ORIGINAL ARTICLE

First UK survey of paediatric type 2 diabetes and MODY

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Aims: To estimate the UK prevalence of childhood type 2 diabetes and maturity onset diabetes of the young (MODY), and distinguish them from each other and from type 1 diabetes.
Methods: The British Society for Paediatric Endocrinology and Diabetes Clinical Trials/Audit Group undertook a cross-sectional questionnaire survey of all paediatric diabetes centres during 2000, collecting data on all children with non-type 1 diabetes.
Results: Of 112 children reported to the survey, 25 had type 2 diabetes and 20 had MODY. In contrast to type 1, type 2 patients presented later (12.8 *v* 9.3 years), were usually female, overweight, or obese (92% *v* 28%), and a greater proportion were of ethnic minority origin (56% *v* 22%). In contrast to type 2, MODY patients were younger (10.8 years), less likely to be overweight or obese (50% *v* 92%), and none were from ethnic minority groups. The crude minimum UK prevalence of type 2 diabetes under 16 years is 0.21/100 000, and of MODY is 0.17/100 000. South Asian children have a relative risk of type 2 diabetes of 13.7 compared to white UK children.
Conclusions: UK children still have a low prevalence of type 2 diabetes. Children from ethnic minorities are at significantly higher risk, but in white UK children with non-type 1 diabetes a diagnosis of MODY is as likely as type 2 diabetes. Childhood type 2 diabetes is characterised by insulin resistance, and is distinct from both type 1 and MODY.

The increasing worldwide rates of adult and child obesity have been associated with the rising prevalence of type 2 diabetes.[1] Type 2 diabetes was first described in childhood in 1979 in Pima Indians, and an increasing prevalence is now recognised associated with obesity and peripheral insulin resistance, particularly in ethnic minority groups.[2] Type 2 diabetes has already been reported in children from places as diverse as Japan, the United States and Canada, Pacific Islands, Hong Kong, and Australia. Among children in Japan, it is already more common than type 1 diabetes, accounting for 80% of childhood diabetes, with an annual incidence which increased from 0.2 to 7.3 per 100 000 children between 1976 and 1995.[3–7] The prevalence of overweight and obesity has also increased in UK children since the mid-80s.[8 9] In 2000 the first UK children with type 2 diabetes were identified: eight girls aged 9–16 years, who were of Pakistani, Indian, or Arabic origin; and there has subsequently been a further report of type 2 diabetes in four obese white UK children.[6 10]

Childhood type 2 diabetes is often confused with monogenic maturity onset diabetes of the young (MODY). These patients have a single gene disorder resulting in β cell dysfunction and do not need to be insulin resistant or obese to develop diabetes. Patients with MODY have endogenous insulin secretion, are usually not insulin dependent or prone to ketoacidosis, and are not known to be insulin resistant. MODY is now known to be a heterogeneous group of single gene disorders with mutations in at least five genes, with more than 80% of MODY patients having a recognised mutation in a MODY gene.[11 12]

There is no information on the population prevalence of childhood type 2 diabetes or MODY in the UK, and there is confusion between the presenting features of different types of diabetes in children, which might lead to erroneous diagnosis. We therefore aimed to estimate the prevalence of type 2 diabetes and MODY in UK children; provide data on mode of presentation so that we could distinguish them from each other and from type 1 diabetes at diagnosis; and provide a baseline for longitudinal studies of changing patterns of diabetes in children.

SUBJECTS AND METHODS

We undertook a cross-sectional postal questionnaire survey of all consultants involved in the care of children with diabetes. In order to identify these consultants, a national reporting system was established and organised from Oxford; this has been described previously.[13] The questionnaire was posted to these 281 paediatricians at the end of year 2000. Reminders were posted after three months.

The background questions asked each paediatrician how many children (under 16 completed years) he or she managed with diabetes, and how many presented in the preceding 12 months. The criteria for reporting children to this study were: all children who were not treated with insulin at the time of the survey; all those with a presumed diagnosis of type 2 diabetes or MODY, even if now insulin treated; and any children regarded as having ''atypical type 1 diabetes''. These may be children initially thought to have type 1 diabetes, but not behaving as if they are insulin dependent—that is, requiring low doses of insulin, excellent control without monitoring, and now out of the honeymoon period.

