children that might provide pointers to the aetiology of the disease include heavier birth weight, method of infant feeding, the age at onset of IDDM in affected fathers and affected siblings, and the family lifestyle as defined by social class of the father.

Insulin dependent diabetes mellitus (IDDM) is currently viewed as resulting from environmental factors initiating progressive pancreatic islet cell destruction in genetically susceptible individuals.¹ As part of a survey of childhood onset diabetes diagnosed before the age of 15 years in the British Isles during 1988,² we documented characteristics of family members of the children concerned, seeking pointers to the aetiology of the disease. The analysis that follows relates to information obtained from postal questionnaires sent to the parents of the children.

Patients and methods

Ethical approval for this national study was obtained from the Bristol and Weston Health Authority and the British Medical Association, and the study protocol was scrutinised by the ethics advisory committee of the British Paediatric Association.

Permission to contact the families was sought from both the reporting paediatrician/physician and the family practitioner. Second and third reminders were sent to doctors if they did not respond to the first request. Questionnaires to the parents were sent two to three months after the diagnosis with a reply paid envelope for their return. If there was no response within one month, a second questionnaire was sent, with a final reminder if no response was forthcoming after a further one month. If a family had left the area, an attempt was made to contact them by obtaining the address of their new family practitioner from the local (then) family practitioner committee.

Special arrangements were made for the 190 children diagnosed in Scotland and the 75 children diagnosed in the Oxfordshire Regional Health Authority area where separate studies were ongoing (the Scottish Study Group for the Care of Young Diabetics³ and the Bart's Oxford Family Study⁴). Questionnaires were not sent to the parents of children in these two areas in order not to prejudice the collection of data by local researchers. There was, however, information from the Bart's Oxford Family Study on family history of first degree diabetes and social class which was relevant to our study. Data were thus available on 1175/1410 (83%) families for family history, social class and age of mother at delivery (British Isles excluding Scotland), and on 1100/1335 families (82%) for birth weight and infant feeding practice. Complete statistics were not always available on every case, giving totals of <1175 for most analyses. Sources of information and families excluded from the study are shown in table 1.

Family history of IDDM was included in the analysis only for those cases where there was information on the biological parents or full siblings. Half siblings with IDDM were included in the analysis of the relationship between age of onset of an affected sibling and that of the index case. Step siblings, parents with diabetes that was not insulin dependent, and parents or siblings known to have developed diabetes after the diagnosis of the index case were excluded.

For diabetic children diagnosed in England and Wales, comparisons of birth weight (recalled by the mother) were made with birth weights of babies born in 1980, the mid-point of year of birth of our study population, available from national published data.⁵ Comparisons of social class were made on 10 000 children who were part of the 1970 British Births Survey and still alive in 1980.⁶ The latter study used the 1970 *Classification of Occupations*.⁷ In our study, social class was based on the occupation (using

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Table 1 Sources of information

Source	No of reported cases <16 years	No of confirmed cases <16 years (% reported)	Study cases <15 years*
Paediatrician	1466	1435 (98)	1412
Physician	80	80 (100)	52
Specialist nurse/health visitor			
Paediatrician care	127	107 (84)†	104
Physician care	52	46 (88)†	27
General practitioner care	1	1	1
Mother	6	6	4
Total	1732	1675 (97)	1600
Excluded from questionnaires:		190 Scotland 75 Oxfordshire Regional Health Authority 2 Deaths 14 Refusals (by doctors)‡ 42 Non-responding general practitioners 3 Emigrations 20 Too late	
Total		346	
Cases sent questionnaires		1254 (78% of 1600)	
No of questionnaires returned		1100 (88% of 1254)	

*Original data collection on cases aged <16 years at diagnosis: study cases restricted to age <15 years at diagnosis; primary cases only.

†By consultant paediatrician or physician.

