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Letter to the editor

Can standard CGM data be used to identify an HNF1B MODY-5 glucotype? Insights from a clinical case

1. Introduction

Diagnosing and managing maturity-onset diabetes of the young (MODY) is clinically challenging. Hepatocyte nuclear factor-1β (HNF1B) diabetes (MODY-5) is infrequent MODY subtype, characterized by mutations leading to a clustered phenotype with high glycemic variability, as seen in type 1 diabetes once residual insulin secretion wanes, and to renal, gynecologic and pancreatic developmental abnormalities [1]. Continuous glucose monitoring (CGM) is a new approach for detecting unusual types of diabetes and tailoring management, although research is very limited [2]. The present case report sought to describe the characteristics of the 24-h glycemic profile of an HNF1B MODY-5 individual, using CGM data, and comparing it with CGM data from type 1 diabetic subjects.

2. Case report

A 31-year-old male was diagnosed with new-onset glycosuria during a routine medical examination scheduled by his employer. Shortly after diagnosis, he was referred to our diabetes clinic. At presentation, he was asymptomatic. He reported no polydipsia, polyuria or abdominal pain. Laboratory results revealed fasting glycemia at 317 mg/dL (17.4 mmol/L) and glycated hemoglobin A1c (HbA1c) at 10.4% (9 mmol/mol) prior to pharmacological glucose-lowering. There was no history of pancreatitis or pancreatic surgery. Familial medical history included type 2 diabetes in the father, and type 1 diabetes in a maternal cousin, diagnosed at the age of 34. Physical examination yielded normal findings: weight 78.5 kg, body mass index (BMI) 23 kg/m^2, and blood pressure 110/70 mmHg. No chronic hyperglycemia-related complications were present. Except for a moderately elevated serum creatinine level of 1.42 mg/dL (CKD-EPI: 66 mL/min/1.73 m^2), biological parameters, including magnesium level, were within normal ranges. Basal insulin was initially used to treat presumptive type 1 diabetes due to the patient's young age and markedly elevated HbA1c at diabetes diagnosis. Initial treatment with basal insulin significantly reduced HbA1c levels. However, subsequent deterioration in glycemic control led to addition of rapid-acting prandial insulin on top of basal insulin. The patient's interstitial glucose was monitored with a 14-day CGM sensor (FreeStyle Libre®). A few weeks later, biological results confirming the absence of anti-glutamic acid decarboxylase antibodies (GADA) and anti-insulin autoantibodies (IA2) prompted further investigations. Considering the patient's profile – young, normal weight, slightly elevated serum creatinine and steady decline in fasting C-peptide (0.28–1.42 nmol/L) from 0.27 at diagnosis to 0.08 nmol/L at 6 months and 0.16 nmol/L at 10 months – and the absence of anti-GAD65 and anti-AI2 antibodies, pancreas CT was performed to screen for morphologic abnormalities. The CT scan disclosed dorsal pancreatic agenesis and splenomegaly, without any associated renal abnormalities. MRI further revealed that only the head of the pancreas was unaffected, without dilation of Wirsung or bile ducts. Following informed consent, a genetic analysis for maturity-onset diabetes of the young (MODY) disclosed a heterozygous c.703C>Tp. (Arg235Trp) mutation in exon 3 of the HNF1-β gene, establishing a MODY-5 diagnosis associated with dorsal pancreatic agenesis.

Studies have shown that CGM opens up new possibilities for identifying glycemic profiles associated with atypical and secondary diabetes, thus enabling innovative approaches for precision medicine [2]. Therefore, to determine whether the 24-h glycemic features characteristic of this monogenic diabetes were different from those of type 1 diabetes (T1D), we analyzed and compared the CGM data of this index MODY-5 individual to a control group of 15 adult T1D patients. The control group included only newly diagnosed T1D individuals who proved anti-GAD$_{65}$ positive, to avoid the bias of including individuals with undiagnosed monogenic diabetes labeled as T1D due to lack of systematic screening for MODY in otherwise phenotypically standard T1D patients.

Data for the first 14 days of CGM monitoring were compared between the MODY-5 index patient and 15 individuals with newly diagnosed T1D. CGM used daily recording on Freestyle Libre® 2, with > 70% duration.

