

Type 1 Diabetes versus Type 2 Diabetes with Onset in Persons Younger than 20 Years of Age

Results from an Indian Multicenter Study

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Type 1 diabetes (T1D) is the most common form of diabetes in children in Western countries. There have been no large studies of childhood diabetes from India. We undertook the MEDI study (Multicenter Survey of Early Onset Diabetes in India) to assess the proportion of various subtypes of diabetes among the young subjects presenting to the endocrinology divisions of seven large teaching hospitals in different regions of India. In addition, we compared the clinical features of T1D and type 2 diabetes (T2D) in Indian subjects. Patients with onset of disease at younger than 20 years of age were included in this study. Six hundred and three subjects (603) were studied of whom 535 subjects (89%) had T1D, 36 (6%) had T2D, 18 (3%) had diabetes related to tropical pancreatitis or other forms of chronic pancreatitis, while other subtypes accounted for the rest. Compared to those with T2D, subjects with T1D were younger, had a lower C-peptide level, higher prevalence of ketosis, lower prevalence of acanthosis nigricans, and lower LDL and triglyceride levels. When compared with that of T2D, a higher proportion of patients with T1D were positive for GAD-65 and IA-2 antibodies, and this difference was statistically significant for GAD-65 antibodies. Overall, this large multicenter study showed that T1D is the commonest form of diabetes in childhood. T2D is the next most common kind, while chronic pancreatitis-related diabetes is uncommon.

Key words: type 1 diabetes; type 2 diabetes; islet antibodies; young

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Introduction

The prevalence of type 1 diabetes (T1D) has been increasing worldwide, in both low- and high-incidence populations.¹ Type 2 diabetes (T2D) is also being increasingly reported in children and adolescents, and it is also being increasingly reported from India too.^{2,3} In some regions of Asia, T2D is a common form of childhood diabetes.⁴ In addition, fibrocalculus pancreatic diabetes (or tropical chronic pancreatitis-related diabetes) has also been reported as an important subtype of diabetes in young subjects from tropical countries.⁵

We undertook this multicenter study to identify the proportion of T1D among various subtypes of diabetes with onset in patients below 20 years of age. We also characterized their clinical profile and microvascular complications. Finally, we sought to identify features that could distinguish T1D from T2D of the young in this setting. This study was carried out in endocrinology divisions of seven major teaching hospitals in India, and was called the MEDI Study (Multicenter Survey of Early Onset Diabetes in India).

Methods

This cross-sectional study assessed clinical features of subjects with onset of diabetes < 20 years of age who presented to endocrinology divisions of tertiary-care teaching hospitals in different regions of India. Seven institutions took part in the study: Amrita Institute of Medical Sciences (Cochin, Kerala), Christian Medical College (Vellore, Tamil Nadu), Government Medical College (Guwahati, Assam), Osmania Medical College (Hyderabad, Andhra Pradesh), Postgraduate Institute of Medical Education and Research (Chandigarh), Sanjay Gandhi Institute of Postgraduate Medical Sciences (Lucknow, Uttar Pradesh), and St. Johns Medical College (Bangalore, Karnataka). The data from Sanjay Gandhi Institute of Postgraduate Medical Sciences have been

previously reported in part.⁶ The study was funded by the Research Society for Study of Diabetes in India (RSSDI), the largest national diabetes association in the country.

Subjects were enrolled over a 2-year period, and American Diabetes Association (ADA) 2004 criteria were used to diagnose diabetes. Each patient underwent history and physical examination to evaluate their nutritional status and microvascular complications. In addition, the following tests were performed in all cases: glycemic status assessment, complete lipid profile, serum creatinine, and urine microscopy (including urine ketones). In a randomly selected group of subjects from Cochin (South India) and Chandigarh (North India), glutamic acid decarboxylase-65 (GAD65) antibodies were measured by Medizym ELISA Kit (Selchow, Germany): this assay has a sensitivity of 92% and a specificity of 98%. The cutoff for GAD-65 positivity was ≥ 5 IU/mL. The intra-assay CV was 4% and interassay CV was 14%. Anti-IA2 antibodies (antityrosine phosphatase) were measured by Medizym ELISA Kit (Selchow, Germany): this assay has a sensitivity of 75% and a specificity of 98%. The cutoff for IA-2 positivity was ≥ 10 IU/mL. The interassay CV was 4% and intra-assay CV was 5%. C-peptide measurements were carried out in the 2-h postprandial state using the DBC ELISA kit (Ontario, Canada), which has a sensitivity of 0.2 ng/mL. The inter- and the intra-assay CV values were 2.7% and 3.5%, respectively. The tests for biochemical analyses were carried out in respective hospitals using an autoanalyzer. Informed consent was obtained from each subject, and the study was approved by the ethics committee of each center.

