INFANTILE TYPE 1 DIABETES MELLITUS (ONSET LESS THAN 1 YEAR OF AGE) – A REPORT OF 8 PATIENTS

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ABSTRACT

Infantile onset type 1 diabetes (with onset ≤1 year of age) is an extremely rare form of diabetes. The present study deals with eight patients with infantile onset diabetes seen at the M.V.Diabetes Specialities Centre at Gopalapuram, Chennai. Mode of presentation varied from classical osmotic symptoms to failure to thrive. The series is presented for its rarity. Differences between infantile onset type 1 diabetes and transient neonatal diabetes are also highlighted.

KEY WORDS: Infantile onset diabetes; Neonatal diabetes; Diabetes infantalis

INTRODUCTION

Despite its strong genetic connection, diabetes is not very frequent in children and it is even more rare in infants. The first reference of childhood diabetes is attributed to Richard Morton who coined the term "Diabetes Infantalis" in 1689 to denote this special subgroup. The US physician Jacobi (1930-1999) described a more rapid course of the disease in infants and children compared to that seen among adults with grave terminal outcome including coma and death (1). Before the discovery of insulin, the expected life of a child after diagnosis of diabetes was less than a year. After the discovery of insulin the mortality has come down from 100% to 6% in most countries and to even less than 1% per year in developed countries (2).

Epidemiological studies show that the yearly incidence of type 1 diabetes among children is 25 per 100,000 children at risk in Finland and Sweden, 19 in USA, Denmark and Scotland, 4 in Israel and France and less than 1 in Japan (3). Yearly incidence of type 1 diabetes in 0-4 years of age group is 2.7 in males and 2.3 in females in the former German Democratic Republic compared to 21.8 in males and 15.6 in females per 100,000 population in Sweden (4).

Most published data on the incidence of type 1 diabetes in children refers to the age group less than 15 years. This paper deals with the profile of the infantile onset of type 1 patients with age at onset ≤1 year seen at a specialized diabetes centre at Chennai.

MATERIAL AND METHODS

Using our diabetes electronic data base, case records of 70,000 consecutive diabetic patients registered at M.V.Diabetes Specialities Centre, a tertiary care centre at Chennai, India, during the period 1991 – 2001 were reviewed retrospectively to assess the prevalence and clinical profile of infantile onset type 1 diabetes. From this huge database of patients, 8 cases were found to have infantile onset diabetes defined as age at onset of diabetes ≤ 1 year of age. The overall prevalence at our centre is therefore 8/70,000 diabetic patients or 1: 8661 patients. Of the total of 1000 patients with type 1 diabetes seen at our centre, this represents 8 /1000 or 1:125 patients.

The medical records of these 8 patients with infantile onset diabetes were analysed with regard to demographic, clinical, biochemical and hormonal profile as well as treatment pattern at the time of the first visit to the M.V.Diabetes Specialities Centre. Wherever possible, the follow-up data was also assessed.

RESULTS

Table 1 shows the prevalence of infantile onset diabetic patients at our centre in comparison with other published series in the world. Of the 8 infantile onset diabetic patients, 7 were female. All the 8 patients were Hindus. Socioeconomic assessment revealed that 7 out of 8 were from middle income group and one was from low-income group. Five were from urban areas and 3 from rural areas. There was a positive family history of diabetes in 5 patients. In 6 patients, diabetes was detected between 11 months to 1 year of age and in others it was detected at the age of 9,3 and 2 months respectively.

Five of the patients reported to our centre immediately after diagnosis and the others later and one as late as 29 years after detection. Mean age at presentation at our centre was 5.1 years with a range of 3 months to 30 years.

Table 2 shows the anthropometric values of the

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Table 1: Incidence of Transient Neonatal Diabetes (TNB) and Permanent Diabetes Mellitus of Infancy (PDMI).

