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Case Report

South Asian version of flatbush diabetes mellitus- A case report and review article

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Ketosis prone type 2 diabetes mellitus which was once described as "atypical diabetes" is being recognized increasingly worldwide; being originally described in African population has been seen in multiple ethnic groups, especially in urban areas. These patients are typically obese, middle-aged men with a strong family history of type 2 diabetes. The pathophysiologic mechanisms involved in its cause are unknown, but preliminary evidence suggests that patients with ketosis-prone type 2 diabetes have a unique propensity to glucose desensitization. These individuals have negative autoantibodies associated with type 1 diabetes but frequently HLA class II DRB1*03 and/or DRB1*04 are detected. Severe impairment of both insulin secretion and insulin action are found at presentation. Aggressive diabetes management results in marked improvement in beta cell function and insulin sensitivity sufficient to allow discontinuation of insulin therapy within a few months of treatment. In the long run, insulin can be substituted with oral hypoglycemic agents in most of these patients under careful supervision and close follow up. Molecular investigations into KPD syndromes utilizing multiple approaches (genomic, metabolic, proteomic) to generate etiological hypotheses can help us understand the underlying defects of insulin secretion and sensitivity in these and other types of diabetic patients.

Key words: Diabetesis mellitus (DM), ketosis prone diabetes (KPD), diabetic ketoacidosis (DKA), latent auto-immune diabetes of adults (LADA).

INTRODUCTION

Diabetes that is not easily classified as either type 1 or type 2 is increasing worldwide, especially in non-Caucasian populations. An episode of diabetic keto-acidosis (DKA) was once considered a hallmark feature that would differentiate individuals with type 1 diabetes mellitus from those with type 2 diabetes mellitus. There are subgroups of patients who present with diabetic ketoacidosis (DKA) or unprovoked ketosis despite lacking the classic phenol-type of autoimmune type 1 diabetes (Winter et al., 1987; Westphal, 1996). These individuals, most commonly obese of African or Hispanic origin, have negative auto-anti-bodies associated with type 1 DM, but frequently HLA class II DRB1*03 and/or DRB1*04 are detected. This peculiar subtype of DM is commonly referred to as flatbush diabetes mellitus. Atypical dia-betes (Flatbush diabetes) was originally described by Banerji et al. (1994) as a unique form of diabetes among African-American patients who presented with diabetic ketoacidosis (DKA) as the initial manifestation of dia-betes, but whose subsequent clinical course resembled typical type 2 diabetes mellitus (T2DM). These patients have no identifiable precipitating cause of DKA (Umpierrez et al., 1999). This atypical presentation has also been reported in other ethnicities as well (Tan et al., 2000). Here, we report the case of a Pakistani patient who exhibited the typical clinical course and described evolution and in whom it was possible to withdraw insulin

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therapy.

CASE REPORT

Clinical presentation

14 year old Pakistani male was presented in June 2004 in emergency room of a local hospital with altered mental status, hyperglycemia high anion gap acidosis and was diagnosed with DKA. The past medical history was unremarkable. There was family history of diabetes in his maternal grandmother. His body mass index (BMI) was 31 kg/m^2. Physical examination showed signs of volume depletion and acanthosis nigricans. Rest of the examination was unremarkable. Laboratory tests revealed no evidence of acute infection, renal or liver dysfunction, or recent alcohol use. The arterial pH was 7.1; anion gap, 26; serum bicarbonate, 8 mmol/liter and urine was positive for ketones (acetoactate). Patient had positive serum -hydroxybutyrate levels and serum glucose was 592 mg/dl. He was admitted to the hospital and received standard treatment for DKA with IV fluids and insulin. He recovered uneventfully and was discharged on the third hospital day on a regimen of NPH insulin 18 units and regular insulin 12 units twice daily before meals. He was followed closely in our diabetic clinic thereafter.

