ORIGINAL ARTICLE

Prepubertal Childhood Onset Type 2 Diabetes Mellitus: Four Case Reports

Anandakumar Amutha[1], Ranjit Unnikrishnan[2], Ranjit Mohan Anjana[3], Viswanathan Mohan[4]

Abstract

Background: The prevalence of childhood onset type 2 diabetes (T2D) is increasing, but prepubertal T2D is still unusual.

Methods: We report four cases of T2D with onset at or below 10 years of age registered at a tertiary diabetes centre in southern India.T2D was diagnosed based on the absence of ketosis, good beta cell reserve as shown by the C peptide assay, absence of GAD antibodies and pancreatic calculi, and response to oral hypoglycemic agents.

Results: All four patients were female, obese and had acanthosis nigricans. Polycystic ovarian syndrome and fatty liver were found in two cases. All were treated with metformin but two patients needed insulin additionally. Two had hypercholesterolemia and hypertension. One patient developed non-proliferative diabetic retinopathy on follow up.

Conclusion: T2D is now beginning to be seen in the first decade of life. A proper clinical work up of children with diabetes will prevent misclassification as type 1 diabetes and help avoid unnecessary insulin therapy.

Editorial Viewpoint

- Prevalence of prepubertal T2D is unusual.
- This study describes 4 cases of T2D with onset ≤10 years of age.
- This report emphasizes proper clinical work up to prevent misclassification as type 1 diabetes and unnecessary insulin therapy.

Introduction

The prevalence of type 2 diabetes (T2D) has reached epidemic proportions. In parallel with the increasing prevalence of T2D, there has also been a decrease in the age at onset of T2D and indeed, onset in youth and childhood is being increasingly reported [1-3]. However, most of the reports of childhood onset T2D reported in the literature have an onset after puberty and reports on T2D presenting in the first decade of life are rare. We report on four cases of T2D with onset at or below 10 years of age, seen at a diabetes centre.

Case Reports

Table 1 depicts the clinical and biochemical characteristics of the 4 cases during their last visit (follow up) to our centre.

Case 1 was diagnosed to have diabetes at the age of 7 years while investigating for giddiness and osmotic symptoms of diabetes. Her body mass index (BMI) was 34.2 kg/m^2 and she had acanthosis nigricans. She was 30 years old at time of last visit to our centre. Both parents had T2D. She had good C-peptide reserve, GAD and ZnT8 antibodies were negative and she was therefore diagnosed to have T2D. She was initiated on metformin and sulfonylurea, but required insulin intermittently for brief periods whenever blood glucose levels were high. She was subsequently lost to follow-up for 6 years, during which time she developed microalbuminuria, non proliferative diabetic retinopathy, hypercholesterolemia and hypertension. However, even after several years, the C-peptide was fairly well preserved. In view of poor glycemic control and presence of complications, she was advised insulin along with oral drugs.

Case 2 was diagnosed at the age of 10 years, while undergoing treatment for symptoms of tiredness and vaginal itching. Both parents had T2D as did her paternal and maternal grandfathers. BMI was 24.2 kg/m^2 and she had acanthosis

[1]Scientist, Madras Diabetes Research Foundation, Chennai, Tamil Nadu; [2]Vice Chairman, Dr. Mohan's Diabetes Specialities Centre & Madras Diabetes Research Foundation, Chennai, Tamil Nadu; [3]Vice President and Managing Director, Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu; [4]President, Madras Diabetes Research Foundation & Chairman, Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu

