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CHANGING PROFILE AND MANAGEMENT CHALLENGES AMONG CHILDREN WITH DIABETES MELLITUS

Paediatrics

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ABSTRACT

Background: Various types of Diabetes Mellitus, T1DM, T2DM paralleling global obesity. Latent Autoimmune Diabetes of the Young (LADY)/T1.5DM and Monogenic DM are being reported in children. **Clinical description:** We report 5 cases -T1DM, T2DM, T1.5DM, Neonatal DM and Wolfram syndrome Type 2, highlighting the changing profile and management challenges. **Management and Outcome:** 13-year-old-boy with T1DM presented with DKA, C-peptide 0.17nmol/L, currently on split-mix insulin (0.9U/kg/day) as basal bolus insulin not affordable. Was diagnosed 6 months back elsewhere, on irregular insulin and oral hypoglycemic agents. 10-year-old-girl with T2DM presented with obesity and diabetic ketosis, C-peptide 1.27nmol/L, initially on insulin (0.6U/kg/day) and Metformin, currently on Metformin only. 13-year-old-boy with T1.5DM/LADY presented with DKA, C-peptide 0.35nmol/L, autoantibodies +ve, currently on basal-bolus insulin (1.5U/kg/day). Was diagnosed elsewhere at the age of 4, on irregular insulin. Preterm 36+1/7 weeker, 1.5kg, 3rd degree consanguinity, developed persistent hyperglycemia from 10 hours of life requiring insulin. C-peptide 0.17nmol/L, thyroid and cortisol levels normal. Neonatal DM-GATA6 mutation +ve, currently on NPH insulin (1.6U/kg/day). 15-year-old-girl with visual defect –optic atrophy, on insulin from 4 years, C-peptide 0.16nmol/L. Wolfram syndrome Type 2 -mutation +ve, with no Diabetes Insipidus or deafness, currently on basal-bolus insulin–glargine and FIASP (0.7U/kg/day). Dietary and lifestyle modifications, logbook maintenance and regular follow-up ensured in all cases. **Conclusion:** This case series highlights the changing profile, management challenges, mostly due to failure of assigning the type of DM at diagnosis. The importance of dietary/behavioural modifications and maintenance of logbook are emphasized. All 5 types required individualised care plan.

KEYWORDS

T1DM, T2DM, T1.5DM/Latent Autoimmune Diabetes of the Young (LADY), Neonatal DM, Wolfram syndrome

INTRODUCTION:

There is a changing profile in Diabetes Mellitus from the previous assumption that children develop Type1 Diabetes Mellitus (T1DM). T1DM is due to autoimmune destruction of pancreatic β-cells with insulin dependence, mortality rate 0.3-0.5% (1). 1/3rd of T1DM present with DKA. Tight glycemic control is required for quality of survival and reduction in microvascular complications (1). T2DM is increasing among children and adolescents, especially in the developing countries, paralleling global obesity, sedentary lifestyle and globalisation (2). DKA is uncommon in T2DM.

Another subset that clinically resemble T2DM, but have immunogenetic markers of T1DM, is a slowly evolving form of autoimmune DM, described as LADY-Latent autoimmune diabetes of young/T1.5DM, similar to LADA-Latent autoimmune diabetes of adult (3).

Various other genetic types are reported among children like Maturity Onset Diabetes of the Young (MODY) syndromes type 1-6, Mitochondrial, Wolfram Syndrome (WS) and Neonatal DM (NDM). NDM has onset between 1st week to 6 months of life, usually occurs in preterm/SGA babies, but may resolve in 50% cases –Transient DM. Persistent NDM types have GATA4, GATA6, RfX6, IPF-1, EIF2AK3, GCK, FOXP3, PTF1A, GLIS3, Ins2 mutations, that require insulin and KCNJ11, ABCC8 mutations respond to sulphonylurea at higher doses. GATA4 mutation has AR inheritance, with pancreatic agenesis/hypoplasia, exocrine insufficiency, cardiac defect and insulin dependence (4).

WS has AR inheritance with Diabetes Insipidus (DI), DM, optic atrophy, deafness (DIDMOAD) and neurological signs-bladder/bowel/temperature regulation dysfunction, psychiatric and endocrinological abnormalities. Classical form WS1 has *WFS1* mutation. WS2 has CDGSH iron-sulphur domain-containing protein 2 (*CIDS2)* mutation, characterised by absence of DI and neurological signs, presence of bleeding, upper intestinal ulcer and defective platelet aggregation (5).

