Chiang et al., J Clin Case Rep 2017, 7:2
DOI: 10.4172/2165-7920.1000929

Journal of Clinical Case Reports

Case Report Open Access

Dilemma on Classifying Diabetes Mellitus in Adolescence: A Case Report and Review of Literature

Che-Ming Chiang[1], Li-Wei Wu[2,3], Wei-Liang Chen[2,3], Chung-Ching Wang[2,3], Shih-Yao Liu[4], Chien-Hsing Lee[5], Kao-Hsian Hsieh[1], Chih-Chien Wang[1] and Chien-Ming Lin[1,2]*

[1]*Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[2]*Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan*
[3]*Department of Family and Community Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[4]*Department of Pediatrics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*
[5]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

Abstract

Diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes mellitus (DM) that is prone to occur in children with type 1 DM (T1DM). We report a 17-year-old overweight girl who was treated with multiple oral antihyperglycemic drugs under the initial impression of type 2 DM (T2DM). Nevertheless, severe euglycemic DKA happened after the additional prescription of sodium-glucose cotransporter 2 inhibitors for two months. Consequently, T1DM was diagnosed on the basis of insulinopenic status in glucagon test and the presence of islet autoantibodies. This case highlighted the importance of precise classification before diabetes treatment in adolescence. A literature review is aimed to help clinicians differentiate various types of DM more specifically in clinical practice.

Keywords: Diabetic ketoacidosis; Latent autoimmune diabetes of adults; Type 1 diabetes mellitus; Type 2 diabetes mellitus

Introduction

The prevalence of diabetic ketoacidosis (DKA) is higher in type 1 diabetes mellitus (T1DM) than type 2 diabetes mellitus (T2DM) [1]. Since DKA is the leading cause of death in children and adolescents with T1DM, early diagnosis and appropriate treatment of diabetes are crucial to avoid life-threatening events [2]. However, the rising incidence of overweight and obesity in adolescents makes an exactly differential diagnosis between T1DM and T2DM become challenging. For example, the previous study reported that approximately 5-10% of patients with autoimmune diabetes were treated as T2DM in the beginning, based on an obese body habitus or age of onset. However, further investigations confirmed the diagnosis as latent autoimmune diabetes in adults (LADA) [3].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the newly-approved oral antihyperglycemic drug (OAD) in T2DM which increase renal glucose excretion to control hyperglycemia. On the other hand, they are associated with increased plasma glucagon level and ketogenesis, then precipitates the development of euglycemic DKA (euDKA) in patients with T1DM [4]. Here we present an overweight girl treated with multiple OADs under the presumed diagnosis of T2DM due to her habitus and family history of T2DM. Nevertheless, severe euDKA developed after the use of SGLT2 inhibitor in two months. Poor β-cell function in response to glucagon test and the presence of glutamic acid decarboxylase antibodies confirmed the diagnosis of T1DM later. This case underscored all newly-onset diabetic adolescents should receive thorough laboratory evaluation to solidify categories of diabetes, in order to provide appropriate therapies and avert the unwarranted complications.

Case Report

A 17-year-old girl presented symptoms of polydipsia, polyphagia, polyuria, and body weight loss two years before. At that time, her height was 165 cm, weight was 70 kg, and body mass index (BMI) was 25.7 kg/m^2. Laboratory tests revealed fasting blood glucose 311 mg/dL, hemoglobin A1c (HbA1c) 16.5%, and normal lipid profiles (Table 1). Her family history, her grandmother was a patient of T2DM. Glucagon test and serum islet autoantibodies were not evaluated so she was presumed to be a case of T2DM initially. She was treated with multiple OADs including metformin, glimepiride, and pioglitazone by a local medical doctor but the glycemic control was poor. Because the deterioration of her diabetic control with recent HbA1C 16% was noticed, dapagliflozin, a SGLT2 inhibitor, was added as the fourth kind of OAD.