We classified each respondent's patient data according to criteria modified from the World Health Organisation (WHO) guidelines; type 2 diabetes by idiopathic non-syndromic insulin resistance (with evidence of acanthosis nigricans, raised insulin or C-peptide, or abnormal lipid profile), in the absence of any known underlying associated syndrome, MODY by a known MODY gene mutation, and secondary diabetes by the presence of a recognised disease association.[14] Overweight and obesity were defined according to the International Obesity Task Force (IOTF) guidelines, which define overweight as a body mass index (BMI) equivalent to a BMI of 25 at age 18, and obesity as a BMI equivalent to a BMI of 30 at age 18.[9] The new Child Growth Foundation BMI charts include these lines.

To estimate the population prevalence we used data from the Office of National Statistics for the mid-year 2000 population estimates under 16 years (www.statistics.gov.uk). Clinical characteristics of subgroups of children were compared by comparison of proportions using the z statistic and using the Mann-Whitney U test to compare medians. To compare clinical data on non-type 1 diabetes with type 1 diabetes, we collected data from the last 50 children diagnosed with type 1 diabetes at Birmingham Children's Hospital, all of whom were diagnosed in the past two years.

RESULTS

The questionnaire and a reminder were posted to 281 consultant paediatricians working in 228 paediatric diabetes centres. The response rate was 75% (177 centres), and these consultants together were responsible for 15 255 diabetic children under 16 years.

We were notified of 128 children with non-type 1 diabetes, but supplied with clinical data on only 112. We classified these children according to our research criteria into those with type 2 diabetes, MODY, and secondary diabetes (table 1). Thirty three children could not be classified due to incomplete data on either insulin resistance or genetic testing for MODY.

Type 2 diabetes

Of the 25 children with type 2 diabetes, 17(68%) were female, presenting mainly in puberty. The majority (14/25, 56%) were of ethnic minority origin. Fourteen (56%) had a positive family history for type 2 diabetes in a parent or sibling, but a further seven had a positive family history in other relatives (overall 84% had a positive family history). Eighteen were obese and all but two were overweight. Six children had ketonuria at presentation. One patient had positive GAD (glutamic acid decarboxylase) antibodies and another had transiently raised autoantibodies (type not recorded). Most were managed on oral antidiabetic agents but seven required insulin: two as monotherapy and four in combination with oral agents. One patient had developed cataracts as a complication of diabetes.

MODY

There were 20 children with mutations demonstrated in MODY genes (10 in glucokinase, nine in HNF1α, and one in whom the nature of the mutation was not recorded). All had a positive family history of diabetes in a first degree relative, 19 (95%) in at least two generations, and none were autoantibody positive. All were of white UK ethnic origin.

Secondary diabetes

Thirty four children had diabetes associated with other conditions. These included recognised disease associations such as cystic fibrosis and Wolfram syndrome,[15] but also iatrogenic causes such as renal and bone marrow transplant.

Unclassifiable

Of the 33 children who could not be classified, the referring consultants suggested that 10 had type 2 diabetes, eight had MODY, and 11 were atypical. None had had investigations for

Table 1 Characteristics of children classified as type 2, MODY, unclassifiable, and secondary diabetes

	Type 2	MODY	Unclassifiable	Secondary
n	25	20	33	34
Sex				
Male	7	6	14	11
Female	17	13	18	18
Not recorded	1	1	1	5
Age				
Median age	12.75	10.79	11.38	11.83
Ethnic origin				
White	11	20	27	23
South Asian	8	0	6	11
Other	6	0	0	0
Body mass index				
Lean	2	7	12	15
Overweight	5	8	6	4
Obese	18	2	11	8
Not recorded	0	3	4	7
First degree family history				
Positive	14	20	20	15
Negative	11	0	13	19
Pubertal stage				
Prepubertal	6	9	14	17
Pubertal	19	11	15	12
Not recorded	0	0	4	5
Ketonuria				
Positive	6	0	7	3
Negative	15	16	23	23
Not recorded	4	4	3	8
Autoantibodies				
Positive	2	0	3	0
Negative	12	7	12	11
Not recorded	11	13	18	23
Management				
Diet	0	9	8	9
Oral antidiabetic agents	18	3	7	5
Combination oral and insulin	5	1	0	1
Insulin	2	1	15	14
Nil	0	5	1	1
Not recorded	0	1	2	4
Complications				
Cataract	1	0	0	0

insulin resistance, although five had been investigated for MODY mutations, with negative results in three and results outstanding in the other two. Nine were managed on diet alone, seven were on oral therapy, and 15 were on insulin.