We report 5 cases -T1DM, T2DM, T1.5DM, NDM and WS2, highlighting the changing profile and management challenges, who presented during the period April 2021-September 2022.

Case 1

Clinical Description

13-year-old boy, 1st born, 3rd degree consanguinity, birth weight 4.2kg with no family history of DM or gestational DM, presented with weight loss >20%, hyperglycemia and ketoacidosis. DM was diagnosed 6 months back elsewhere, not fully evaluated and was started on insulin, later given oral hypoglycemic agents. He had poor compliance to therapy. O/E: thin built, generalized wasting+, vitals stable, Weight 27kg, Height 159cm, BMI 10.95kg/m^2, SMR stage 2, systemic examination- within normal limits.

Management and Outcome:

At admission, RBS- 524mg/dl, HbA1c 15.6%, VBG: pH 7.15 -corrected 7.20, PCO2 15 -corrected 10, HCO3 16, corrected 14, Na^+ 132, K^+ 4.5, Cl^- 94, Anion gap 26.5, urine sugar 3+, ketones +ve. VBG to ABG correction formula: pH: VBG pH+0.05, pCO2: VBG pCO2 – 5, HCO3: VBG HCO3 – 2 (6). Moderate ketoacidosis confirmed and managed using Milwaukee protocol over 48 hrs. GRBS, electrolytes and VBG monitored and choice of fluid and tonicity changed accordingly and stabilized on intermittent subcutaneous regular insulin. C-peptide 0.17nmol/L, value <0.2 confirmed T1DM (7). He was discharged on split-mix regimen using NPH and regular (0.9U/kg/day) as basal bolus insulin not affordable. Family was counselled regarding the need for adherence to insulin therapy, importance of physical activity, disciplined diet and maintaining log book. He was given a written-emergency care plan with contact telephone number of treating team.

On follow-up, the child showed good compliance to insulin therapy, and dietary/behavioral modification.

Case 2

Clinical Description:

10-year-old girl with obesity, acanthosis nigricans grade 3 and polyphagia, high socio-economic status, positive family history of DM, presented with headache and nausea for 2 months. She was

evaluated elsewhere and on Topiramate suspecting migraine, with no relief. O/E: conscious, oriented, vitals stable, Weight 64.5kg, Height 138cm, BMI 31.5kg/m^2 ->27th adult equivalent, waist circumference 76cm-70th-90th centile (8), SMR stage 2, systemic examination within normal limits.

Management And Outcome:
At admission, RBS -575mg/dl, HbA1c 13.1%, Urine sugars 3+, ketones +ve. VBG showed no acidosis, managed as diabetic ketosis without acidosis. Anti-glutamic acid decarboxylase (anti-GAD) 5.2IU/ml and Anti-islet cell antibodies (anti-ICA) 1:10, both negative. Total Cholesterol 216mg/dl, elevated total cholesterol:HDL ratio-5.4:1. Electrolytes, urea and creatinine normal. C-peptide high, 1.27nmol/L and T2DM confirmed. initiated on basal-bolus insulin (0.6U/kg/day) and Metformin. Family was counselled regarding adherence to insulin therapy, importance of physical activity, disciplined diet and maintaining log book and keeping in touch with the treating team.

On follow-up, as blood sugar values were between 150-200mg/dl, insulin stopped, currently only on metformin with dietary/behavioural modifications.

Case 3
Clinical Description:
13-year-old boy, with no family history of DM, diagnosed elsewhere, presented with DKA. At 4 years of age, diagnosed with DKA, not fully evaluated and was on intermediate-acting isophane low dose insulin 4U three times daily and had good exercise tolerance. O/E: lethargic, arousable, signs of dehydration +, thin built with generalized wasting, Vitals: tachycardia, low volume pulses, CRT 3secs, Weight 32kg, Height 158.5cm, BMI 12.8kg/m2. Systemic examination within normal limits.

Management And Outcome:
At admission, GRBS 566mg/dl, HbA1c 14.2%, VBG: pH 7.07 -corrected 7.12, PCO2 13 -corrected 27, HCO3 10, corrected 8, Na^+ 130, K^+ 5, Cl^- 97, Anion gap 28, urine sugar 3+, ketones +ve. Severe ketoacidosis confirmed and managed using Milwaukee protocol over 48 hrs. GRBS, electrolytes and VBG monitoring done and choice of fluid and tonicity changed accordingly, and later changed to intermittent subcutaneous regular insulin. C-peptide 0.35nmol/L, Anti-GAD 65 antibody 250IU/ml and Anti-ICA 1:4, both positive. C-peptide >0.2nmol/L, +ve antibodies and initial low insulin requirements confirmed T1.5DM/LADY. Currently on basal-bolus regimen:Glargine and Regular (1.5U/kg/day). Family was counselled regarding adherence to insulin therapy, importance of physical activity, disciplined diet and maintaining log book and keeping in touch with the treating team.