Diagnostic testing

Glycosylated hemoglobin (HbA1c) at presentation was 12.4%. Auto-antibodies to glutamic acid decarboxylase (GAD) 65 and islet cell antibodies (IA-2) were absent in the serum. Cell functional reserve was assessed during hospitalization after resolution of DKA by serum C-peptide levels. The fasting C-peptide level was below normal at 0.6 ng/ml.

Evolution of beta-cell function and clinical course

Cell functional reserve was assessed three months later in our clinic. Fasting C-peptide level had come up to 3.6 ng/ml. At that time patient was on basal (NPH) 18 units and bolus (regular) insulin 12 units twice daily before meals and later an attempt was made to switch him to oral hypoglycemic agents in lieu of his repeat C-peptide level of 3.6 ng/ml. He was started on glimepiride 2 mg and metformin 850 mg bid and insulin was discontinued. Patient had another episode of DKA two months later. Oral agents were stopped, he was treated for DKA and this time was sent home on NPH insulin 22 units and regular insulin 14 units twice daily before meals. He did fine on insulin regimen for next one and half year when patient and family insisted on re-evaluation of his status to see if oral hypoglycemics can be given a chance again. This time after overnight fasting, his C-peptide was 6 ng/ml. After detailed discussion with the patient and family decision was made to switch him back to oral agents, provided patient can check his blood glucose at least four times daily and can come to clinic every other day for evaluation. Insulin was slowly tapered off after starting patient on metformin, pioglitazone and glicalazide. Patient did fine on oral agents this time and glicalazide had to be stopped later on because of hypoglycemic episodes. Now for the last two years he is on metformin 1000 mg bid and pioglitazone 30 mg q d without any episode of DKA. His last HbA1C done in our clinic one month ago was 6.3%.

Conclusion

This 14 years old obese Pakistani patient with family history of diabetes had no evidence of -cell auto-immunity and had signs of insulin resistance presented with DKA. Initial attempt after three months of his presentation to switch him to oral hypoglycemic agents resulted in repeat DKA in this patient. Second attempt for that switch one and half year later was fruitful and he continued to do fine on insulin sensitizers. We believe that he still had left over effect of glucose toxicity and shocked beta cells when first attempt was made to change his regimen to oral hypoglycemics. But he did fine on second attempt to switch him on oral agents for his DM one and half year later because beta cells had recovered significantly by then. One of the limitations in our work was non-availability of HLA typing in our medical set up

Historical perspective of flatbush diabetes

In the 1960s, Adadevoh (1968) and Dodu (1967) reported that some adult patients with diabetic ketoacidosis were able to discontinue insulin therapy after a relative short time and remain in near-normoglycemic remission for several months to years. This unique, transient insulin-requiring profile was recognized mainly in patients with newly diagnosed diabetes and was reported as “temporary diabetes in adult Nigerians.” Subsequent reports from other African groups noted the difficulty in classifying such patients as having type 1 and type 2 diabetes during their initial presentation (Oli, 1978). In 1987 Winter et al. (1987) described a cohort of obese African-American children who were atypical because they lacked islet cell autoantibodies. They were presented with DKA as the initial manifestation of diabetes, and became insulin independent over time. Banerji et al. (1994) described a somewhat different atypical syndrome in overweight, adult Afro-Caribbean patients who had clinical characteristics of type 2 dia-betes but presented with DKA. The term, Flatbush dia-betes entered the literature at this point in recognition of the region in NY, where most of

these subjects resided.

The following year, Umpierrez et al. (1995) carefully characterized obese African-American patients in Atlanta, Georgia, who had late-onset diabetes presenting with DKA. The researchers also recognized the presence of measurable pancreatic insulin reserve, absence of autoimmune indicators of beta cell destruction, and increased frequency of HLA-DR3 and HLA- DR4 and that it improved further after 12 weeks of treatment. These investigators introduced the concept of BMI as a means to distinguish two phenotypes (obese or lean) of patients presenting with DKA, based on their immunological and beta cell functional differences (Umpierrez et al., 1999).

