ORIGINAL ARTICLES

Childhood Onset Diabetes Mellitus In India: An Overview

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INTRODUCTION

Insulin-dependent diabetes mellitus (IDDM) is one of the most common chronic diseases in childhood. Very little is known about the epidemiology, determinants and clinical profile of childhood diabetes mellitus in India and a lot more work is still needed today to improve the health care of these children in our country.

In the early part of 20th century, nutritional deficiencies and infectious disorders were the most prevalent health problems of the economically underprivileged and developing countries. It was generally believed that chronic degenerative disorders were virtually nonexistent. Observations by astute clinicians in earlier years followed by school surverys by research teams proved that rheumatic diseases are one of the most common chronic disorders of childhood in India. The story of childhood diabetes is not different either. Many physicians and ediatricians still believe and teach that childhood diabetes is rare. Childhood diabetes does not form part of undergraduate medical curriculum in many medical colleges, probably due to this apparent "rarity". The diagnosis in childhood is usually made in an emergency or often on a routine evaluation of blood sugar for an associated disease. There is also reason to believe that most diabetic children in India probably die before a diagnosis in established in a may medical facilities or soon after diagnosis (1). Sadly, blood glucose or ketone or even urine glucose is not routinely carried out even in emergency situations which could be due to diabetes mellitus or its associated complications. This calls for adequate awareness and a high index of suspicion among treating physicians about the disease.

EPIDEMIOLOGY OF CHILDHOOD DIABETES MELLITUS IN INDIA

There is relative paucity of information regarding childhood diabetes in India. The classification of diabetes into various subtypes by the National Diabetes Data Group and World Health Organization has helped in the study of the clinical features and differences in presentation of distinct subtypes in later years. Most of the Indian studies carried out in the earlier years do not classify the clinical presentation according to presently accepted norms and most often include data from both adults and children. The data collected from hospital-based studies from India suggest that young diabetics (onset of diabetes before the age of 15 years) constitute about 1-4% of the total diabetic population as shown in table 1 (2-9). The observe difference between reports from different centres could be due to many factors including differences in socioeconomic status, health awareness, accessibility and quality of medical care besides true differences in disease incidence. In a recent survey of a very small sample of rural children in South India, the prevalence of random glycosuria was 0.1 per 100 (10). In the natural history of diabetes mellitus, the interval between onset of glycosuria and clinical symptomatoloty of diabetes, including ketoacidosis and death, is relatively very short. Hence this strategy of "glycosuria screening" can underestimate the population burden of childhood diabetes mellitus.

Preliminary studies have confirmed the existence of islet cell autoimmunity and HLA association of classical type I diabetes mellitus (IDDM) in India with features similar to those observed in the West. However, besides IDDM, few other "types" or "variants" of diabetes in the young have been reported from India as well as the economically underprivileged developing countries. They are described below.

1. NON-ALCOHOLIC CHRONIC PANCREATITIS

(With or without pancreatic calculi) is seen in many parts of India and assumes endemic proportions in the southern coastal state of Kerala (11). Despite incrimination of certain nutritional

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factors, the precise etiology of this form of diabetes is unknown.

2. Over the years several investigators have reported on a special clinical varient of diabetes in the young, variously referred to as *Ketosis resistant diabetes of young, J type of diabetes, or malnutrition related diabetes mellitus-subtype protein-deficient diabetes mellitus* (MRDM-PDDM) (12). The associated features include a male proponderance, low socio-economic status, absence of a family history of diabetes mellitus, onset of diabetes usually in the second or third decade, features of malnutrition, ketosis resistance, absence of pancreatic calcification, intermediate beta cell reserve as indicated by a C-peptide secretion between IDDM and NIDDM controls (13). Inspite of some studies and intense speculation, whether malnutrition is a cause or consequence is yet unclear.

3. Maturity-onset diabetes of young (MODY) or bib-insulindependent diabetes of the young (NIDDY). A high incidence of NIDDY has been reported from a few selected centers from South India (14). MODY is characterized by autosomal dominant inheritance with vertical transmission in families. About half of the offsprings of MODY patients subsequently develop diabetes mellitus. These children have reduced insulin secretion as judged by insulin and C-peptide response to glucose load (15). MODY has also been reported among Indians in South Africa (16).

