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Case Report
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Cessation of Multiple Daily Insulin Injections in a Person with Twenty-Nine Years of "Type 1 Diabetes"

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Abstract

Diabetes mellitus is a complex and etiologically heterogeneous metabolic disorder. Therefore, accurate classification of patients into diabetes-subtypes remains a challenge in clinical practice.

We report a 50-year-old, non-obese (Body Mass Index (BMI) 22.4 kg/m^2) Chinese lady who was diagnosed with Type 1 Diabetes Mellitus (T1DM) at age 21. This diagnosis was made owing to abnormal glucose tolerance detected during pregnancy and the young-onset nature of the disease. Subsequently, a multiple daily insulin injection (MDI) regime was initiated and maintained for almost three decades. Given a few clinical features atypical of T1DM (i.e. relatively stable fasting and post-absorptive glucose profile along with being non-ketotic prone despite occasional interruption of MDI, suggesting preserved pancreatic β cell insulin secretory function), the diagnosis was re-visited. She was subjected to deep re-sequencing of a panel of 16 candidate genes implicated in monogenic diabetes (or Maturity Onset Diabetes of the Young [MODY]) using Next Generation Sequencing (NGS) technology. A glucokinase (GCK) coding non-synonymous mutation (S441W), novel among Asians was discovered. The mutation was predicted to be functionally deleterious by multiple bioinformatics algorithms. Additionally, one recent *in vitro* site-directed mutagenesis study reported reduced enzyme-substrate (i.e. glucose) affinity associated with this variant. This suggested a revised diagnosis of MODY2. Notwithstanding the long-standing duration of diabetes, she was successfully weaned off from all anti-diabetic agents over the next few months with modest impact on her global glycemic profile (HbA1c 6.4% to 6.9%).

Averting unnecessary long-term pharmacotherapy often means substantial health-cost savings, avoidance of potential treatment-related adverse-effects and importantly, better quality of life for the person and their family members. This case-report serves as an important reminder to reconsider the diagnosis and consider the option of genetic testing (especially in the era of NGS), among diabetic individuals with features atypical of the classic forms of diabetes.

Keywords: Maturity onset diabetes of the young (MODY); Misdiagnosis; Next-generation sequencing (NGS); Glucokinase (GCK) mutation

Introduction

Diabetes is traditionally thought to be an etiologically-complex disorder stemming from the culmination of many factors including impaired insulin action and defect in pancreatic β-cell insulin secretion. Individualized therapeutics that effectively addresses the root cause is therefore challenging, and at times elusive. There is however, a subset of patients who suffer from diabetes resulting predominantly from a single gene mutation i.e. monogenic diabetes or traditionally called-maturity onset diabetes of the young (MODY). Each mutation has a high degree of penetrance, resulting in high blood glucose concentration characteristic of diabetes. While the genetic architecture of MODY continue to evolve, well established major candidate genes include Glucokinase (GCK), hepatic nuclear factor (HNF)1α, HNF4α and HNF1β, which collectively explain more than 90% of all MODY in most population [1]. Guided by precise molecular diagnosis, treatment targeting the root cause is likely to be more effective i.e. precision medicine. Unfortunately, such patients are often misdiagnosed as suffering from the more common T1DM (or young-onset type 2 diabetes (T2DM)) due to the young age of onset of the disease. Consequently, insulin treatment is often initiated and maintained indefinitely with unintended consequences.

Case Report

A non-obese (with body mass index (BMI) 22.4 kg/m^2) 50-year-old Chinese lady was diagnosed with Type 1 Diabetes Mellitus (T1DM) at age 21, owing to abnormal glucose tolerance detected during pregnancy. Subsequently, multiple daily insulin (MDI) injections of long-acting insulin Detemir 10 u bed time and short-acting insulin Lispro 2 u TDS were given. This resulted in stable glycemic control (HbA1c hovering around the range of 6.4% to 7.2%) for close to three decades.