Classification of Ketosis Prone DM (KPD) including Flatbush DM

By definition, ketosis prone DM is any type of diabetes where patient can develop DKA and Flatbush diabetes is one of the types of KPD. The ADA classification scheme lacks flexibility to accommodate the heterogeneity of KPD because it applies only to patients with type 1 diabetes, which is defined as those with complete beta cell failure, requiring insulin for survival. A striking aspect of KPD is that a substantial proportion of patients, especially (but not exclusively) of non-Caucasian ethnicity, do not have complete beta cell failure and do not require insulin for long- term survival. To address this discrepancy in existing terminology Maldonado et al. (2006) suggested a classification system based on autoimmunity (A) and beta cell function ( ) for KPD as shown below.

KPD type 1A (Type 1A DM)

These patients have permanent and complete beta cell failure with serologic markers of islet cell autoimmunity (A+, -). They require lifelong exogenous insulin therapy.

KPD type 1B (Type 1B DM)

These patients have permanent and complete beta cell failure but lack serologic markers of islet cell autoimmunity (A-, -). They require lifelong exogenous insulin therapy.

KPD type 2A (LADA)

These patients have preserved beta cell function at the time of diagnosis but also have serologic markers of islet cell autoimmunity (A+, +). In the long run these patients lose their beta cell reserve and require lifelong exogenous insulin therapy.

KPD type 2B (Flatbush DM or KP type 2 DM)

These patients have preserved beta cell function and lack serologic markers of islet cell autoimmunity (A-, +). The majority (especially if new onset) can discontinue exogenous insulin therapy and can be managed with oral hypoglycemics for long time.

Prevalence

There are only a handful of studies available regarding exact incidence and prevalence of ketosis prone type 2 diabetes mellitus. Based on reports from these studies, it is clearly evident that incidence of this type of diabetes is clearly more than what was considered to be in the past. In the United States, the prevalence of KPD has been estimated to be between 20 and 50% in African-American and Hispanic patients with new diagnoses of diabetic ketoacidosis (Diabetes et al., 2001; Balasubramanyam et al., 1999) and half of these patients have Flatbush diabetes. In agreement with the U.S. experience, African studies have reported the incidence to be the same (Sobngwi et al., 2002; Oli, 1978). The prevalence of ketosis-prone type 2 diabetes seems to be lower in Asian and white persons and may represent fewer than 10% of cases of diabetic ketoacidosis (Maldonado et al., 2003; Yamada and Nonaka, 1996).

Etiology and pathophysiology

Metabolic factors

The insulin response to oral and intravenous glucose load, test meals, and nonglucose secretagogues has been reported after resolution of DKA by different investigators in patients with Flatbush diabetes. Umpierrez et al. (2007) have examined the roles of glucotoxicity and lipotoxicity in inducing the severe but partially reversible beta cell functional defect in an obese African- American patient with the phenotype of unprovoked A- , + KPD shortly after resolution of the index episode of DKA. The investigators measured the effects of exposure to 20 h of hyperglycemia and 48 h of hyperlipidemia (by lipid infusion) on C-peptide secretion. Acute hyperglycemia but not acute hyperlipidemia caused severe blunting of the C- peptide response to glucose stimulation, and chronic hyperglycemia was associated with reduced expression and insulin-stimulated threonine-308 phosphorylation of Akt2 in skeletal muscle. These data suggest that severe glucotoxic blunting of an intracellular pathway leading to insulin secretion may contribute to the reversible beta cell dysfunction characteristic of A-, + KPD patients, and that hyperglycemia may be exacerbated by defects in skeletal muscle glucose uptake resulting from glucotoxic down-regulation of skeletal muscle insulin sig-

naling. One mechanism of glucotoxic beta cell dysfunction is increased oxidant stress in the islets.