‡For example family bereavement, adverse social conditions.

the 1980 *Classification of Occupations*⁸ together with educational qualifications) of the mother's partner at the time of diagnosis, regardless of whether or not he was the diabetic child's biological father. In order to reduce the bias introduced by changes in class composition between the 1970 and 1980 definition of classifications,⁹ social class was aggregated into non-manual (I+II+IIINM) and manual (IIIM+IV+V) occupations. For breast feeding comparisons we used national data available from the Office of Population Censuses and Surveys (OPCS) collected on children born during 1980.¹⁰ Maternal ages at the delivery of the diabetic children were compared with unpublished national data on maternal age (OPCS).

STATISTICS

Analyses were performed using the statistics packages SPSS and BMDP (for survival analysis¹¹). Non-parametric tests were used, except where it was appropriate to use parametric tests. Methods for direct standardisation and confidence intervals were described in Armitage and Berry¹² and Kirkwood.¹³

Results

RESPONSE

Of the 858 reporting hospital doctors, 844 (98%) confirmed their newly diagnosed cases, and of 1301 family practitioners subsequently contacted 1259 (97%) responded. Questionnaires

were returned by parents of 88% of the cases (1100/1254, or 69% of the original 1600 children).

THE FAMILIES

From the questionnaires completed, there was information on 1091 mothers and 1072 fathers. There were 18 twin pairs: six identical (one of whom had previously developed IDDM), 10 not identical, one query, and one unknown; and one set of triplets.

ETHNIC ORIGIN

All the parents who responded completed the section on ethnic origin. Of the 1087 cases where full data were available for England and Wales, 1041 (95.8%) children were of European origin, 18 (1.7%) were of Indian subcontinent origin, five (0.5%) of African origin, and 23 (2.1%) of mixed origin. There are similar to the proportions from the British Births Survey: 96.7% white, 1.7% Indian subcontinent, 1.4% African, and 0.2% other (10 year follow up, unpublished data).

BIRTH WEIGHTS

The mean (SD) birth weight of 21 study children born to mothers who had themselves developed diabetes before their children (n=22, one birth weight not available) was not significantly different from that of the 1057 study children born to non-diabetic mothers (3600 (810) g compared with 3370 (560) g respectively; $t=1.30$). However, the mean (SD) birth weight of 14/21 children (group A) whose mothers developed diabetes before the deliveries of the index cases was significantly less than that of 7/21 children (group B) whose mothers developed diabetes after their deliveries (3330 (780) g compared with 4140 (570) g; $t=2.75$, $p<0.02$). The heavier birth weights of group B were not due to birth order (not significant by Fisher's exact test), an excess of males (not significant by Fisher's exact test), nor maternal age (Mann-Whitney, $z=1.37$). There was no relationship between birth weight and the diabetic status of the fathers ($F=0.50$), nor the children's age at diagnosis (Spearman's rank correlation coefficient, $r=-0.054$).

In order to compare the birth weights of the diabetic children with national data on singleton children born in 1980 only those study children who were singletons, resident in England and Wales, and whose mothers did not have insulin dependent diabetes at delivery were included. Birth weights were divided into three groups: <2500 g, 2500–<4000 g, and ≥ 4000 g, and the numbers of study children in each group were compared with the number of children similarly grouped by OPCS. There were more diabetic children in the heaviest group than expected ($\chi^2=16.51$, $p<0.001$ (2df); table 2).

BREAST FEEDING

Of 1009 study children born in England and Wales where information was available, 556

Table 2 Number (%) of children with IDDM* compared with children from OPCS† data grouped by birth weight: singletons, England and Wales (z =standardised normal deviate)

	Birth weight		
	<2500 g	2500–<4000 g	≥ 4000 g
IDDM (1973–88)	65 (7)	783 (82)	104 (11)
OPCS (1980)	32 779 (6)	509 707 (86)	46 012 (8)

$\chi^2=16.51$, $p<0.001$ (2df).

*Excludes children with IDDM mothers (n=21/22).