The CGM parameters were as listed in the recommendations: mean glucose (mg/dL), glycemic variability (%CV), time above range (TAR) > 250 mg/dL (> 13.9 mmol/L), TAR > 180 mg/dL (> 10.0 mmol/L), time in range (TIR) 70–180 mg/dL (3.9–10.0 mmol/L), time below range (TBR) < 70 mg/dL (< 3.9 mmol/L), and TBR < 54 mg/dL (< 3.0 mmol/L) [3]. To assess whether MODY-5 patients were different from or similar to other T1D patients as regards the above CGM parameters, we compared their relative position in each Gaussian distribution with respect to the overall mean and standard deviation of the values for each parameter. This comparison was made using a Z-score, which measures the number of standard deviations by which a point's value is above or below the mean. A Z-value close to 0 indicates that the patient is close to the overall average for this parameter, while a Z-value far from 0 (positively or negatively) indicates a significant difference from the average of other patients. A Z-score beyond −2 or +2 is often considered significantly different from the average. The results of the CGM Z-scores for MODY-5 patients were: TAR > 180 mg/dL had a Z-score of 0.14, while TAR > 250 mg/dL had a Z-score of 0.07; TBR < 54 mg/dL had a Z-score of −0.44, and TBR < 70 mg/dL had a Z-score of −0.58; TIR 70–180 mg/dL had a Z-score of −0.08; and %CV had a Z-score of 0.21. In Fig. 1, all Gaussian distribution curves are shown in black, with the MODY-5 patient for each CGM parameter highlighted by a black dot. These adjusted results indicate that MODY-5 patients' CGM metrics were very close to the mean for most parameters. However, there were

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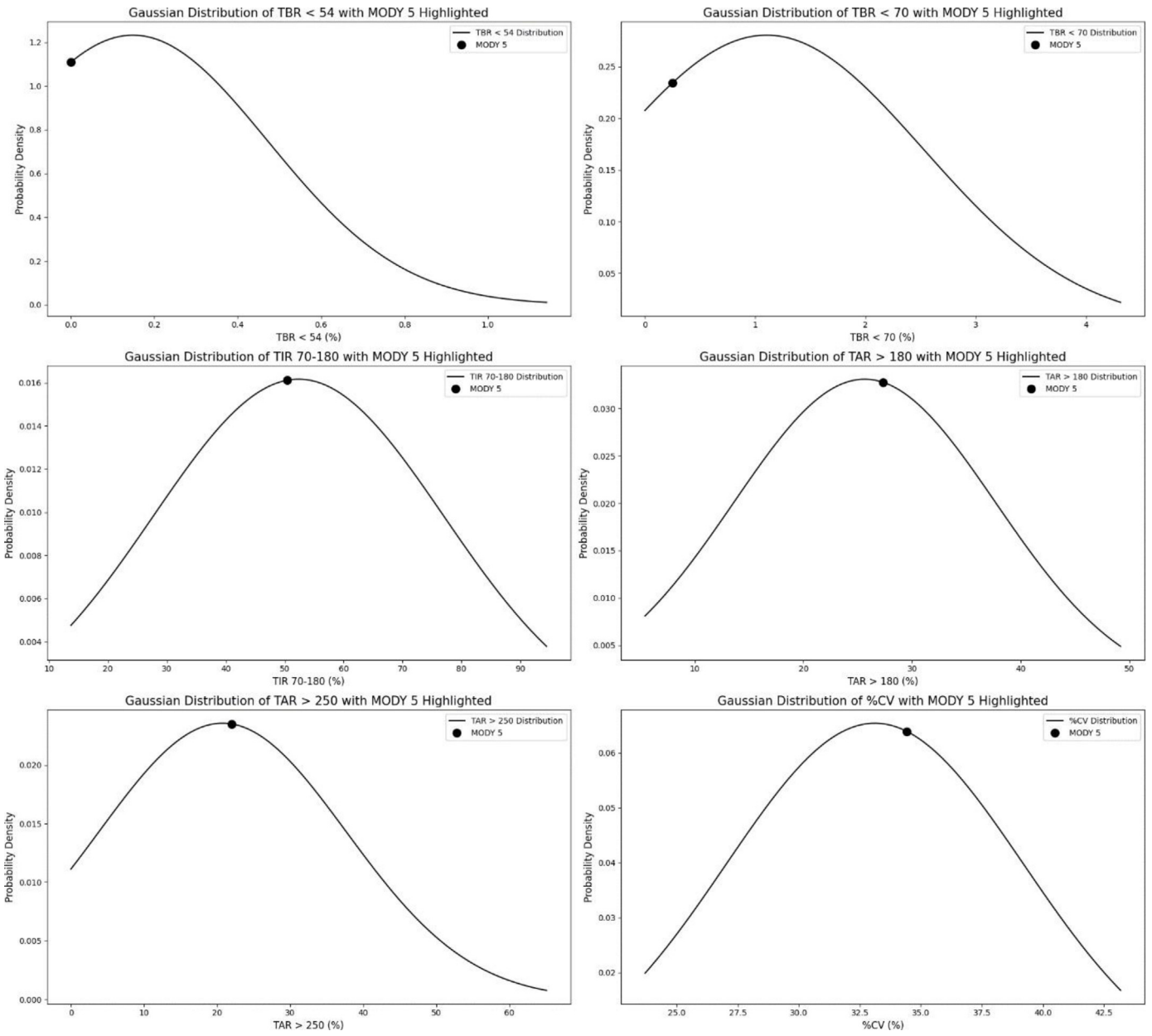

Fig. 1. Gaussian distribution curves for all patients are shown in black, with the MODY-5 patient indicated by a black dot.

slight deviations for TBR < 54 and TBR < 70, where the values were slightly below the mean.