Received; 20.04.2016; Revised: 09.06.2016; Accepted: 27.06.2016

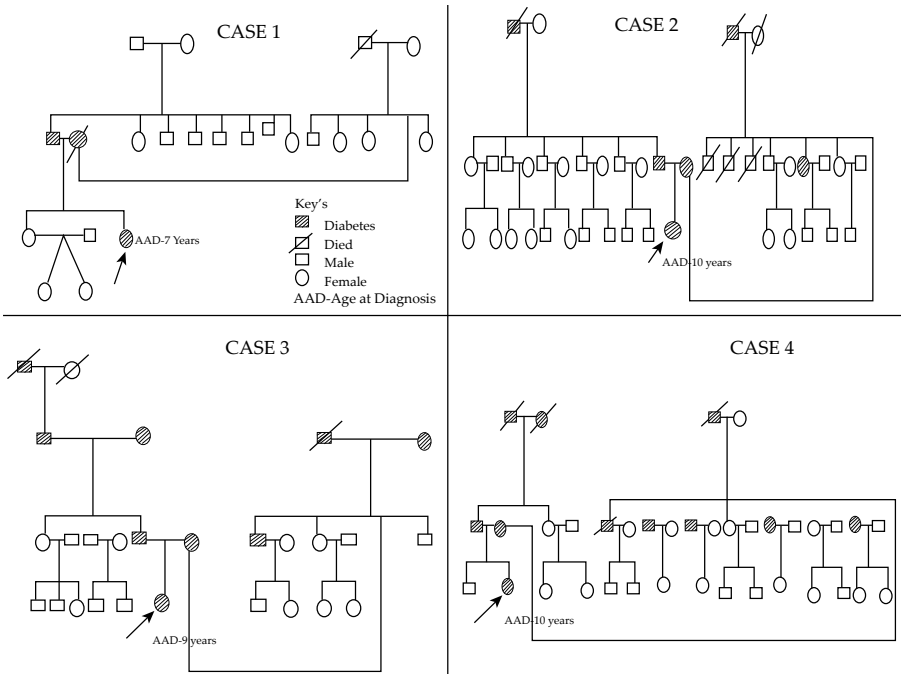

Fig. 1: Pedigree charts of the four cases

nigricans. HbA1c was 9.6%, C-peptide was still preserved (fasting 1.0 and stimulated 2.3 pmol/ml) and GAD antibodies were negative. Ultrasound abdomen revealed an enlarged fatty liver (grade 1) and bilateral PCOS. She was initiated on metformin 500mg twice a day; she was irregular with diet, exercise and clinic visits and ultimately required insulin on account of poor control of blood glucose.

Case 3 was diagnosed at the age of 9 years while investigating for blurred vision. She was overweight, with a BMI of 27.7kg/m^2. Her mother had gestational diabetes. Her C-peptide was good and pancreatic islet cell antibodies were found to be negative. She also had hypertension and hypercholesterolemia. At the time of diagnosis, she was initiated on insulin and metformin, with regular physical activity and meal plan. Within 6 months, she was able to stop insulin and was continued on metformin .She maintained good C-peptide levels (Table 1), and the HbA1c came down to 5.8%.

Case 4 was diagnosed at the age of 10 years while investigating for bedwetting. She also had complaints of polydipsia, itching in legs and burning sensation in the toes. She had not attained menarche. Her mother had gestational diabetes mellitus. At presentation, her HbA1c was 12.6%, but C-peptide assay showed fairly good beta cell reserve and GAD and ZnT8 antibodies were negative. BMI was 26.7kg/m^2. She was initially treated with insulin to correct glucotoxicity along with life style modification i.e. physical activity and diet plan. After three months, the HbA1c came down to 5.9% and she was able to stop insulin and maintain good control on metformin alone. Figure 1 shows the pedigree chart of the four cases.

Discussion

Type 1 diabetes (T1D) is one of the commonest endocrine disorders in children; indeed, almost all cases of diabetes in youth and childhood were earlier thought to be T1D. This scenario changed in the 1990s and increasing number of children and adolescents were diagnosed with T2D worldwide. Rapid rise in urbanisation, sedentary lifestyles, physical inactivity and high calorie diets have been proposed as the predominant reasons for the rise in the incidence of T2D in children.[3]

Children with T2D often get treated with insulin as they are misdiagnosed as T1D. All these four cases were classified as T2D after a full work up at our centre. T2D in children usually occurs during the pubertal age (i.e 10 to 14 years among girls and 15 to 19 years among boys). There are very few reports on children with T2D diagnosed in prepubertal ages i.e. at 10 years or below and even these are often included along with studies of T1D.[4,5] The SEARCH study reported three children aged less than 10 years presenting with T2D all of whom were Asia Pacific Islanders and they were excluded from further analysis due to either missing data or insufficient data to classify their type of diabetes.[6,7]

The mean age at diagnosis of diabetes in the children in this series was nine years and our youngest patient was only seven years old when she was diagnosed. In the literature, the youngest reported patient with T2D is a four year old Pima Indian.[3] From India, the youngest patient with T2D reported so far, was a nine year old child.[8] In an earlier study we have reported that adolescent girls had higher risk of developing T2D compared to boys [9]. Case reports from Australia[10,11] and Nigeria[12] also show that girls are more prone to get childhood onset diabetes and they also tend to get it earlier during both pre and post pubertal stages. The age at menarche of the four cases was between 9 and 14 years.