Type of Diabetes	Author	Country	Year	Population or Clinic Based	No. of Cases	Prevalence
TNB	Von Muhlendahl et al[6]	Germany	1995	Population based	20	1:600,000 liver births / year
PDMI	Rosenbouer J, et al[10]	Germany	1999	Population based	19	1.43 to 1.96 per – 100,000 population / year
	Soliman AT et al[8]	Sultanate of Oman	1999	Population based	—	1.788 per 100,000 population / year
	Iafusco D, et al[9]	Italy	2002	Population based	111	1.7 per 100,000 population year
	Present Study	Chennai, India	2002	Clinic based	8	1 in 8,661 of all diabetes patients, or 1 in 125 type 1 diabetes patients

study group compared with the expected values of standard Indian children of the corresponding age (5). It can be seen that the majority of patients were shorter and lighter than the expected average for their respective ages.

Mode of presentation of diabetes shown in Table 3. Five out of eight patients had history of hypoglycemic episodes after diagnosis and of which two needed hospitalization indicating that these patients are sensitive to insulin. One patient gave a history of switching over from breast milk to cow's milk before detection of diabetes. One patient had a history of neonatal glycosuria and blood glucose tests at the age of 3 months confirmed the diagnosis of diabetes.

Table 3: Clinical Data of Infantile Onset of Type 1 Diabetes

Mode of presentation at first detection		No. of patients
i.	Osmotic Symptoms	2
ii.	Vomiting	2
iii.	Failure to thrive	1
iv.	Urinary infection	1
v.	Passing high colored urine	1
vi.	Fever and breathlessness	1

Abdominal x-ray did not reveal pancreatic calculi in any of the patients and hence ruled out Fibrocalculous Pancreatic Diabetes (FCPD). Biochemical profile and initial insulin requirement of the patients are shown in Table 4. Initial insulin requirement varied from 0.6 to 2.0

Table 2 : Anthropometric Studies in the Study Group

S.No.	Height			Weight		
	Expected (in cm)	Actual (in cm)	%variation in relation to expected value	Expected (in kg)	Actual (in kg)	%variation in relation to expected value
Case 1	93.9	99.0	+5.4%	14.1	11.7	-17.1%
Case 2	77.9	—	—	10.1	8.4	-16.8%
Case 3	60.2	57.0	- 5.3%	5.4	5.0	- 7.4%
Case 4	72.3	—	—	9.2	8.2	- 10.7%
Case 5	156.0	139.0	- 10.9%	49.75	48.0	- 3.5%
Case 6	101.0	98.0	- 2.9%	16.0	14.7	- 8.1%
Case 7	75.0	73.0	-2.67%	9.5	9.4	- 1.1%
Case 8	60.2	—	—	5.4	5.2	- 3.6%

+ = More than expected value
- = Less than expected value

Table 4: Biochemical Profile and Initial Insulin Requirement

S. No	Variables	Results Range	Normal value
1	Fasting blood sugar (mg/dl) (n=8)	Median 323 (137-581)	<60mg
2	Glycosylated hemoglobin 11.7% (n=6)	<5.6% (8.5 – 14.3%)	Mean (%)
3	C-peptide assay (ng/dl) (n=6)		
	i. Fasting	Mean 0.13 (0.1 – 0.2)	0.5 – 1.5
	ii. Stimulated	Mean 0.13 (0.1 – 0.2)	1.0 – 2.5
4	Initial insulin requirement 1.1 —— (units / kg. body weight)	(0.6 – 2.0)	Mean

Follow-up period (mean value 1 year) was uneventful for the majority of patients. One patient inspite of intensive follow-up had extreme fluctuations of blood sugar values and was diagnosed to have "brittle diabetes". Another patient after attaining good glycemic control discontinued the insulin for a few days but was readmitted at our centre with high fasting blood sugar and glycosylated hemoglobin levels with hepatomegaly, hyperlipidemia and raised liver enzymes raising the possibility of a glycogen storage disease. One patient who reported for the first time to our centre at the age of 30 years, was detected to have the diabetes related complications like nephropathy (24 hour urinary protein excretion of 856 mg), sensory neuropathy and proliferative diabetic retinopathy.

DISCUSSION

Infantile onset type 1 diabetes is a very rare entity and to our knowledge, there is no published data from India so far. The present study identified 8 patients out of 70,000 registered diabetic patients registered at a major diabetes centre during a 10-year period. Our study showed that 6 of the 8 patients were detected after 6 months (180 days) of age which is similar to the observation of the Early Onset Diabetes Study Group (6). Our study further shows that there is a marked female predominance in infantile onset diabetes although the reason for this is not clear. Anthropometric studies showed growth retardation with lower heights and weights compared to the standard Indian children of corresponding age. As "failure to thrive" was the mode of presentation in one case, diabetes should also be considered in the differential diagnosis of children with such a presentation.