3. Discussion

The inherent complexity of identifying candidates for genetic screening in monogenic forms of diabetes, particularly the rare HNF1B – MODY-5 form caused by mutations in the HNF1B gene, is well reported in the literature. MODY-5 is often misdiagnosed as GAD65 antibody-negative T1D due to clinical similarities, underscoring the critical need for a more refined and specific diagnostic approach [4,5]. Research aims to create a scoring system for MODY-5 using clinical, imaging, and biological markers to select candidates for HNF1B genetic testing [6]. In our case, the patient was thin, C-peptide level was low, and HbA1c was high at diagnosis, suggesting T1D; only the absence of antibodies and the partial agenesis of the pancreas redirected the initial diagnosis [1]. The study conducted by Warncke et al. [1], examining 35 patients with MODY-5, highlighted the critical importance of thoroughly characterizing these patients through their clinical and metabolic data, and revealed several distinctive features of MODY-5 that clearly differentiate it from type 1 diabetes (T1D):

- greater age of diagnosis, typically over 25 years;
- low body mass index (BMI);
- absence of pancreatic β-cell antibodies;
- occasional presence of exocrine pancreatic insufficiency;
- specific renal, hepatic, gynecological and/or pancreatic abnormalities.

In MODY-5 cases such as the present, half the patients start insulin treatment because of high initial glycemia and HbA1c. According to Dubois-Laforgue et al. [7], 80% of patients still had residual insulin secretion after a median 9 years progression of diabetes, indicating that complete C-peptide loss is not systematic in

MODY-5: i.e., although a decrease in insulin secretion is typical of MODY-5, complete C-peptide loss is not always observed.

However, Mateus et al. suggested that some MODY-5 patients may have a severe insulin secretion defect at the time of diagnosis; 47% of patients had symptomatic hyperglycemia (polyuria, weight loss) and 5% had ketoacidosis [8].

The frequency of C-peptide loss in MODY-5 is not well documented, and further research is needed to clarify the dynamics, and particularly to distinguish this from the rapid decline typically seen in T1D. In the present case report, we were unable to determine precisely whether the rapid decline in C-peptide secretion was due to endogenous or exogenous factors, leading to initiation of insulin therapy.

Hypomagnesemia and hypokalemia are common in MODY-5. These electrolyte abnormalities can provide important clinical clues as to whether an HNF1B mutation is involved. However, in the present case, magnesium levels were within the normal range. On the other hand, Dubois-Laforgue et al. [7] highlighted the presence of kidney disease in the majority of adults with MODY-5, underlining the importance of early diagnosis for better management of these patients.

Also, some authors suggested that CGM could provide a new diagnostic marker for MODY [2,9,10].

Using CGM to identify unique glucose patterns could differentiate certain types of monogenic diabetes from T1D and T2D. However, despite the potential of this approach, research into the application of CGM to specifically distinguish MODY-5 from T1D is still limited.

In the present clinical case, we studied the CGM parameters of a newly diagnosed and treated patient with the MODY-5 mutation, and compared them with 15 newly diagnosed T1D patients. To the best of our knowledge, this is the first case report analyzing these CGM parameters in the context of MODY-5. Fig. 1 summarizes a comprehensive analysis of the glucotype of the MODY-5 patient in comparison to the T1D cohort. The MODY-5 patient had a lower frequency of hypoglycemic episodes, which is an indication of inherently more stable glycemic control. The time within target glucose range was similar to the average for the T1D group, indicating that glycemic management was as effective as in T1D. The CV of the MODY-5 patient was marginally above the average for the controls, but the deviation was negligible, reinforcing the similarity in glycemic fluctuation patterns.