Obesity is the most powerful predictor for developing type 2 diabetes and also other chronic diseases including cardiovascular disease, hypertension and many other non communicable diseases. The weight of all the four children was above the 97thpercentile according to recent Indian Academy of Paediatrics revised growth charts for Indian children.[13] They also had

Table 1: Characteristics of type 2 diabetes individuals at their last visit to the centre

First visit details	Case 1	Case 2	Case 3	Case 4
Gender	Female	Female	Female	Female
Age at diagnosis of diabetes (in years)	7	10	9	10
Age at first visit (years)	17	12	10	10
Current age in 2015 (in years)	30	22	10	10
Age at menarche (years)	14	12	9	11
Duration of diabetes in 2015 (in years)	23	12	1	2 days
Parental history of diabetes	Both parents	Both parents	Mother	Mother
Height (cm)	147	167	151	139
Weight (kg)	70.7	71.1	62.5	55.5
Body mass index (kg/m^2)	32.7	25.5	26.6	28.9
Systolic blood pressure (mmHg)	126	116	110	120
Diastolic blood pressure (mmHg)	76	80	70	72
Fasting plasma glucose (mmol/L)	9.4	12.7	4.5	4.7
Post prandial plasma glucose (mmol/L)	16.4	15.9	5.0	6.7
Glycated hemoglobin (% [mmol/mol])	12.4[112]	9.1[76]	5.8[40]	5.9[41]
Serum Cholesterol (mmol/L)	7.8	4.6	4.1	3.9
Serum Triglycerides (mmol/L)	1.8	1.4	1.8	1.8
HDL Cholesterol (mmol/L)	1.2	1.0	0.8	0.8
LDL Cholesterol (mmol/L)	5.9	3.0	2.5	2.2
C Peptide Fasting (pmol/ml)	0.9	1	1.6	1.3
C Peptide Stimulated (pmol/ml)	2.2	2.3	3.7	2.2
GAD IU/ml	1.3	1.0	<1.0	<1.0
IA2 IU/ml	-	-	<1.0	-
Zn8 Transporter U/ml	<1.0	-	<1.0	<1.0
Retinopathy	Non Proliferative Diabetic Retinopathy	No	No	No
Neuropathy	No	No	No	No
Microalbuminuria	Yes	No	No	No
MODY 1, 2 & 3 mutations	None	None	None	None
Associated conditions	PCOS,Acanthosis nigricans, Hypothryroidism	PCOS, Acanthosis nigricans	Acanthosis nigricans, Hypothyroidism	Acanthosis nigricans
Ultrasound Abdomen	Fatty Liver	Fatty liver	Normal	Normal

higher body mass indices. All four cases had acanthosis nigricans. Two had PCOS and fatty liver, all of which are pointers to T2D. In two cases, the mother had GDM. They were advised regarding weight reduction by diet and increasing physical activity.

C-peptide estimations along with a combination of clinical criteria are helpful in differentiating T1D and T2D in children. Measuring C-peptide once the glucotoxicity is corrected is better initially C peptide levels can be low due to glucotoxicity. Assessment of GAD antibodies was negative in all four cases, while ZnT8 and IA-2 could additionally be measured in three cases and one case respectively and they were also negative. Thus a high clinical index of suspicion along with a full clinical and biochemical work up can help to diagnose T2D when children present with diabetes.

Management of T2D in children and adolescents starts with life style intervention if the initial glucose levels are only mildly elevated. If diet and physical activity are unsuccessful in controlling blood glucose levels, metformin should be added and the dosage and frequency can be increased according to the glycemic control. In our report, two of the cases were started with metformin initially while the other two were additionally given insulin but later switched over to metformin. During their follow up, whenever glucose levels were high additional oral hypoglycaemic agents like sulfonylurea were added along with metformin to achieve glycemic control.

Lifestyle modification should be the first and foremost strategy to prevent type 2 diabetes. While everyone should be encouraged to maintain a healthy weight, children particularly should be encouraged to attain and maintain weight for height in the normal range. An intensive lifestyle change can be achieved through maintaining

healthy body weight with the help of diet and physical activity. The main diet restrictions would be reduction of calories especially carbohydrates. Physical activity of moderate intensity for at least 30 min on most days of the week is to be encouraged.[14]