Comparison with type 1 diabetes

The characteristics of the children with type 2 diabetes and MODY were compared with data on type 1 from the last 50 children diagnosed with type 1 diabetes at Birmingham Children's Hospital (table 2). The characteristics of children with type 2 diabetes are significantly different when compared with the type 1 group and the MODY group. Children with type 2 diabetes are significantly more overweight or obese than both those with type 1 or MODY, and are more likely to come from ethnic minority backgrounds; none of the children reported with MODY from the UK have been from ethnic minority backgrounds. Children with MODY are significantly more likely to have a first degree family history than children with type 2.

Prevalence estimates

The UK mid-year 2000 population estimate under 16 years is 11 668 400, of which 10 600 000 are white UK and 563 000 South Asian (source: Office of National Statistics and General Register Office for Scotland; www.statistics.gov.uk). From this we calculated the crude minimum prevalence of type 2 diabetes as 0.21/100 000 under 16 years. This compares to a crude minimum prevalence of MODY of 0.17/100 000. The prevalence of type 2 diabetes in white UK children (0.10/100 000) is significantly less than the prevalence in South Asian children (1.42/100 000; $p < 0.001$). This gives a relative risk for type 2 diabetes in an Asian child compared to a white UK child of 13.7. A white UK child with non-type 1 diabetes is as likely to have MODY as type 2 diabetes.

DISCUSSION

Our survey has shown that type 2 diabetes has a minimum UK prevalence of 0.21/100 000 children under 16 years, and has significant clinical differences compared to both type 1 diabetes and MODY. This is the first reported survey of childhood type 2 diabetes to provide case definitions, national minimum prevalence estimates, and comparisons with other diabetes types.

Our crude minimum prevalence estimates for type 2 diabetes show that we are still in a low prevalence type 2 diabetes child population. The national prevalence of 0.21/100 000 is far lower than the prevalence of 3.8/100 000 that we previously reported in Birmingham children.[16] This suggests that there may be large regional variations in type 2 diabetes prevalence which may reflect differences in regional ethnic composition. The reported prevalence of type 2 diabetes in North America is 5–45% of diabetic children; our prevalence of 0.16% of diabetic children is far lower than this.[17]

Our survey almost certainly underestimates type 2 diabetes, MODY, and secondary diabetes. Some children with non-type 1 diabetes may have been wrongly diagnosed and commenced on insulin; it is also known that children with type 2 diabetes can be asymptomatic and may not have come to medical attention, hence all prevalence estimates based on diagnosed cases will be an underestimate.[6] Not all children with secondary diabetes were reported, as some children with diabetes secondary to cystic fibrosis are managed by respiratory paediatricians, who were not approached for this survey. The survey also had a 25% non-response rate.

This is the first study of prevalence that has included data on MODY. This survey underestimates the MODY prevalence, as many patients are not genetically tested and in a minority of MODY the causative gene is not known. Despite this we show that in white UK children the prevalence of MODY is similar to the prevalence of type 2 diabetes, and no cases of MODY come from high prevalence racial groups where the majority of type 2 patients are found. Patients with MODY are less obese and more likely to have an affected parent than type 2 patients, but neither criterion is a good single discriminator, as 50% of MODY were overweight or obese and 56% of type 2 patients had an affected parent. Differentiating MODY from type 2 is important as the best treatment for a patient with the commonest form of MODY due to a mutation in HNF-1a is a sulphonylurea;[18] however, if they have type 2 diabetes metformin may be more appropriate due to its insulin sensitising effects.

Comparison with the last 50 type 1 diabetic children diagnosed at our centre has the advantages of using data on British children in the same timeframe as the survey, hence obesity rates will be directly comparable with our survey results. The frequency of overweight or family history in our local cohort is not significantly different to published international studies of type 1 diabetic patients: overweight 35% in an Italian study,[19] family history 13% in a Danish study.[20]

On the basis of our survey we suggest a flow diagram for a diagnostic approach to diabetes in the young (fig 1). It cannot be stressed enough, however, that if there is diagnostic doubt, the safest option is to treat as type 1 diabetes until a firm diagnosis can be made.