HLA STUDIES IN IDDM IN INDIA

HLA typing for detection of antigens of the HLA-A and B loci using the modified microlymphocytotoxicity test, was performed in 54 unrelated North Indian patients with IDDM (17). The frequency of BW2 was significantly high in diabetics compared to controls, whereas the frequency of B7 was significantly reduced . The relative risk of 12.27 with regard to BW21 is the highest ever recorded for a single B locus antigen in IDDM (17). This appears to be a unique feature of the Indian population, emphasizing the racial specifically of association between disease and HLA antigens.

In a subsequent study, DR antigens (DR 1-7) were typed in 88 North Indian patients with type I diabetes and 113 unaffected controls (18). The frequency of ER-3 was significantly increased in IDDM compared to controls (78.4%) with a relative risk of 10.52 which is higher than that reported in Western IDDM population. There was significant negative associated with DR2, but DR4 had no relationship with IDDM in this study. Recently we had studied the HLA profile in 25 newly diagnosed IDDM children below 15 years and found significant association with DR3 and DR4 antigens (19).

HLA haplotype segregation in 7 IDDM multiplex families of North Indian children has also been reported (20). The high risk of IDDM haplotype appeared to be A28, BW21, BFS1, DR3 and the low risk haplotype conferring resistance or protection was A3, B7, DRZ; this is a common observation in most other studied populations.

Table 1
Juvenile diabetes (onset below 15 years) in India: Prevalence among all diabetics: Hospital and/or clinic based data.

S. No.	Region	Year	Prevalence %	References
1.	Ahmedabad	1964	<1	Gupta OP (2)
2.	Delhi	1965	2.4	Ahuja MMS et al (3)
3.	Madras	1966	0.8	Viswanathan M (4)
4.	Bombay	1968	1.43	Udani PM et al (5)
5.	Delhi	1974	2.1	Vaishnava H et al (6)
6.	Cochin	1989	3.61	Abraham A et al (7)
7.	Cuttack	1989	2.0	Samal KC et al (8)

Similar studies conducted on South Indian diabetic children showed that both DR-3 and DR-4 were independently increased, but not the combination of DR-3/DR-4 (21), in contrast to Europeans where this combination causes the highest risk for IDDM. Restriction fragment length polymorphism studies have shown that the highest relative risk for IDDM is seen in DQ beta region (22). HLA B15 was absent in Asian Indians studied in England (23).

AUTOMMUNITY AND ISLET CELL AUTOANTIBODIES

Islet cell antibodies constitute a basic serological marker of islet cell autoimmunity and hence play an important role in the understanding of etiopathogenesis of diabetes mellitus. Serum samples of 110 North Indians patients with IDDM with an age of onset less than 30 years were screened for pancreatic islet cell antibodies (ICAb), gastric parietal cell antibodies, and adrenal antibodies using indirect immunofluorescence technique (17). Thyroglobulin and thyroid microsomal antibodies were detected titrated with commercial haemagglutination kits. ICAb was positive in 31% of the diabetics , irrespective of the duration of diabetes, and only 0.8% of controls. The maximum prevalence was within a month of onset of diabetes (67%) and persistence for long period was seen in patients with consistent autoimmunity. These characteristics are similar to those described in the West. A subsequent study on 51 IDDM patients from North India showed ICAb positivity of 29% (18). These studies also demonstrated a higher prevalence of organ-specific thyrogastric antibodies in IDDM patients as well as their family members.

Using a newly standardized (internationally validated by JDF/Immunology of Diabetes workshops) assay for ICAb by indirect immunofluorescence technique (FITC protein A conjugate) using fresh frozen monkey pancreatic substrate, we had recently analysed sera from 107 IDDM patients with onset of disease before 20 years. Overall ICAb was positive in 40% subjects with childhood onset IDDM.