Definitions

Subjects with an episode of ketoacidosis or requiring insulin for survival or requiring insulin within the first year of diagnosis for control of hyperglycemia were classified as having T1D. Subjects who did not require insulin, with

no history of ketoacidosis, whose condition was controlled on oral drugs for >1 year after diagnosis were grouped as having T2D. Patients with a history of chronic abdominal pain with evidence on ultrasonography or CT scan or endoscopic retrograde cholangiopancreatoduodenography (ERCP) of pancreatic calcification and/or ductal dilatation were grouped as having fibrocalculous pancreatic diabetes (FCPD). Subjects with a heritable pattern of diabetes that was consistent with autosomal dominant inheritance, with transmission across three generations, were classified as having mature-onset diabetes of the young (MODY). Patients having a distinct, separate subtype of diabetes (such as hemochromatosis) were grouped as having other specific types. Thus, criteria for diagnosing diabetes were based on clinical features, and not on antibody/C-peptide testing.

Complications were defined as follows: Neuropathy was defined as failure to elicit the knee and/or ankle reflexes after reinforcement with or without symptoms of neuropathy or gross sensory disturbance in both feet, in the absence of any other cause of neuropathy or an abnormal biothesiometry/nerve conduction velocity study. Nephropathy was defined as quantitative 24-h urine protein excretion of >500 mg per 24 h or the presence of microalbuminuria, in the absence of other renal diseases. Retinopathy was established by ophthalmoscopy by a trained ophthalmologist/endocrinologist and classified as background or proliferative retinopathy.

Statistical Analysis

SPSS for Windows (Version 11) was used for data management and statistical analysis. Association between two categorical variables was tested using the chi-square test or the Fisher's exact test wherever appropriate. Student's *t*-test was used for comparison between continuous variables. A *P*-value of <0.05 was considered statistically significant.

TABLE 1. Proportion of Various Subtypes of Diabetes in the Young (*n* = 603)

Kind of diabetes	Number	Percent
Type 1 diabetes	535	89
Type 2 diabetes	36	6
FCPD ^a	18	3
Others	14	2

^aFCPD = fibrocalculous pancreatic diabetes

Results

Over a period of 2 years, 603 subjects were evaluated. Of these, 535 (89%) had a diagnosis of T1D (Table 1), 36 (6%) had T2D, and 18 (3%) had fibrocalculous pancreatic diabetes. Other subtypes of diabetes accounted for the rest (*n* = 14; 2%); this included one patient with hemochromatosis, while the others (*n* = 13) could not be classified into either T1D or T2D on the basis of the criteria.

HbA1c levels in T1D ($9.3 \pm 2.3\%$) were not significantly different from levels in T2D ($8.7 \pm 2.1\%$). Except for patients with T2D, all patients were on insulin. All the 36 subjects with T2D were treated with metformin. In addition, 2 of these 36 subjects were treated with thazolidinedione, and another patient was on glibenclamide.

The profiles of T1D and T2D are compared in Table 2. In brief, the statistically significant results among the study subjects were that patients with T1D were younger and had a lower body mass index (BMI). Subjects with T1D had a higher prevalence of ketoacidosis. Patients with T2D had a higher prevalence of acanthosis nigricans. A lower proportion of subjects with T1D (22%) gave a family history of T2D in comparison to 67% of subjects with T2D (*P* < 0.05). The C-peptide (mean \pm SEM) levels in T2D (64.7 ± 42.0 ng/ml; *n* = 18) were higher (*P* = 0.001) than values in T1D (1.4 ± 0.3 ng/ml; *n* = 128).

In 68 subjects with T1D, GAD-65 antibodies (Abs) were measured, and 49 (72.0%) were positive. None of the 20 subjects with T2D were positive for GAD-65 antibodies. In the 70

TABLE 2. Comparison of Type 1 versus Type 2 Diabetes in the Young

Variables	Type 1 (<i>n</i> = 535)	Type 2 (<i>n</i> = 36)	<i>P</i> -value
Diabetes onset age (years; mean ± SD)	12.0 ± 5.4	16.2 ± 2.9	<0.001
Current age (years; mean ± SD)	17.6 ± 7.8	18.90 ± 4.9	0.04
Males [<i>n</i> (%)]	284 (53.1)	21 (58.3)	0.374
Family history [<i>n</i> (%)]	119 (22)	24 (67)	<0.0001
BMI (kg/m ² ; mean ± SD)	17.4 ± 4.3	25.5 ± 5.6	<0.001
Hypertension [<i>n</i> (%)]	15 (0.03)	1 (0.03)	0.99
Ketoacidosis/ketosis [<i>n</i> (%)]	500 (93.4)	1 (2.7)	<0.0001
Acanthosis nigricans [<i>n</i> (%)]	14 (2.6)	17 (47.2)	<0.0001
Peripheral neuropathy [<i>n</i> (%)]	32 (6)	0 (0)	0.12
Retinopathy [<i>n</i> (%)]	27 (5)	0 (0)	0.16
Nephropathy [<i>n</i> (%)]	29 (5.4)	0 (0)	0.14
Total cholesterol (mg/dL; mean ± SEM) ^a	148.68 ± 5.1	190.60 ± 15.1	0.087
LDL (mg/dL; mean ± SEM) ^a	84.72 ± 5.0	127.5 ± 53.9	0.03
VLDL (mg/dL; mean ± SEM) ^a	19.5 ± 9.8	25.1 ± 6.6	0.201
TG (mg/dL; mean ± SEM) ^a	95.9 ± 77.4	169.1 ± 171.6	0.037
HDL (mg/dL; mean ± SEM) ^a	35.8 ± 21.5	41.6 ± 11.5	0.78

^aLipid profiles were done in 15 subjects with type 2 diabetes and 135 with type 1 diabetes.