Our results confirm certain features of type 2 diabetes in childhood: high prevalence of obesity and family history, female preponderance, pubertal age of onset, and high frequency of ethnic minority children affected. The majority of children reported to this survey were autoantibody negative, although one did have positive GAD antibodies. It is known that up to 10% of adults with type 2 diabetes can have GAD autoantibodies and that these individuals may represent a distinct subgroup with early progression to insulin therapy.[21] There is now a need for studies to elucidate

Table 2 Comparison of type 2, MODY, unclassifiable, secondary, and type 1 diabetes in children

	Type 2	MODY	Unclassifiable	Secondary	Type 1
n	25	20	33	34	50
Female (%)	17 (68)	13 (65)	18 (56)	18 (62)	30 (60)
Median age (range)	12.8 (3.7–15.9)*	10.8 (4.2–14.8)	10.1 (2.7–15.4)	11.8 (0.1–15.3)	9.3 (0.6–15.6)
Ethnic minority (%)	14 (56)*†	0	6 (18)	11 (32)	11 (22)
Overweight/obese (%)	23 (92)*†	10 (50)	17 (59)	12 (44)	14 (28)
First degree family history (%)	14 (56)*†	20 (100)*	20 (61)	15 (44)	7 (14)
Pubertal (%)	19 (76)*	11 (55)	15 (52)	12 (41)	15 (30)
Ketonuria (%)	6 (24)†	0*	7 (23)	3 (12)	37 (74)

*$p<0.005$ *v* type 1.
†$p<0.005$ *v* MODY.
Statistical tests used: z test to compare proportions and Mann-Whitney U test to compare medians.

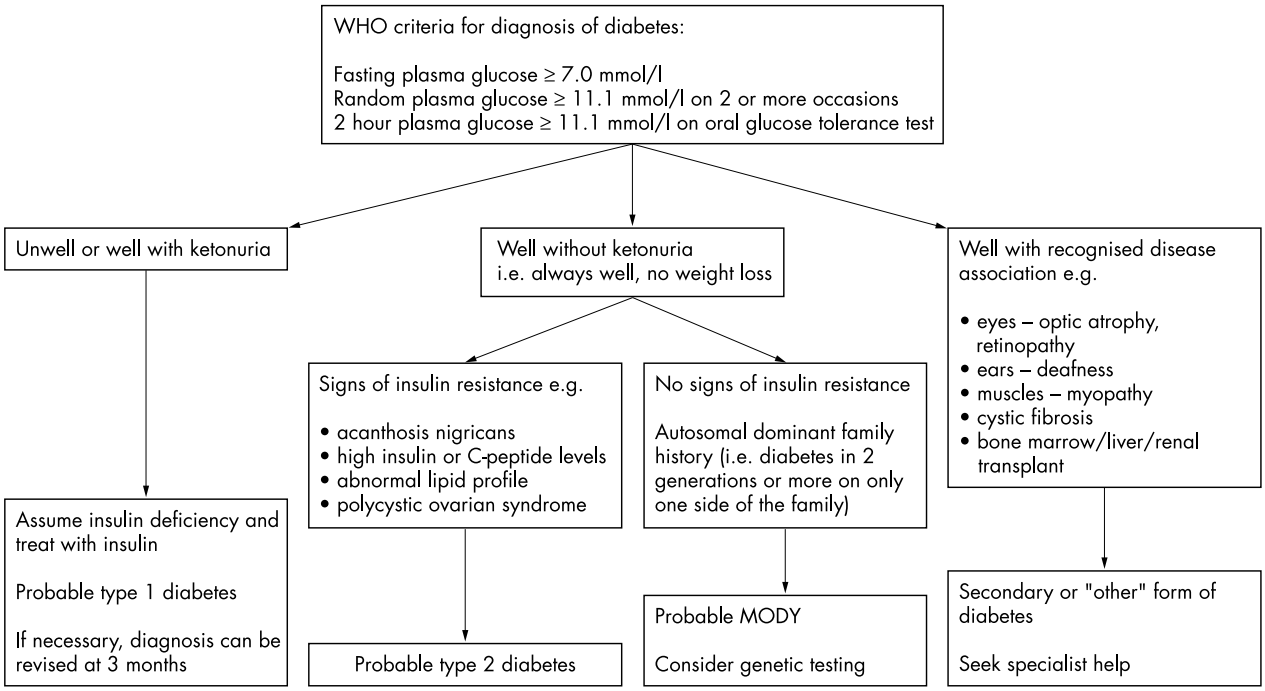

Figure 1 Diagnostic approach to diabetes in the young.

the underlying mechanism of interaction of these risk factors with insulin resistance. It is not clear why some insulin resistant children develop impaired glucose tolerance, which children are most at risk, why ethnicity confers risk, and what the implications are for the wider paediatric population. Our study has identified risk factors that make screening for type 2 diabetes in children a possibility, and there is now an urgent need for epidemiological data to examine the prevalence of impaired glucose tolerance and type 2 diabetes in at-risk populations. This study provides a baseline from which to begin to answer these research questions.

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