†Includes children with IDDM mothers.

were initially breast fed (55%). After using the method of direct standardisation to correct for mothers' education,¹² an important factor in the analysis of breast feeding, the adjusted proportion for the infants who were breast fed and subsequently developed diabetes was 58% (99% confidence interval 51% to 64%), which is significantly lower than the breast feeding proportion in the 1980 infant feeding study¹⁰ of 67% (99% confidence interval 65% to 69%, $p<0.01$). In order to remove any potential bias introduced by our question: 'Was the child breast fed?' being phrased differently from question in the infant feeding study: 'Did you ever put your baby to the breast (even if it was once only)?', further analyses were carried out which avoided the immediate postpartum period. Diabetic children and control children who had never been breast fed or breast fed for less than two weeks were grouped together and compared with children who had been breast fed for two weeks or longer; the result was significant ($\chi^2=9.865$, $p<0.01$, table 3). When the duration of breast feeding was divided into three categories: 2-<6 weeks, 6 weeks-<4 months, and ≥ 4 months, there were more study children than expected who had discontinued breast feeding at 2-<6 weeks ($\chi^2=14.609$, 2df, $p<0.01$, table 4). As breast feeding rates in England and Wales were low in 1975,¹⁰ we reanalysed the data for the cases born 1978-82 (bracketing the 1980 control data); after correcting for mothers' education, the adjusted proportion for the study infants was 60% (99% confidence interval 57% to 64%, $p<0.01$). However, the detailed analyses subdividing the postpartum period as above were not significant (division at two weeks of age: $\chi^2=0.56$ and duration of breast feeding: $\chi^2=2.08$).

FAMILY HISTORY OF DIABETES

There were 105/1175 (8.9%) study children with at least one first degree relative with IDDM. There were 41 (3.5%) affected fathers (nine diagnosed as having IDDM after the birth of the index case); seven fathers had diabetes

that was not insulin dependent (all diagnosed before the birth). There were 22 (1.9%) affected mothers, seven of whom had IDDM diagnosed after the delivery of the index case; two mothers had diabetes that was not insulin dependent (all diagnosed before the delivery). There were 50 (4.2%) siblings with IDDM.

FATHERS AND MOTHERS WITH IDDM

Sixty two diabetic children had at least one biological parent with IDDM. The age at diagnosis of children with an affected parent was significantly less than that of children without an affected parent (median ages of children 5.8 years and 8.9 years respectively, Mann-Whitney, $z=2.31$, $p=0.02$). Using simple non-parametric statistical techniques, we found a significant relationship between the age at onset of affected parents and the age at onset of their diabetic children ($n=63$, Spearman's rank correlation coefficient $r=0.445$; $p<0.02$). When the 41 fathers and 22 mothers were considered separately the relationship was apparent only with the fathers ($r=0.445$, $p<0.01$ (fig 1); mothers: $r=0.388$, not significant).

The associations with the child's age at diagnosis of paternal or maternal age at diagnosis could have been due simply to the amount of time that the parent had in which to develop diabetes. Older diagnosed children would have older fathers (or mothers), who may have developed the disease in later life; for children diagnosed younger this was not possible. Therefore survival analysis, using a Cox proportional hazards model,¹¹ was used to model the time during which the fathers' (or mothers') lives had been observed: from their birth until they or their children developed diabetes. The age at which the child developed diabetes was entered as a covariate, and was found to be a significant factor in the model for fathers but not for

Table 3 Breast feeding in children who subsequently developed IDDM, date of birth 1973-88, compared with national data (OPCS 1980¹⁰) (results are number (%) of children in each group)

	Breast fed		Total
	Never or <2 weeks	≥ 2 weeks	
IDDM (1973-88)	522 (52)	487 (48)	1009 (100)
OPCS (1980)	1731 (46)	2023 (54)	3754 (100)

$\chi^2=9.865$, $p<0.01$.

Table 4 Duration of breast feeding in children who subsequently developed IDDM, date of birth 1973-88, compared with national data (OPCS 1980¹⁰) (results are number (%) of children in each group)

	Duration of breast feeding			Total
	2-6 weeks	6-12 weeks	>12 weeks	
IDDM (1973-88)	147 (30)	134 (28)	206 (42)	407 (100)
OPCS (1980)	450 (22)	574 (28)	999 (50)	2023 (100)

$\chi^2=14.608$, $p<0.01$ (2df).

Figure 1 Relationship between age at diagnosis of 41 children with IDDM and that of their similarly affected fathers.

mothers (table 5). Thus we can say that the age at diagnosis of both father and child were associated, but this was not necessarily so for mothers.