She was referred to a secondary care diabetes center for consideration of continuous subcutaneous insulin infusion (CSII) therapy with the aim of more consistently achieving a HbA1c target of ≤6.5%. However, unlike individuals with longstanding T1DM (or T2DM), she had a very stable fasting and post-absorptive (pre-meal) glucose profile largely hovering around 5.0 mmol/L [2,3] (Table 1). Additionally, she was non-ketotic prone despite occasional interruption of MDI. These clinical features suggested preserved pancreatic β-cell insulin secretory function atypical of an individual with longstanding T1DM (or T2DM). Furthermore, she was tested negative for glutamic acid decarboxylase (GAD) antibody-a maker of T1DM associated β-cell autoimmunity, known to be fairly durable among Asians [4]. Therefore, the diagnosis of T1DM was re-visited.

The patient was enrolled in a monogenic diabetes pilot study [5].

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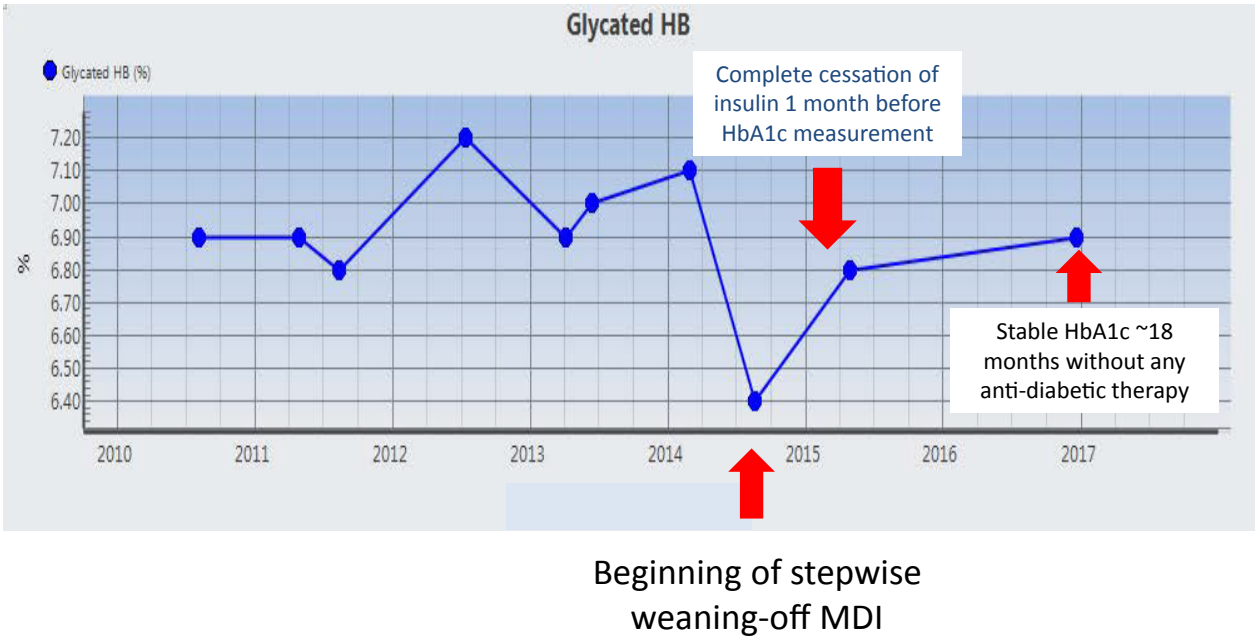

Figure 1: Serial HbA1c before and after stepwise weaning and eventual cessation of multiple daily insulin injections (MDI).

Breakfast		Lunch		Dinner	
Pre	Post	Pre	Post	Pre	Post
5.1	7.7	5.2	8.0	4.9	6.9
5.0	8.1	4.8	7.4	5.1	8.3
4.9	7.9	5.6	8.2	5.5	7.5
5.2	8.2	5.4	9.9	5.3	8.4
5.1	7.8	5.5	8.8	5.2	9.3

Table 1: Self glucose monitoring results showing very stable fasting and post-absorptive (pre-meal) blood glucose (in mmol/L) profile, consistent with preserved pancreatic β-cell insulin secretory function, which is atypical of an individual with longstanding "Type 1 Diabetes".