As recommended by the ADA, all the cases were advised to undergo screening for complications. Except one patient (who had non proliferative diabetic retinopathy), all of them were free of diabetes complications during their follow up at our centre. However, it is likely that more will develop complications as the duration of diabetes increases. Indeed we showed in an earlier report that in childhood and adolescent onset T2DM, 85% develop retinopathy after 15 years duration of diabetes [9] showing that the earlier the onset of T2DM, the greater the risk of developing micro and macro vascular complications as the duration of exposure to hyperglycemia is that much longer. Indeed several reports indicate that childhood onset T2DM has a worse prognosis than T1DM.[15]

In India, we have to rule out other types of diabetes in children and adolescents including MODY and Fibro Calculous Pancreatic Diabetes (FCPD). Differential diagnosis of diabetes in youth criteria[16] were checked for these four cases to reach final diagnosis as type 2 diabetes. In our series, genetic tests for MODY 1 to 3 were negative for all four patients and none of them had evidence of pancreatic calculi, ruling out FCPD. It is important to note that FCPD has been reported in children as young as 5 years of age.[17]

In summary, we report on four cases of T2D with onset at or below 10 years of age. Long term follow up studies are needed to elucidate the natural history of this early onset form of T2D. Aggressive long term treatment is needed to prevent complications of diabetes in these young patients as the duration of exposure to hyperglycemia tends to be very long.

Table 1 depicts the clinical and biochemical characteristics of the 4 cases during their last visit (follow up) to our centre.

Conflict of interest statement

The authors have not declared any conflict of interest.

Author Contributions

VM conceived the study and revised all drafts of the article. AA coordinated, checked the integrity and accuracy of data. AA wrote the first draft of the article and carried out the corrections in consecutive drafts. RU and RMA gave valuable suggestions and helped in revising the manuscript.

Acknowledgments

We thank the participants and the staff of Dr. Mohan's Diabetes Specialities Centre and the Madras Diabetes Research Foundation, Chennai, India, for their help with this study.

References

1. Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M; Consensus Workshop Group. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. *Diabetes Care* 2004; 27:1798-811.
2. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. *Indian J Med Res* 2007; 125:217-30.
3. American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000; 23:381-389.
4. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 2000; 136:664-72.
5. Acton KJ, Burrows NR, Moore K, Querec L, Geiss LS, Engelgau MM. Trends in diabetes prevalence among American Indian and Alaska native children, adolescents, and young adults. *Am J Public Health* 2002; 92:1485-90.
6. Liese Ad, D'agostino Rb Jr, Hamman Rf et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics* 2006; 118:1510–1518.
7. Liu LL, Yi JP, Beyer J, Mayer-Davis EJ, Dolan LM, Dabelea DM, Lawrence JM, Rodriguez BL, Marcovina SM, Waitzfelder BE, Fujimoto WY; SEARCH for Diabetes in Youth Study Group. Type 1 and Type 2 diabetes in Asian and Pacific Islander U.S. youth: the SEARCH for Diabetes in Youth Study. *Diabetes Care* 2009;32 Suppl 2:S133-40.
8. Ramachandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay V. Type 2diabetes in Asian-Indian urban children. *Diabetes Care* 2003; 26:1022-5.
9. Amutha A, Datta M, Unnikrishnan R, Anjana RM, Mohan V. Clinical profile and complications of childhood- and adolescent-onset type 2 diabetes seen at a diabetes center in south India. *Diabetes Technol Ther* 2012; 14:497-504.
10. Kevat D, Wilson D, Sinha A. A 5-year-old girl with type 2 diabetes. *Lancet* 2014; 383:1268.
11. Phillips J, Phillips PJ. Children get type 2 diabetes too. *Aust Fam Physician* 2009; 38:699-703.
12. Otaigbe BE, Imafidon EE. Type 2 diabetes mellitus in a Nigerian child: a case report. *Afr Health Sci* 2011; 11:454-6.
13. Khadilkar VV, Khadilkar AV. Revised Indian Academy of Pediatrics 2015 growth charts for height, weight and body mass index for 5-18-year-old Indian children. *Indian J Endocrinol Metab* 2015; 19:470-6.
14. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. *Diabet Med* 2007; 24:451-63.
15. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, Twigg SM, Yue DK, Wong J. Long-Term Complications and Mortality in Young-Onset Diabetes: Type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care* 2013; 36:3863-9.
16. Mohan V, Jaydip R, Deepa R. Type 2 diabetes in Asian Indian youth. *Pediatr Diabetes* 2007; 8 Suppl 9:28-34.
17. Premalatha G, Mohan V. Fibrocalculous pancreatic diabetes in infancy--two case reports. *Diabetes Res Clin Pract* 1994; 25:137-40.