If the index cases were divided into age groups 0–4 years and 5–14 years at diagnosis, a higher proportion of children than expected in the age group 0–4 years had fathers with IDDM ($\chi^2=10.54$, $p<0.005$); there was no such difference in proportions for the children of mothers with IDDM (table 6).

SIBLINGS WITH DIABETES

There were 44 full siblings (one an identical twin) and six half siblings with IDDM who were diagnosed before the index case. Six siblings were diagnosed less than one year before the index case; all but three siblings were diagnosed under the age of 15 years. There was no difference between the age at diagnosis of study children with an affected sibling compared with that of those without (Mann-Whitney $z=1.26$). There was a positive correlation between the age at onset of diabetes in the index cases and that of their affected siblings ($n=50$, Spearman's rank correlation coefficient, $r=0.316$, $p=0.03$, fig 2).

The age at diagnosis of affected siblings was also considered using survival analysis to model the time over which the siblings' lives had been observed. The age at diagnosis of the study child was entered as a covariate and found to be a significant factor in the model (global $\chi^2=15.63$, 1df, $p=0.0001$): thus we can say that the

Table 5 Survival analyses of diabetic parents to investigate the relationship between parental age at diagnosis and child's age at diagnosis (age of child was entered as a covariate: its significance relates to the p value)

Diabetic parent	No of diabetic pairs	Global χ^2	p Value
Mothers + fathers	63	13.44	0.0002
Fathers	41	10.22	0.001
Mothers	22	3.24	NS

Table 6 Number (%) of children aged 0–4 years and 5–14 years at diagnosis with fathers and mothers with IDDM

	Age at diagnosis		
	0–4 years	5–14 years	
Father:			
With IDDM	20 (7)	21 (2)	$\chi^2=10.54$ $p<0.005$
Without IDDM	279 (93)	840 (98)	
Total	299 (100)	861 (100)	
Mother:			
With IDDM	7 (2)	15 (2)	$\chi^2=0.68$ NS
Without IDDM	293 (98)	848 (98)	
Total	300 (100)	863 (100)	

Table 7 Social class of fathers of diabetic children compared with fathers of children from the British Births Survey followed up in 1980 (unpublished data) (results are numbers (%) of children in each group)

	Social class		Total
	Non-manual	Manual	
IDDM (1973–88)	509 (55)	419 (45)	928 (100)
British Births Survey (1980)	4353 (40)	6572 (60)	10 925 (100)

$\chi^2=79.00$, $p<0.001$.

Figure 2 Relationship between age at diagnosis of 50 children with IDDM and that of their similarly affected siblings.

age at diagnosis of both sibling and child were associated. When further survival analyses were carried out for cases with siblings of the same or different sex, the results were significant for same sex pairs ($n=26$, global $\chi^2=10.89$, 1df, $p<0.001$), but not significant for different sex pairs ($n=24$, global $\chi^2=0.01$, 1df).

SOCIAL CLASS

There were higher proportions than expected of diabetic children whose fathers were in non-manual occupations compared with children in the British Births Survey followed up in 1980 aged 10 years (unpublished data) (table 7).

AGE OF MOTHERS AT DELIVERY OF INDEX CASE

From 1973–88, the mean age at delivery of the mothers of the diabetic children was significantly higher than that of mothers in the general population (OPCS, unpublished data, $n=16$ years, Wilcoxon matched pairs test $T=7.5$, $p<0.01$).

Discussion

It was not possible to quantify any bias in the analyses that may have been introduced by not contacting the parents of children diagnosed in Scotland or the Oxfordshire Health Authority, nor to evaluate any differences in family characteristics between the parents who responded to the questionnaire and those who did not. With these reservations in mind, analyses based on questionnaire information nevertheless suggest that certain characteristics of diabetic children and their families distinguish them from non-diabetic groups.