Infantile onset diabetes needs to be distinguished from "Neonatal diabetes" which is a rare entity and defined as hyperglycemia occurring within first 30 days of life and which needs insulin as life support. In the majority of such cases, however, the diabetes disappears within few weeks to few months and this condition is termed as "Transient Diabetes Mellitus of New Born" (TDNB) or "Transient Neonatal Diabetes Mellitus" (TNDM). Very few of these cases continue to have permanent diabetes whereas onset of diabetes after one month of age i.e. infantile onset diabetes is likely to be permanent and therefore termed as Permanent Diabetes Mellitus of Infancy (PDMI) (6,7).

Table 5 shows the reported differences between Transient Neonatal Diabetes (TND) and Permanent Diabetes Mellitus of Infancy (PDMI). It is clear that all our patients in the present report have PDMI and not TND (7).

There is very little data available on diabetes in infants. Von Muhlendahl et al (6) in former West Germany estimated the prevalence of "neonatal onset diabetes" to be about 1 in 600,000 live births. A study conducted in the Sultanate of Oman reported an incidence of 1.78 per 100,000 live births / year (7,8). An extensive study in Italy by the Early Onset Diabetes Study Group of the Italian Society of Paediatric Endocrinology and Diabetology reported an incidence rate of 1.7 / 100,000 which was comparable to that estimated in Germany in 1993 and 1995 as 1.43 and 1.96 per 100,000 live births respectively (9,10).

As this is a retrospective study, we were unable to perform more detailed studies such as HLA, islet cell or insulin autoantibodies to classify them better. Moreover, as the numbers are small, such studies would probably not be very meaningful anyway. However, a very recent report on infantile onset diabetes from Europe showed that 76% (16 of 21 available results) of the infants with onset before 180 days of age had a protective "HLA genotype" whereas only 11.9% (5 of 42 available results) patients with onset between 181 and 365 days had a protective "HLA genotype". Also, 15.4% of early onset group compared to 65% of the late onset group were associated with markers of autoimmunity (9).

This study also shows that the serious vascular complications of diabetes like retinopathy and neuropathy do occur in this condition if the duration of diabetes is long and glycemic control is poor. Hence, control of diabetes should be attempted in these patients

Table 5: Comparison of Transient Neonatal Diabetes (TND) and Permanent Diabetes Mellitus in Infancy (PDMI)

Factor	Transient Neonatal Diabetes (TND)	Permanent Diabetes Mellitus in Infancy (PDMI)
Etiology	· Family history positive in one-third cases · Number of Islet cells may be normal, reduced or even excess · Most likely maturational delay in development of cAMP mediated insulin release · Delayed maturation of beta cells	· Pancreatic dysgenesis or type 1 diabetes mellitus · Pancreatic dysgenesis ranging from mild hypoplasia to complete agenesis causing both exocrine and endocrine insufficiencies
Clinical features	· Small for gestational age · Prone to birth asphyxia · Emaciation with loss of subcutaneous fat · Open eyed alert facies · Severe dehydration of acute onset without vomiting or diarrhea · Polyuria, polydypsia · Honeyed nappies · Prone to infection · Needs insulin for a short period only	Pancreatic dysgenesis : (I) Mild cases – mild hyperglycemia and glycosuria specially during infection. 2) Moderate cases – Intrauterine (growth retardation (IUG) Type 1 diabetes mellitus · Normal weight · Insidious in onset · History of polyuria, polydipsia and polyphagia · May present with ketoacidosis
Laboratory findings	· Hypoglycemia · Blood sugars >200 mg/dl · Glycosuria · Absent or mild ketonemia or ketonuria · Low insulin, C-peptide, IGF – 1 level	· Hypertriglyceridemia · Auto Insulin auto-antibodies present Anti-islet cell antibodies or anti-GAD antibodies may be present

to prevent the vascular complications of diabetes, at least after the child is seven years of age, as suggested by the American Diabetes Association based on the DCCT Study findings (11). Till then the control of diabetes should be done very cautiously as these children are insulin sensitive and prone to hypoglycemia.

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