On follow-up, child showed good compliance to insulin therapy, and dietary/behavioral modification.

Case 4:
Clinical description:
Preterm 36+1/7 weeker, male, 3rd degree consanguinity with severe oligohydramnios and IUGR, SGA -1.5kg. O/E: RR: 75/min, retractions +, Spo2: 94%, pallor +, bilateral periorbital, scrotal and pedal edema +. Systemic examination -systolic murmur + upper sternal border. Other systems within normal limits.

Management and Outcome:
Admitted to NICU, treated with IVF, prophylactic antibiotics, PRBC transfusion (Hb 7.6g/dl). Echocardiogram: ACHD–PFO, 2mm PDA (L→R), severe PAH, no CCF. Persistent hyperglycemia noted after 10 hours of life, dextrose concentration changed accordingly, required insulin infusion (0.05U/kg/hour). C-peptide 0.17nmol/L, thyroid and cortisol levels normal. NDM-GATA4 mutation +ve. Stabilized on intermediate-acting insulin–NPH (1.6U/kg/day). Parents were counselled regarding the need for adherence to insulin therapy, maintaining logbook and keeping contact with the treating team.
On follow-up, infant showed good compliance to insulin therapy.

Case 5:
Clinical description:
12-year-old girl, 3rd degree consanguinity, birth weight 3kg, no family history of DM presented with polyuria. DM diagnosed at 4 years of age, on insulin. Developed defective vision by 8 years of age, no hearing loss. She had recurrent abdominal pain and malena. Endoscopy showed non-specific changes. O/E: moderately built, vitals stable, Weight 42kg, Height 156cm, BMI 17.3kg/m^2, menarche attained, systemic examination -within normal limits.

Management and Outcome:
At admission, RBS 325mg/dl, HbA1c 8.9%, Urine sugars 2+, ketones negative. Lipid profile, electrolytes, urea, creatinine normal. C-peptide 0.16nmol/L. Anti-GAD 2.1IU/ml and Anti-ICA 1:10, both negative. Polyuria evaluated using water deprivation test and DI ruled out. Vision B/L 6/60, impaired colour vision, fundus-optic atrophy. Hearing-OAE normal. WS2 mutation +ve. Currently on basal-bolus insulin–glargine and ultra-fast-acting aspart-FIASP (0.7U/kg/day), from a charitable program. Family was given genetic counselling, dietary advice, physical activity, importance of maintaining log book and keeping contact with treating team.

On follow-up, the child showed good compliance to insulin therapy and dietary/behavioral modification.

DISCUSSION
The five different types of DM presented with challenges in diagnosis and treatment plan. The delay in assigning the type at diagnosis was the major hurdle. All of them required individualized plan of action. The varying clinical and laboratory profile of the different types are summarised in Table1.

Diagnostic criteria for DM include, fasting plasma glucose ≥126mg/dl, HbA1c ≥6.5% and/ 2-hour glucose level ≥200mg/dl with oral glucose tolerance test (9,10), but further tests are necessary to assign the type of DM.

Case 1 was T1DM with insulin dependence, C-peptide <0.2nmol/L, positive autoantibodies, frequent DKA. As C-peptide was not checked initially, inadvertently put on oral hypoglycemics along with irregular insulin. The current management challenge was the choice of the insulin regimen due to financial constraints.

C-peptide and fasting insulin are low in T1DM but high/normal in T2DM. C-peptide <0.2 nmol/L and positive autoantibodies indicate T1DM (7). Features of metabolic syndrome and insulin resistance like obesity, acanthosis nigricans, hypertension, dyslipidemia, PCOS and history of SGA are common in T2DM.

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) >2.5 denotes insulin resistance, with good sensitivity and specificity among Indian adolescents (11). Low adiponectin-to-leptin ratio is noted in T2DM (12).

Case 2 was T2DM, with insulin resistance, genetic predisposition, strong positive family history in 1st/2nd degree relatives, obesity and features of insulin resistance. C-peptide, negative autoantibodies, obesity, acanthosis nigricans and metabolic syndrome confirmed as T2DM. Her insulin could be stopped, requiring only dietary/ behavioural modification and Metformin.