4. Conclusion

This case report highlights the complex challenges associated with the diagnosis of MODY-5. The phenotype of MODY-5 is very heterogeneous in initial presentation and can often mimic the clinical signs of newly diagnosed type 1 diabetes. However, subclinical features such as hypomagnesemia, renal cysts or pancreatic abnormalities should raise suspicion of MODY-5. Emerging research into the use of continuous glucose monitoring (CGM) for glucotype analysis may be able to distinguish the different types of MODY from type 1 and type 2 diabetes, but our results in a single case suggest that the standard CGM parameters currently used in practice are insufficient to effectively differentiate MODY-5 from T1D. Although current CGM parameters have been shown to be inadequate, exploration of alternative CGM parameters may be a promising avenue.

Consent

The patient has given written informed consent for the publication of this case report, and the patients in the control group have given written informed consent for their data to be analyzed, in accordance with European data protection guidelines, once the data are downloaded on the Libreview platform. All recordings of CGM parameters were performed routinely during consultations via the Libreview platform at the outpatient diabetes clinic of the Mouscron Hospital (Belgium).

Disclosure of interest

P. Oriot is the guarantor of the manuscript and assumes responsibility for the work, including, data access and the decision to submit and publish the manuscript.

During the preparation of this work, the authors used ChatGPT in order to perform Fig. 1. Having used this tool, the authors have revised and edited the content as necessary and take full responsibility for the content of the publication.

The authors declare that they have no competing interest.

References

[1] Warncke K, Kummer S, Raile K, Grulich-Henn J, Woelfle J, Steichen E, et al. Frequency and characteristics of MODY 1 (HNF4A mutation) and MODY 5 (HNF1B mutation): analysis from the DPV database. J Clin Endocrinol Metab 2019;104:845–55, http://dx.doi.org/10.1210/jc.2018-01696 [PMID: 30535056].
[2] Steenkamp DW, Cheney MC, Ju Z, Rodbard D, Wolpert HA. Proof-of-concept application of continuous glucose monitoring data analytics to identify diabetes glucotypes. J Endocr Soc 2023;7, http://dx.doi.org/10.1210/jendso/bvad038 [bvad038. PMID: 37035501; PMCID: PMC10074392].
[3] Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–603, http://dx.doi.org/10.2337/dci19-0028 [Epub 2019 Jun 8. PMID: 31177185; PMCID: PMC6973648].
[4] Francis Y, Tiercelin C, Alexandre-Heyman L, Larger E, Dubois-Laforgue D. HNF1B-MODY masquerading as type 1 diabetes: a pitfall in the etiological diagnosis of diabetes. J Endocr Soc 2022;6, http://dx.doi.org/10.1210/jendso/bvac087 [bvac087. PMID: 35733830; PMCID: PMC9206723].
[5] Colclough K, Patel K. How do I diagnose maturity onset diabetes of the young in my patients? Clin Endocrinol (Oxf) 2022;97:436–47, http://dx.doi.org/10.1111/cen.14744 [Epub 2022 May 2. PMID: 35445424; PMCID: PMC9544561].
[6] Faguer S, Chassaing N, Bandin F, Prouheze C, Garnier A, Casemayou A, et al. The HNF1B score is a simple tool to select patients for HNF1B gene analysis. Kidney Int 2014;86:1007–15, http://dx.doi.org/10.1038/ki.2014.202 [Epub 2014 Jun 4. PMID: 24897035].
[7] Dubois-Laforgue D, Cornu E, Saint-Martin C, Coste J, Bellanné-Chantelot C, Timsit J, et al. Diabetes, associated clinical spectrum, long-term prognosis, and genotype/phenotype correlations in 201 adult patients with hepatocyte nuclear factor 1B (HNF1B) molecular defects. Diabetes Care 2017;40:1436–43, http://dx.doi.org/10.2337/dc16-2462 [Epub 2017 Apr 18. PMID: 28420700].
[8] Mateus JC, Rivera C, O'Meara M, Valenzuela A, Lizcano F. Maturity-onset diabetes of the young type 5 a MULTISYSTEMIC disease: a CASE report of a novel mutation in the HNF1B gene and literature review. Clin Diabetes Endocrinol 2020;6:16, http://dx.doi.org/10.1186/s40842-020-00103-6 [PMID: 32864159; PMCID: PMC7448977].
[9] Lunt H, Heenan H, Chan H. Exploring phenotype-genotype correlations using interstitial glucose results in a family with a glucokinase mutation. J Diabetes Sci Technol 2018;12:1248–9, http://dx.doi.org/10.1177/1932296818784064 [Epub 2018 Jun 26. PMID: 29944009; PMCID: PMC6232740].
[10] Ren Q, Zhang P, Pang W, Ma Y, Gong S, Ba T, et al. A comparison of daily glucose fluctuation between GCK-MODY and type 2 diabetes using continuous glucose monitoring technology. Diabetes 2023;72:812–8, http://dx.doi.org/10.2337/db22-0566 [PMID: 36939643].

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