Genetic factors

There is definitely genetic susceptibility to ketosis-prone type 2 diabetes but it is not known whether the model is polygenic or has a major gene influence. Analyses of relative frequencies of HLA alleles in these patients have produced conflicting results. Some investigators have failed to find an association with HLA susceptibility alleles (Mauvais -Jarvis et al., 2004) . In contrast, others have found an increased frequency of HLA-DR3 and HLA-DR4 compared with non-diabetic populations (Banerji et al., 1994). A point mutation Gly574Ser in the HNF1- gene was proposed as a marker of ketosis-prone type 2 diabetes in African-American children and adolescents (Boutin et al., 1999), but a recent report in adults excluded this association (Mauvais-Jarvis et al., 2003). Recently, a mis-sense mutation (Arg121Trp) of PAX4 has been implicated in early and insulin-deficient type 2 diabetes in Japanese patients (Shimajiri et al., 2001). PAX4 is a transcription factor that is essential in the differentiation of embryonic pancreatic progenitors into insulin-producing beta cells in the mammalian pancreas (Shimajiri et al., 2001). Sobngwi et al. (2005) investigated the possibility of X-linked glucose-6-phosphate dehydrogenase (G6PD) deficiency as a genetic basis for the male-predominant Flatbush diabetes phenotype in West African patients. They found a higher prevalence of functional G6PD deficiency in the KPD patients compared with patients with type 2 diabetes and a relationship between beta cell functional reserve and erythrocyte G6PD activity. Mauvais-Jarvis et al. (2004) found high frequency of a polymorphism leading to an amino acid substitution (R133W) in *PAX4*, a transcription factor essential for islet morphogenesis beta cell development, among patients with phenotypes of A-, + KPD. Because this variant is found in a high percentage of West Africans and African-Americans with and without type 2 diabetes, but not in Caucasians, its pathophysiological significance in the specific context of KPD is unclear.

Clinical features and natural history of disease

Patients with Flatbush diabetes are lot more different phenotypically compared with typical DKA patient of type 1 DM. These patients are obese, middle-aged persons with newly diagnosed diabetes who present with unprovoked diabetic ketoacidosis. The initial presentation is usually acute. These patients have a history of polyuria, polydipsia, and weight loss for less than 4 to 6 weeks (Maldonado et al., 1997). At the time of diagnosis they may also have nausea, vomiting, abdominal pain, lethargy and somnolence depending on the level of decompensation. Patient may also be hypotensive, tachycardiac and tachypneic from dehydration and acidosis.

The mean age at diagnosis is 40 years (range: 33 to 53 years). Several series of patients with ketosis-prone type 2 diabetes show a 2- or 3-fold higher prevalence in men (Pin˜ero-Pilon˜a and Raskin, 2001) in contrast to series of white patients with type 1 diabetes. The male predominance in ketosis-prone type 2 diabetes seems to be independent of the degree of obesity and age at presentation. The reason for the sex difference is unknown; however, it has been attributed to hormonal factors, body fat distribution, and changes in insulin sensitivity. Physical examination reveals signs of dehydration, dry mucous membranes, and tachycardia. Glucose level and acid-base parameters at presentation are similar to those reported in lean patients with diabetic ketoacidosis.

Disease course of KPD after the initial episode of DKA depends on the presence of autoantibodies and long-term beta cell reserve. Long-term beta cell reserve and absence of autoimmunity is the key determinant of long-term glycemic control and insulin dependence. McFarlane et al. (2001) described the clinical course of African-American persons from Brooklyn admitted to the hospital with newly diagnosed ketoacidosis who were followed for at least 1 year. Remission was defined as a hemoglobin A1c level of 6.3% or less and a fasting plasma glucose level of less than 6.6 mmol/L (120 mg/dL) 3 months after therapy with all pharmacologic agents was discontinued. Forty-two percent of patients achieved remission after a mean of 83 days and remained in remission during 20 months of follow-up. There were no differences in age, sex, plasma glucose level at presentation, changes in body mass index, magnitude of weight change, or pharmacologic agents used between patients who achieved remission and those who did not. Studies reported that 60 and 67% of patients with ketosis-prone type 2 diabetes relapsed into hyperglycemia within 2 years if treated with diet alone (Umpierrez, 1995). In such patients, treatment with sulfonylurea or metformin has proven effective in pro-longing the duration of normoglycemic remission and in preventing read-mission for ketoacidosis (Umpierrez et al., 1997a,b).