She was noted to have a weight loss of 1.5kg within 2 months after using dapagliflozin. Two days before admission, she suffered from extreme thirst, nausea, and intermittent abdominal pain. No infectious symptom or sign was noted. Because of progressive drowsiness to semi coma, she was sent to our emergency room. Upon arrival, her height was 169 cm (97th percentile), weight was 61.5 kg (85th-97th percentile), and BMI was 22.7 kg/m^2 (85th percentile). The body temperature was 36.7°C, blood pressure was 126/75 mmHg, heart rate was 132 beats/min, and respiratory rate was 44 breaths/min with Kussmaul pattern. Her abdomen had diffused tenderness without muscle guarding. Her pubertal development was at Tanner Stage V without acanthosis nigricans. Chest X-ray revealed no specific abnormality. Blood tests showed glucose 242 mg/dL, ketone 6.3 mmol/L, pH 6.972, PaCO2 6.6 mmHg, PaO2 139.7 mmHg, HCO3 1.5 mmol/L, base excess -28.3, sodium 138 mmol/L, potassium 4.7 mmol/L, and anion gap 23.5 mmol/L. Urine analysis showed marked glucosuria (4+) and ketonuria (4+). Glucagon test was done at 0 and 6 min showed C-peptide 0.19 and 0.41 ng/ml, respectively. Positive glutamic acid decarboxylase antibodies (GADA) and anti-thyroglobulin antibody (ATA) were detected. She was then diagnosed as T1DM with ketoacidosis based on poor β-cell function and islet autoimmunity.

She was treated with intravenous fluid, electrolytes, and insulin supplement at pediatric intensive care unit for severe ketoacidosis. Her

***Corresponding author:** Chien-Ming Lin, Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taiwan, Tel: 886-02-87927025; Fax: 886-02- 87927293; E-mail: ming.sandra@msa.hinet.net

Received February 05, 2017; **Accepted** February 25, 2017; **Published** February 28, 2017

Citation: Chiang CM, Wu LW, Chen WL, Wang CC, Liu SY, et al. (2017) Dilemma on Classifying Diabetes Mellitus in Adolescence: A Case Report and Review of Literature. J Clin Case Rep 7: 929. doi: 10.4172/2165-7920.1000929

consciousness gradually recovered and the breathing pattern returned to normal after metabolic acidosis was corrected. She was transferred to our general ward in two days and treatment was shifted to only subcutaneous insulin injection. Her HbA1c was 12% three months later and 5.1 % eight months later during follow-up, respectively.

Discussion

Approximately 10% of patients with autoimmune diabetes could be misclassified as T2DM due to obesity or family history [3]. Regardless of age, metformin monotherapy is the first line pharmacologic agent for T2DM if not contraindicated [5]. When blood glucose is ≥ 300 mg/dL (16.7 mmol/L) or A1C is ≥ 10% (86 mmol/mol), early insulinization should be considered to prevent glucose toxicity [6]. Reviewing the disease course, insulin therapy should be used in our case at first. Meanwhile, worse diabetic control even under multiple combinations of OADs implied underlying insulinopenia and rapidly deteriorated β-cell function. On the other hand, patients with T2DM tend to have metabolic syndrome rather than those with T1DM (Table 2). The lack of typical presentations of metabolic syndrome in our patient, such as dyslipidemia and hypertension, also made the diagnosis of T2DM confusing. These discriminations gave us clues to reconsider the possible pathogenesis of autoimmune diabetes in this patient.

Traditionally, LADA belonged to autoimmune diabetes and was considered as a genetic admixture of T1DM and T2DM. Subjects having all of the following three criteria were diagnosed to have LADA: Age at onset more than 30 years, the presence of circulating islet autoantibodies, including GADA, insulin autoantibody (IAA), antibodies to islet cell cytoplasma (ICA) or tyrosine phosphatase like protein(IA-2A), and slow requirement of insulin therapy after diagnosis [7]. Unlike the typical manifestations of LADA, our patient presented with highly elevated HbA1c (16.5 %) in the beginning, which indicated insufficient insulin secretion to overcome glucose dysmetabolism in an early stage. The results of the 6-min glucagon test and islet autoantibodies assessment in our patient provided robust evidence of T1DM as well.

In respect to molecular diagnosis, an increasing validity in candidate genes to predict the type of diabetes has been reported [8,9]. However, only HLA genes were found to have a better odds ratio in predicting T1DM while the predictive value of T2DM by other genetic variants was disappointing [9,10]. Most importantly, the genetic tests to predict and classify diabetes are not always available in clinical practice. To prevent malpractice and severe diabetic complications, we recommended that a detailed history taking with investigations including glucagon test for β-cell function, serum islet autoantibodies, and lipid profiles should be addressed before treatment.