TABLE 3. GAD-65/IA-2 Antibody Positivity in Relation to Duration of Type 1 Diabetes

Duration of diabetes	<1 year <i>n</i> /total (%)	1–3 years <i>n</i> /total (%)	3–5 years <i>n</i> /total (%)	>5 years <i>n</i> /total (%)
GAD-65 Ab-positive (<i>n</i> = 49)	22/29 (76)	9/12 (75)	7/11 (64)	11/16 (69)
IA-2 Ab-positive (<i>n</i> = 24)	9/27 (33)	6/13 (46)	4/12 (33)	5/18 (28)

subjects with T1D in whom IA-2 antibodies were measured, 24 (34.3%) were positive. Among the 20 subjects with T2D who were tested, two were positive for IA-2 antibodies (10%). Both GAD-65 and IA-2 antibodies were positive in a higher proportion of subjects with T1D as compared to subjects with T2D. This difference between T1D and T2D was statistically significant for GAD-65, but not IA-2 antibodies ($P < 0.0001$ and $P = 0.09$ respectively). As shown in Table 3, both GAD-65 and IA-2 antibody positivity rates varied with increasing T1D duration. The prevalence of GAD-65 and IA-2 antibodies was not statistically different when grouped according to the duration of T1D. In T1D, the C-peptide values (mean ± SEM) in autoantibody positive subjects were compared with autoantibody-

negative subjects. The C-peptide levels of IA-2 antibody-positive subjects with T1D was 1.89 ± 1.29 ng/mL, which was not significantly different from the value of 3.68 ± 1.35 ng/mL in IA-2 antibody-negative subjects ($P = 0.39$). The C-peptide (mean ± SEM) levels of GAD-65 antibody-positive subjects with T1D was 0.63 ± 0.15 ng/mL, which was not significantly different from the value of 0.77 ± 0.40 ng/mL in GAD-65 antibody negative subjects ($P = 0.70$).

Discussion

The results of this study indicate that T1D is the commonest subtype of diabetes in the young among Indians. Three previous studies

from India have also shown that in younger subjects, T1D is more common than T2D.⁶⁻⁸ T2D can occur in young Indian subjects, and our study corroborates a previous study from India documenting this occurrence.³ However, T2D in the young continues to be an uncommon entity. Only 6% of the young subjects with diabetes in our study had T2D. It is likely that our study, which was done in tertiary-care endocrinology centers in urban India, might have overestimated the prevalence of T2D. While the proportion of FCPD reported in this multicenter study was low, nevertheless it is an important diagnosis to consider in young Indian patients. In earlier studies, the proportion of FCPD varied from 9–33%.⁶⁻⁸ However, it has been recently suggested that the clinical spectrum of FCPD is changing, and that it is becoming a disease of older subjects, especially adults.⁹

T1D may be difficult to distinguish from T2D in some subjects, especially at disease onset. Our study suggests certain distinctive features in T1D which could help differentiate it from T2D. When compared to those with T2D, patients with T1D were significantly younger at disease onset, had a lower BMI, higher prevalence of ketosis, and lower C-peptide levels and were less likely to have a positive family history. On the other hand, features suggesting insulin resistance and dyslipidemia, such as acanthosis nigricans, higher triglyceride values, and raised LDL were all present in T2D. In another study from India, subjects with T2D (mean age at diagnosis = 21 years) showed three distinctive features when compared with healthy controls: higher prevalence of hypertriglyceridemia, high waist–hip ratio, and a family history of diabetes.¹⁰

Our study shows that islet autoantibodies could assist in diagnosing T1D in this setting. Our results also suggest that GAD-65 antibodies are a more useful test than IA-2 antibodies for distinguishing T1D from T2D in children and adolescents. The absence of GAD-65 antibodies could point to the diagnosis of T2D. In a recent study of early-onset T2D

from India, GAD-65 antibodies were present in only 3% of subjects and IA-2 antibodies were absent in all subjects with onset of diabetes <30 years.¹¹

Our study also showed that microvascular diabetes complications are present in T1D even at an early age. Among subjects with T1D, the prevalence values of peripheral neuropathy, nephropathy, and retinopathy were 6%, 5.4%, and 5%, respectively. It would therefore be prudent to screen all young subjects with diabetes for complications starting from a prepubertal age. The subjects with T2D in our study, however, did not have microvascular complications. In contrast to young subjects, it has been reported that about 7–48% of adult-onset T2D is associated with microvascular complications at diagnosis.¹²

To summarize, our multicenter study shows that T1D is the commonest subtype of diabetes in Indian subjects who are below 20 years of age. Simple clinical, anthropometric, biochemical and autoantibody-related parameters may help in distinguishing T1D from other subtypes.

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Conflict of Interest

The authors declare no conflicts of interest.

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