The birth weight of the diabetic children was

greatest in the seven cases where the mother herself developed diabetes after the delivery, indicating perhaps the early stage of the maternal diabetogenic process. The 14 children born to mothers with established IDDM were of normal birth weight, presumably reflecting carefully monitored pregnancies. There were more children who developed IDDM in 1988 than expected weighing more than 4000 g at birth (11% of cases) compared with national birth weight data (8% of the population). How birth weight might relate to the subsequent development of diabetes is not clear, but it is interesting to note that adult males with impaired glucose tolerance or newly diagnosed diabetes appear to have been of lower than average birth weight.¹⁴ Could the pattern of intrauterine growth influence or reflect the long term function of the immune system?

Children who subsequently developed IDDM were less likely to have been breast fed in infancy compared with the children in the 1980 infant feeding study. Because of the differences in the way the two sets of data were collected, the results must be confirmed with case-control data before they can be accepted with any confidence. Nevertheless, our lower proportion is in agreement with other researches,¹⁵⁻¹⁷ and supports the proposal that breast feeding affords some protection against the development of diabetes. Researchers in Finland, where the incidence of diabetes in childhood is the highest in the international league, found that newly diagnosed children (mean age 9.1 years) had significantly higher concentrations of IgA antibodies to cows' milk compared with age matched controls.¹⁸ This suggests a link between the initiation of the diabetogenic process, and the reciprocal effects of an antigenic challenge of cows' milk protein and the reduction in gastrointestinal immune defence available from breast milk.¹⁹

It has been shown that the risk of developing diabetes for children of fathers with IDDM (4%–6%) is greater than for children of mothers with IDDM (2%–3%).^{20, 21} In our study, the number of affected fathers was almost double that of affected mothers (41:22), there were more children than expected aged 0–4 years at diagnosis with an affected father, and there was a significant relationship between the age at diagnosis of children with IDDM and the age at diagnosis of their affected fathers. The last finding is not dissimilar to the pattern noted in Huntington's disease, in which fathers diagnosed young produce children diagnosed young; moreover, as in our study, a significant relationship exists between age at diagnosis of affected sibling pairs.²² We did not, however, observe that a stronger correlation existed in mother-child pairs compared with father-child pairs, as in Huntington's disease, but the number of mothers with diabetes is small. It has previously been noted the mothers of diabetic children are older at delivery than mothers of control children,^{19, 23} and the mean age at delivery of the mothers of our cases was greater than that of mothers in national studies.

Compared with national data, a higher proportion of diabetic children than expected came

from families in which the father's occupation was classified as non-manual. Non-responding parents (154/1254, 12%) would have included a number of fathers with manual occupations, who may have been less willing or less able to complete a questionnaire, thus introducing bias into our data. Nevertheless, even if these 154 families were all included in the manual group and the analysis repeated, the results still indicate a significantly greater number of children with diabetes who have fathers in non-manual occupations ($\chi^2=27.90$; $p<0.001$). In two local studies in England the prevalence of IDDM in children has been shown to be significantly over-represented in social class I.^{24, 25} In a study from Montreal incidence rates for IDDM in children aged 0–14 years were higher in wealthier neighbourhoods than in poorer ones.²⁶ In contrast, a study in Denmark showed that incidence rates for children aged 0–14 years in Copenhagen county were twice as high in the southern poorer area than in the northern more prosperous area.²⁷ A Swedish study demonstrated a higher proportion of fathers in manual occupations compared with a control population,²⁸ and a recent study from the north of England suggests that diabetes is more common in families who are socially deprived.²⁹ We found a high incidence of childhood diabetes in the Northern region and Wales among children with unemployed fathers. These diverse and apparently conflicting results illustrate the difficulty of analysing data based on the social class of the father (or father figure), which takes no account of the mother's occupation or family income and leaves fatherless children in an 'unclassified' category. To clarify these relationships a case-control study will be necessary using more refined measures to define differences in the domestic scene, such as diet^{30, 31} and the frequency of viral infection,³² which may contribute to the aetiology of diabetes.

We have defined certain characteristics of family members associated with IDDM in children. These include birth weight and the method of infant feeding, the age at onset of IDDM in affected fathers and affected siblings, and the family lifestyle as defined by social class of the father. A case-control study will be necessary to quantify the risks associated with such variables: this we are undertaking as part of a further national study of childhood onset IDDM in the British Isles.

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