DKA without marked hyperglycemia was referred as euDKA. In addition, partial insulin treatment, intercurrent illness, reduced food and fluid intake, history of alcohol intake or using SGLT2 inhibitors were regarded as potential triggers of euDKA [11]. Currently, SGLT2 inhibitors including canagliflozin, dapagliflozin, and empagliflozin were approved to use in T2DM recently, but not in T1DM. Pharmacologically, the anti-hyperglycemic mechanism of SGLT2 inhibitors was through decreasing glucose reabsorption in proximal renal tubules, subsequently leading to decreased insulin secretion, vicariously increased glucagon levels, and then potentially could exaggerate the process of ketogenesis [4]. As a result, the misuse of SGLT2 inhibitors in autoimmune diabetes can pose a high risk to develop euDKA, as the present case illustrated. Interestingly, our case had severe metabolic acidosis (pH 6.972 and HCO3 1.5 mmol/L) along with borderline hyperglycemia (blood glucose 242 mg/dL) [12-15]. These extremely discordant data had not been reported in patients with T1DM yet. Likewise, random glucose levels were fallible to determine the severity of DKA, particularly in T1DM patients concomitant with SGLT2 inhibitor treatment.

Features	DM	DKA	Reference range
Clinical features			
Age of onset (years)	15	17	
BMI (kg/m^2)	25.7	22.7	18.5-24
Glucose metabolism			
$HbA1_C$ (%)	16.5	17.9	4.0-5.7
FPG (mg/dL)	311	242	70-100
Serum ketones (mmol/L)	0.5	6.3	<0.6
pH	-	6.972	7.35-7.45
Bicarbonate (mmol/L)	-	1.5	23-25
CO_2 (mmHg)	-	6.6	35-45
C-peptides (ng/mL)			
0 minute	-	0.19	0.81-3.85
6 minutes	-	0.41	0.81-3.85
Lipid profiles			
Total cholesterol (mg/dl)	150	143	<200
Triglycerides (mg/dl)	40	32	<200
HDL-C (mg/dl)	55	53	>40
LDL-C (mg/dl)	98	93	<100
Autoantibodies			
GADA (U/mL)	-	2.10	<1.00
IA-2A (U/mL)	-	0.556	<1.00
IAA (% B/T)	-	6.7	<10
Anti-TPO (IU/mL)	-	2.3	<5.61
Anti-TG (IU/mL)	-	5.66	<4.11

Anti-TG: Antibodies to Thyroglobulin; Anti-TPO: Antibodies to Thyroperoxidase; BMI: Body Mass Index, DKA: Diabetes Ketoacidosis; DM: Diabetes Mellitus; FPG: Fasting Plasma Glucose; GADA: Glutamic Acid Decarboxylase Antibodies; HbA1C: Hemoglobin A1C; HDL-C: High Density Lipoprotein Cholesterol; IAA: Insulin Autoantibodies; IA-2A: Tyrosine Phosphatase-like Insulinoma Associated Protein 2 Autoantibodies; LDL-C: Low Density Lipoprotein Cholesterol

Table 1. Clinical features and laboratory data upon diagnosis of DM and DKA.

Characteristics	T1DM	LADA	T2DM	Reference
Risk genotypes	*INS VNTR, PTPN22, CTLA4, IL2RA, STAT4, IFIH1*	*INS VNTR, PTPN22, TCF7L2*	*TCF7L2, CAPN10, PPARG, FTO, KCNQ1, KLF14, CDKAL1, CDKN2A/2B, IGF2BP2, HHEX.*	[8, 9]
Link of HLA-DQ haplotypes	High	Low	Very low	[12]
Diabetes-susceptible haplotype				
DQA1*03-DQB1*0303	36%	22%	17.5%	
DQA1*03-DQB1*0401	10%	8%	4.4%	
DQA1*05-DQB1*0201	18%	8.5%	3.6%	
Diabetes-protective haplotype				
DQA1*0102-DQB1*0602	1.5%	2.6%	7%	
Clinical features				
Family DM history	Uncommon, <15%	Common, 39%	Common, 40-70%	[13-15]
Average age at diagnosis	5-7 yr of age and the time of puberty	>30 yr	>50 yr	[1]
Body weight	Lean to normal. Overweight (rare)	Normal to overweight or obese	Overweight to obese	[16]
Acanthosis nigricans	Absent	Absent	Present ~52%	[17]
Metabolic syndrome	Infrequent, 10-32%	Variable, 42%	Frequent, 88%	[18]
Frequency of DKA	Frequent, 20-40%	Could present	Less common, 10%	[1]
Time to insulin therapy	At diagnosis	Earlier than T2DM (months to years)	Might need at the end stage (years)	
Laboratory data				[19, 20]
C-peptides	Low	Low to normal	Normal to high	
Insulin autoantibody	Often detected	Often detected	Negative	
GADA	Common in adults than in children	More common than in T1DM	Rare, positive may indicate LADA	
IA-2A	Often positive in newly diagnosed T1DM	Often detected	Negative	

Table 2. Comparisons of clinical characteristics of T1DM, LADA, and T2DM.