Diabesity, co-existence of diabetes and obesity, is considered the modern epidemic which needs early intervention (13). Metformin, approved >10 years, has a benefit of moderating weight gain with mild weight loss. In the early stages and when T2DM does not respond to dietary/behavioural modification, insulin is crucial for glycemic control (14).

Immune-mediated diabetes in children is a classic disease with insulin deficiency at diagnosis with variable β-cell destruction. Among 747 children with newly diagnosed T1DM, remission up-to 18 months was reported in only 3.4% with positive autoantibodies (15). Similar to the slowly progressive form, occurring in adults-Latent Autoimmune Diabetes in Adults (LADA), children develop LADY-Latent Autoimmune Diabetes in the Young/T1.5DM (16). LADY is prevalent in youth with T2DM phenotype and forms a continuous spectrum from LADY to LADA, but LADY shows greater autoimmunity. Autoimmune markers of T1DM are positive in up-to 1/3rd adolescents with DM, which are absent in T2DM (13).

Case 3 was T1.5DM/LADY with C-peptide >0.2nmol/L, positive antibodies and increasing insulin requirements during the course. He had an atypical course, initial low insulin requirements, infrequent

DKA, with both GAD and ICA +ve. The management challenge was stabilizing severe ketoacidosis and convincing the need for higher insulin requirement.

Monogenic DM is rare, but distinct types like NDM and syndromes like WS present with diagnostic and management challenges.

Case 4 was NDM with persistent hyperglycemia and PDA, GATA4 mutation +ve. Initially managed using insulin infusion, currently on low dose NPH insulin twice day.

NDM is considered in persistent insulin-dependent hyperglycemia >250mg/dL for >7-10 days. Urine ketones, C-peptide, serum insulin and ultrasound abdomen are advisable to rule-out pancreatic agenesis. Early genetic testing is suggested whereas autoantibody testing delayed till 6 months of life, due to persistence of maternal autoantibodies in those with T1DM (17).

Case 5 was WS2, genetic mutation +ve, with DM, visual defect, abdominal pain and malena, no DI, hearing loss or endocrinological or neurological/psychiatric manifestations. She was on glargine and FIASP under a charitable scheme. FIASP mimics the physiologic prandial insulin release more closely than currently available rapid-acting insulin products (18).

W S1 is an AR condition with DI, DM, OA, deafness (DIDMOAD), neurological, psychiatric, endocrinological and urological features with ER dysfunction resulting in β-cell death and neurodegeneration and WS2 has absence of DI and neurological signs, presence of bleeding, upper intestinal ulcer and defective platelet aggregation (5). GLP1 agonists-Exenatide is recommended in WS2. In WS2, iron overload results in DM and treatment with deferiprone and N-acetyl cysteine has shown to reduce mitochondrial iron levels in invitro studies. Human in-vivo studies are yet to validate its use (19).

Treatment of DM remains challenging because of the variable spectrum and difficulty in adapting lifestyle changes. optimum intervention is combination of optimal drug therapy, good adherence and dietary/behavioural modification. Current guidelines recommend the use of self-monitoring of blood glucose in children with DM. Self-monitoring, maintenance of logbook proper interpretation of data by family and clinician improve glycemic control by facilitating timely treatment regimen modulation (20).

CONCLUSION:

This case series highlights the changing profile of DM and management challenges, mostly due to failure of assigning the type of DM at diagnosis. All 5 types required individualised care plan. The importance of dietary/behavioural modifications, adherence to medications and maintenance of logbook in DM is emphasised.

Lessons learnt:

1. in view of the changing profile of DM among pediatric population, relevant tests are recommended to assign the subtypes: T1DM, T2DM, T1.5DM/LADY and monogenic DM at diagnosis for proper management and individualised precision care.
2. In view of the diabesity pandemic, children with obesity and acanthosis nigricans/ features of metabolic syndrome should be screened for T2DM.
3. Strict compliance to therapy, maintenance of log book, keeping close contact with the treating team and adherence to physical activities and behavioural modifications remain the main stay in care of children with DM.