Table 2
Islet cell antibodies (ICAb) and duration of diabetes

Duration	No. of Patients	ICAb +ve	%
1-3 months	28	13	46.4
4-12 months	26	10	38.5
13-60 months	29	8	27.6
61-120 months	14	6	42.8
> 120 months	10	5	50.0
Total	107	42	39.25

Table 3
Islet cell antibodies (ICAb) and age of onset

Age of onset	No. of Patients	ICAb +ve	%
1-5 years	13	6	46.1
6-10 years	39	17	43.6
11-15 years	29	10	34.5
16-20 years	26	9	34.6
1-20 years	107	42	39.25

Table 4
C- peptide levels (pmol/ml) in young diabetes (mean ± SD)

Age at onset (no)	Basal	Stimulated	Increment
0-5 (2)	0.04 ± 0.03	0.08 ± 0.06	0.04 ± 0.03
5-10 (13)	0.05 ± 0.05	0.06 ± 0.06	0.02 ± 0.02
10-15 (16)	0.10 ± 0.09	0.13 ± 0.11	0.03 ± 0.02
15-20 (15)	0.17 ± 0.14	0.24 ± 0.24	0.07 ± 0.11
Control (5)	0.36 ± 0.10	0.55 ± 0.18	0.14 ± 0.10

Table 5
Profile of childhood diabetes in India-Regional variations

Region	Age of Onset of Diabetes (years)	Total no. of subjects studied	IDDM %	FCPD %	NIDDM %
I. General Hospitals					
Delhi/north	< 20	168	99	0.5	0.5
Cuttack/east	< 15	90	88	12	0
Madras A/South	< 20	160	95	4	1
II. Private Institutions					
Madras B/South	< 20	252	67	11	22
Cochin/South	< 20	58	67	19	14

The highest prevalence was seen soon after diagnosis in the first 5 months (46.4%) and prevalence declined progressively with time (Table2). There was an increased prevalence of ICAb in a subset of patients with longer duration of diabetes, possibly indicating persistence of associated multi-organ specific autoimmunity. The prevalence of ICAb positivity declined progressively with increasing age at onset of IDDM, the highest prevalence (46%) being in children with age of onset of 1-5 years. (Table 3). Similar studies form South Indian showed that the ICAb persisted in circulation for a shorter time (24).

BETA-CELL FUNCTION STUDIES

There is paucity of studies on beta-cell function in childhood diabetes in India. Using intravenous glucagons as the stimulus, Shah et al studied the beta-cell function in 46 IDDM subjects (age at onset than 20 years) by estimating C-peptide concentration at 0 and 6 minutes (26). Very low basal and stimulated C-peptide values were observed compared with non-diabetic controls (Table 4) , indicating severely compromised endogenous insulin reserve. There appeared to be decrease in the severity of beta-cell destruction with increasing age at onset of diabetes. In a present study conducted by us in 25 diabetic children (mean age of onset = 7.25 years, mean diabetes duration = 2.08 years) below 12 years, the C-peptide levels, both basal and incremental to administration of IV glucagons, were also very low (19). These observations indicate that the major type of diabetes occurring in childhood is IDDM (type I) in the population studied (particularly by combining studies on beta cell functions with HLA typing and islet cell antibodies)

CHILDHOOD DIABETES REGISTRIES IN INDIA

The first childhood diabetes registry was established at New Delhi under the auspices of Diabetes Foundation (India) supported by the Indian Council of Medical Research and All Indian Institute of Medical Sciences, New Delhi. Between January 1984 and July 1989, 89 children with onset of diabetes before the age of 20 years were enrolled. All except one were IDDM Development of childhood diabetes registries in different region of India is in progress.

PROFILE OF CHILDHOOD DIABETES IN INDIA-REGIONAL VARIATIONS

Preliminary reports of the profile of childhood onset diabetes from various regional centers were presented at the Annual Scientific Meeting of the Research Society for Study of Diabetes in India held in October 1989 at Madras. The results of these studies are provided in Table 5 . The details are discussed elsewhere in this issue of the "Bulletin". Despite some observed regional variations in disease profile, it appear that the predominant type of "juvenile" diabetes mellitus (onset of diabetes before the age of 20 years) seen in Indian is IDDM . It is hoped that further studies will clearly delineate the clinical biochemical, genetic and immunological profile of childhood diabetes in our country.

DIABETES IN INDIAN MIGRANTS ABROAD

It is well known that the crude prevalence of diabetes mellitus is almost twice more in Asian Indians in Southall (UK) compared to whites and Afrocarribeans. Recently Samanta et al (27) from Leicester, UK showed a higher prevalence of childhood diabetes as evidenced by the study on Ugandan Asians which showed an increase of 10-fold (23). These observations have stimulated further research on Indian heritage in the etiology of diabetes towards better understanding of the disease (28).

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