In conclusion, this case report highlights the importance of glucagon test and islet autoantibodies detection to achieve a correct diagnosis of adolescents with newly-onset diabetes. Only the correct classification of diabetes leads to appropriate treatment and prevents life-threatening complications. Besides, adolescents with suspected T2DM who have been treated with multiple OADs but still presented with poor glycemic control should always take autoimmune diabetes into consideration [16-20].

References

1. Kliegman R, Nelson WE (2016) Nelson textbook of pediatrics. (20th ed), Philadelphia, PA : Elsevier.
2. White NH (2000) Diabetic ketoacidosis in children. Endocrinol Metab Clin North Am 29: 657-682.
3. Zimmet PZ, Tuomi T, Mackay IR, Rowley MJ, Knowles W, et al. (1994) Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. Diabet Med 11: 299-303.
4. Ogawa W, Sakaguchi K (2016) Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig 7: 135-138.
5. Phung OJ, Baker WL, Tongbram V, Bhardwaj A, Coleman CI (2012) Oral antidiabetic drugs and regression from prediabetes to normoglycemia: a meta-analysis. Ann Pharmacother 46: 469-476.
6. American Diabetes Association (2017) Pharmacologic approaches to glycemic management. Sec. 8. In Standards of Medical Care in Diabetes. Diabetes Care 40: S64-s74.
7. Palmer JP, Hampe CS, Chiu H, Goel A, Brooks-Worrell BM (2005) Is latent autoimmune diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age? Diabetes 54 Suppl 2: S62-67.
8. Laugesen E, Ostergaard JA, Leslie RD (2015) Latent autoimmune diabetes of the adult: current knowledge and uncertainty. Diabet Med 32: 843-852.
9. Groop L, Pociot F (2014) Genetics of diabetes--are we missing the genes or the disease? Mol Cell Endocrinol 382: 726-739.
10. van Hoek M, Dehghan A, Witteman JC, van Duijn CM, Uitterlinden AG, et al. (2008) Predicting type 2 diabetes based on polymorphisms from genome-wide association studies: a population-based study. Diabetes 57: 3122-3128.
11. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, et al. (2015) Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care 38: 1687-1693.
12. Lin J, Zhou ZG, Wang JP, Zhang C, Huang G (2008) From Type 1, through LADA, to type 2 diabetes: a continuous spectrum? Ann N Y Acad Sci 1150: 99-102.
13. Steck AK, Rewers MJ (2011) Genetics of Type 1 Diabetes. Clin Chem 57: 176-185.
14. Adeleye OO, Ogbera AO, Fasanmade O, Ogunleye OO, Dada AO, et al. (2012) Latent Autoimmune Diabetes Mellitus in Adults (LADA) and it's characteristics in a subset of Nigerians initially managed for type 2 diabetes. Int Arch Med 5: 23.
15. Ahlqvist E, Ahluwalia TS, Groop L (2011) Genetics of Type 2 Diabetes. Clin Chem 57: 241-254.
16. Appel SJ, Jones SJ (2012) Latent autoimmune diabetes of adulthood: a case presentation. Nurse Pract 37: 6-9.
17. Bahadursingh S, Mungalsingh C, Seemungal T, Teelucksingh S (2014) Acanthosis nigricans in type 2 diabetes: prevalence, correlates and potential as a simple clinical screening tool - a cross-sectional study in the Caribbean. Diabetol Metabol Syn 6: 77.
18. Hawa MI, Thivolet C, Mauricio D, Alemanno I, Cipponeri E, et al. (2009) Metabolic syndrome and autoimmune diabetes: action LADA 3. Diabetes Care 32: 160-164.
19. Poudel RR (2012) Latent autoimmune diabetes of adults: From oral hypoglycemic agents to early insulin. Indian J Endocrinol Metabol 16: S41-S46.
20. Hosszufalusi N, Vatay A, Rajczy K, Prohaszka Z, Pozsonyi E, et al. (2003) Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. Diabetes Care 26: 452-457.