A panel of 16 candidate genes commonly implicated in monogenic diabetes were deep re-sequenced using Ion Torrent PGMTM (Life Technologies) with an average read-depth of 100 times. These 16 candidate genes include 13 known MODY genes (*GCK, HNF1A, HNF4A, HNF1B, NEUROD1, INS, CEL, PDX1, PAX4, BLK, KLF11, KCNJ11* and *ABCC8*), one insulin resistance gene (INSR) and two lipodystrophy associated diabetes genes (*LMNA* and *PPARG*). A GCK coding non-synonymous mutation (S441W), novel in Asian populations, was discovered and subsequently confirmed by bi-directional Sanger capillary sequencing technology. The mutation was predicted to be functionally deleterious by open-resource bioinformatics tools SIFT and PolyPhen-2. The *GCK* gene codes for glucokinase which phosphorylates glucose to glucose 6-phosphate. This takes place in the first step of the glycolysis pathway, metabolizing glucose to release its stored energy. By means of this reaction, glucokinase functions as the glucose sensor of pancreatic β-cells [6]. The missense mutation, substituting tryptophan for serine at position 441, decreases the glucose affinity of glucokinase [7], thereby leading to a right-shift in the β-cell glucose-sensitivity. Therefore, glucose homeostatic mechanisms are still functional albeit at a mildly elevated glucose set-point. Hence, the patient was re-diagnosed as having MODY2 and was advised to wean off insulin replacement therapy.

To ensure safety, a stepwise insulin reduction algorithm was adopted. Therefore, the prandial ultra-rapid action insulin-Lispro was first omitted for breakfast. When glucose monitoring suggested blood glucose profile to be no different from previous values after 3 days, insulin-Lispro was then omitted for lunch. Likewise, prandial insulin at dinner was omitted 3 days later. Patient's preference was to be kept on bedtime Detemir 10 u for a few more weeks to ensure no ketosis. Subsequently, Detemir was stepwise-reduced by 2 units every week till total daily dose of 4 units, which was stopped when fasting glucose remained stable. Hence, despite almost 3 decades of MDI treatment, she was completely taken off insulin successfully (Figure 1).

Discussion

There are several clinical lessons to be gleaned from this case-report.

Firstly, awareness of the etiological heterogeneity of diabetes mellitus needs greater highlight among clinicians. Notwithstanding its high prevalence, diabetes remains a challenge which defies accurate classification. In the clinics, it is not uncommon to meet patients with features atypical of the classic forms of type 1 or 2 diabetes [8]. Therefore, high degree of awareness of less common diabetes-subtype, assisted by web-based open-resources such as the "MODY-calculator" may help identify individuals eligible for genetic testing [9]. High-throughput NGS may potentially revolutionize the diagnostic algorithm of diabetes thereby ushering in the era of pharmacogenetics i.e. precision medicine for diabetes [10,11].

Secondly, the present recommendation to actively screen for gestational diabetes (GDM) with a set of strict blood glucose criteria among expecting women can be exploited to facilitate the case-finding for MODY2 [12]. Therefore, expecting women with glucose intolerance harboring clinical features atypical of GDM (e.g. slim individual, as in our case-report) may warrant consideration of other form of diabetes such as MODY2. Given the potential implication of fetal growth and glycemic management during pregnancy in the setting of maternal-fetal discordance in GCK mutation status, confirming the diagnosis of

MODY2 is not just an academic exercise [13]. Hence, stake-holders in the field of GDM may wish to incorporate case-finding for MODY2 in the overall diagnostic workup.

Thirdly, careful consideration should be made to modify treatment (in this case, gradual cessation of insulin) informed by the genetic diagnosis (i.e. MODY2). It has been reported that MODY2 requires no specific pharmaco-therapeutics. Importantly, the omission of anti-diabetic treatment does not lead to vascular complications among these subjects despite a median duration of 48.6 years of hyperglycemia [14,15]. Therefore, the most appropriate treatment based on accurate diagnosis often means substantial health-cost savings, avoidance of potential treatment-related adverse-effects and importantly, better quality of life for the person and their family members [16].

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