Table 1: Clinical and Laboratory Profile of Various types of DM among Children

Type of diabetes	T1DM	T2DM	T1.5DM	Monogenic DM	Wolfram syndrome
Age of onset	6 months to 18 years	Puberty, rare <10 years, more common in females	Adolescents	< 6 months	6-11 years
Etiology	Autoimmune, genetic predisposition (HLA)	Obesity, maternal GDM, genetic and ethnic predisposition	Autoimm une	KCNJ11, ABCC8, INS, GATA6, GATA4	WFS1 mutation in WS1, mutations in CIDS2 in WS2, HLA predisposition, Autosomal recessive inheritance
Clinico-investigatory findings	Weight loss, low C-peptide <0.2 nmol/L, positive auto-antibodies	Obesity, acanthosis nigricans, fatty liver disease, metabolic syndrome, positive family history, usually auto-antibodies absent	Weight loss, initial low insulin requirements, good exercise tolerance, C-peptide >0.2, auto-antibodies positive	Failure to thrive	Diabetes insipidus*, Diabetes mellitus, optic atrophy, sensorineural deafness and neurological signs* (* absent in WS2)
Clinical Course	Thyroid autoimmunity	PCOS in females	-	-	Diabetic retinopathy, neurological disorders (cerebellum, psychiatric)
Presentation	present with DKA (25%)	present with DKA (5-20%)	Present as DKA	Presents as DKA	Rarely present as DKA
Treatment	High doses of insulin	Lifestyle modification, Metformi, Insulin	Insulin, initially low, later high doses	Sulphonylurea for KCNJ11 and ABC C8, Insulin for others	Insulin – lower doses give satisfactory control

REFERENCES:

1. Katsarou A, Gudbjotnsdottir S, Rawshani A et al. Type 1 diabetes mellitus. Nat Rev Dis Primers. 2017; 3:17016.
2. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr. 2005; 146:693-700.
3. Bering B, Devendra D. Latent autoimmune diabetes in the young. Clin Med (Lond). 2009; 9:93-4.
4. Lemelman MB, Letourneau L, Greelay SAW. Neonatal Diabetes Mellitus: An Update on Diagnosis and Management. Clin Perinatol. 2018; 45:41-59.
5. Urano F. Wolfram syndrome: Diagnosis, Management, and Treatment. Curr Diab Rep. 2016; 16:6.
6. Chong WH, Saha Bk, Medarov BI. Comparing Central Venous Blood Gas to Arterial Blood Gas and Determining Its Utility in Critically Ill Patients: Narrative Review. Anesth Analg. 2021; 133:374-378.
7. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 2017; 8:475-487.
8. Khadilkar A, Ekbote V, Chiplonkar S et al. Waist circumference percentiles in 2–18-year-old Indian children. J Pediatr. 2014; 164:1358-62.
9. Chiang JL, Kirkman MS, Laffel LM, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care.2014;37:2034-54.
10. Libman I, Haynes A, Lyons S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes. 2022;23(8): 1160.1174.
11. Singh Y, Garg MK, Tandon N, Marwaha RK. A study of insulin resistance by HOMA-IR and its cut-off value to identify metabolic syndrome in urban Indian adolescents. J Clin Res Pediatr Endocrinol. 2013; 5:245-51.
12. Morales A, Wassserfall C, Brusko T et al. Adiponectin and leptin concentrations may aid in discriminating disease forms in children and adolescents with type 1 and type 2 diabetes. Diabetes Care. 2004; 27:2010-4.
13. Farag YM, Glaballa MR. Diabesity: an overview of a rising epidemic. Nephrology Dialysis Transplantation. 2011; 26:28-35.
14. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 2001;107: E55.
15. Sabbah E, Savola K, Kulmala P et al. Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes. The Childhood Diabetes in Finland Study Group. J Clin Endocrinol Metab. 1999; 84:1534-9.
16. Lohmann T, Nietzschmann U, Keiss W. “Lady-like”: is there a latent autoimmune diabetes in the young? Diabetes Care. 2000; 23:1707-8.
17. Beltrand J, Busiah K, Vaivre-Douret L et al. Neonatal Diabetes Mellitus. Front. Pediatr. 8:540718.
18. Paquot N, Scheen AJ. Le médicament du mois. L'insuline «faster aspart» (Fiasp®) [Faster aspart insulin (FIASP®)]. Rev Med Liege. 2018; 73:211-215.
19. Rosanio FM, Di Candia F, Occhiati L et al. Wolfram Syndrome Type 2: A Systematic Review of a Not Easily Identifiable Clinical Spectrum. Int J Environ Res Public Health. 2022; 19:835.
20. Selvan C, Thukral A, Dutta D, Ghosh S, Chowdhury S. Impact of Self-monitoring of Blood Glucose Log Reliability on Long-term Glycemic Outcomes in Children with Type 1 Diabetes. Indian J Endocrinol Metab. 2017; 21:382-386.