Management of ketosis prone type 2 diabetes mellitus

Clinical management of KPD includes:

A) Acute management of DKA;
B) Outpatient management after resolution of DKA.

Management of DKA

Acute management of DKA is not any different in this

condition than the usual DKA of type 1 DM. All patients who present with DKA should be treated according to established principles of acute management of the metabolic decompensation. The most urgent goals are rapid intravascular repletion, correction of hyperglycemia and acidosis and management of electrolyte imbalance (Balasubramanyam et al., 2006). Treatment should occur in intensive care settings. It is important to note that inpatient treatment during the episode of DKA should be the same regardless of the apparent phenotype of the KPD patient, and that all KPD patients should be discharged from the hospital on a regimen that provides 24 h insulin coverage on basal-bolus regimen.

Outpatient management after resolution of DKA

After resolution of DKA, patient should be discharged home on multiple daily injections of insulin. Assessment of beta cell secretory reserve and beta cell autoimmunity should be performed after complete resolution of DKA to minimize any acute effects of glucose toxicity or desensitization on beta cell function, generally 4- 8 weeks after resolution of ketoacidosis. Fasting blood glucose, C-peptide levels and C-peptide response to glucagon should be assessed. Patients are classified as - if the fasting ser-um C-peptide concentration is less than 1 ng/ml (0.33 nmol/liter) and the peak serum C- peptide response to glucagon (measured at 5 and 10 min after iv injection of 1mg glucagon) is less than 1.5 ng/ml (0.5 nmol/liter), and they are classified as + if the fasting serum C-peptide concentration is at least 1 ng/ml (0.33 nmol/liter) or the peak serum C-peptide response to glucagon is at least 1.5 ng/ml (0.5 nmol/liter) . These cutoffs accurately predict cell function after 6 months and 1 year (Balasubramanyam et al., 2006) . Auto-immunity against beta cells should be assessed as well because in patients with +, positive autoimmunity helps to predict long term dependence of these patients on insulin compared with the ones which are + and have negative autoimmunity. Patient should be categorized based upon above results. Only patients who turn out to be KPD type 2B (A-, +) (other names for this entity are Flatbush DM or KP type 2 DM) based on previously mentioned classification can be tried cautiously on oral hypoglycemics under careful supervision. For rest of the groups it is not prudent to take them off insulin. After discontinuation of insulin therapy for patients with negative GAD and with fasting or stimulated C-peptide levels 1 and 1.5 ng/ml, respectively, we recommend starting therapy with low-dose sulfonylurea (glyburide, 1.25–2.5 mg/d) and metformin (500 mg twice per day). The duration of this process of insulin withdrawal is variable and may range from 10 to 14 wks or longer. Patients with positive GAD or with inadequate insulin secretion are more likely to relapse and in these patients insulin therapy should be continued, and patients should be carefully monitored for recurrence of hyperglycemia or ketosis.

SUMMARY

Ketosis prone type 2 diabetes mellitus which was once described as “atypical diabetes” is being recognized increasingly worldwide; being originally described in African population has been seen in multiple ethnic groups, especially in urban areas. These patients are typically obese, middle-aged men with a strong family history of type 2 diabetes. The pathophysiologic mechanisms involved in its cause are unknown, but preliminary evidence suggests that patients with ketosis-prone type 2 diabetes have a unique propensity to glucose desensitization. These individuals have negative autoantibodies associated with type 1 diabetes but frequently HLA class II DRB1*03 and/or DRB1*04 are detected. Severe impairment of both insulin secretion and insulin action are found at presentation. Aggressive diabetes management results in marked improvement in beta cell function and insulin sensitivity sufficient to allow for discontinuation of insulin therapy within a few months of treatment. In the long run insulin can be substituted with oral hypoglycemic agents in most of these patients under careful supervision and close follow up. Molecular investigations into KPD syndromes utilizing multiple approaches (genomic, metabolic, proteomic) to generate etiological hypotheses can help us understand the underlying defects of insulin secretion and sensitivity in these and other types of diabetic patients.

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