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A Family of GCK-MODY, About 02 Cases and Review of the Literature

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Abstract

Positive diagnosis of diabetes is currently easy, but typing diagnosis of diabetes still remains a challenge for every clinician. It is currently accepted that types of diabetes apart from T1D and T2D can expand and include several forms of diabetes mellitus; From gestational diabetes, to all forms of secondary diabetes mellitus due to medications, intercurrent disease but also infections, and finally monogenic diabetes, whose diagnosis is not always easy to establish. The aim is to reveal the difficulties that clinicians may face in the process of etiological diagnosis regarding the suspicion of this type of monogenic diabetes, through the study of 2 cases, in which MODY type diabetes was suspected. Today we recognize 17 different genetic mutations that can all lead to MODY diabetes, the most common mutation of which is GCK coding for the glucokinase, the real sensor of pancreatic Beta-cell. The truly stable glycemic profile, with an A1C ranging between 7% and 7.5%, confirmed with a TIR always above 70% and a good MAGE, but also the rarity of degenerative complications and pharmacological therapeutic abstention which can last for years, these would be the most striking clinical characteristics of a GCK MODY.

Keywords

Maturity Onset Diabetes of the Young, Diabetes Typing, Glucokinase GCK Mutation

1. Introduction

First described by Robert Tattersall in 1974, MODY type diabetes is a specific entity of diabetes mellitus; characterized by beta cell dysfunction to varying degrees with abnormalities in insulin synthesis [1]. This is an often-overlooked pathology of diabetes mellitus and above all underdiagnosed despite the great

similarity between this monogenic condition and other entities of diabetes mellitus. Its reported prevalence ranging from 1% to 5% among all patients diagnosed with diabetes [2], and 1% - 6% of pediatric cases of diabetes [2] [3]. The main characteristics of this type of diabetes are the young age of its discovery, generally before the age of 25, the insidious and long-term non-insulin-dependent nature, and its autosomal dominant hereditary nature [4]. The GCK mutation could affect up to one in 1000 people in the general population, making them the statistically most common monogenic form. On a genetic level, and alongside the GCK mutation, there are today 16 other forms of MODY diabetes, thus totaling 17 subtypes of MODY type diabetes, with different levels of pathogenicity; The 6 classic mutations have a certain pathological potential because they meet both criteria, and are said to be consistent (GCK, HNF1A, HNF4A, KCNJ11, NEUROD1 and HNF1B), with an OR of 6.36 in terms of penetrance [5] [6]. 7 other mutations are considered "inconclusive" and these are the ABCC8, KLF11, RFX6, PCBD1, WFS1, INS and PDX1 mutations, finally there are 4 other mutations called inconsistent because they lack specific genotypic and phenotypic criteria (PAX4, CEL, BLK and APPL1) [6]. The clinical presentation, as well as the degenerative profile and therapeutic attitudes of MODY-type diabetes, differ widely depending on the type of mutation in question. For example, patients with MODY 2 (GCK MODY) are considered those expressing moderate hyperglycemia levels with less frequent use of oral anti-diabetics and ultimately much less use of insulin, unlike other MODY subtypes. We report two observations of a little girl the eldest of two siblings and her youngest brother, in whom the suspicion of MODY type diabetes was justified on the basis of a range of clinical and biological arguments, and a final diagnosis of GCK MODY was confirmed by genetic sequencing.

2. Our Observations

Case 1: this is a young girl aged 15 years and 03 months, a schoolgirl, with good psychomotor development, pubescent and whose menarche appeared at the age of 13. Her cognitive abilities are excellent and her academic performance is satisfactory. She is athletic with considerable dedication to martial arts. In his background; there is an iron deficiency anemia and irritable bowel syndrome. Furthermore, there is no family history of diabetes, use of corticosteroids or pancreatic pathology. Hyperglycemia was revealed by chance on an assessment requested as part of monitoring his anemia. Plasma fasting glucose = 1.40 g/l (7.7 mmol/L), controlled PFG: 1.56 g/l (8.58 mmol/L) with an A1C = 6.8% thus diagnosing diabetes mellitus. The evaluation finds a pubescent girl whose Tanner stage 3, a normal auxology compared to the target size, without any dysmorphic syndrome, nor mental delay. Its BMI is 22.8 kg/m^2 and we do not find any acanthosis nigricans in the neck or in the folds, we do not find any signs orienting towards a secondary diabetes, in particular the absence of Cushing syndrome nor Thyrotoxicosis. There is no hypoacusis or retinal disease either.

Faced with the modest level of dysglycemia and the absence of initial diabetic ketosis, as well as the ideal weight without the stigma of a metabolic syndrome and without acanthosis, monogenic type diabetes was strongly suspected, hence the prescription of autoimmunity assays aimed to rule out T1D. Anti-GAD Antibodies = 12.8 IU/L negative, Anti-IA2 < 4 IU/L negative, Anti-ZnT8 < l0 IU/L negative as well. C-peptide = 644 pmol/L, which is a very comfortable level. The rest of the autoimmunity assessment was also normal; Anti-TPO = 13 (Normal < 34). Anti-transglutaminase IgA and IgG Antibodies also came negative. An abdominal ultrasound in search of liver, renal or pancreatic anomalies (hemangioma or cysts) had returned without particularity. Family diabetes family screening has been requested and returned in favor of prediabetes from his younger brother.

Case 2: He is an 11-year-old boy, impuberate. Without mental delay or dysmorphic syndrome too. His BMI is ideal at 24.1 kg/m^2. With a normal auxology compared to his age, and whose Tanner stage is 1. There are no nigricans acanthosis or signs of secondary diabetes as well. His glycemic assessment was requested in the context of family screening from the index case (his sister); Plasma fasting glucose = 1.06 g/l (5.83 mmol/L) and his A1C = 6.2% thus defining a state of prediabetes. Faced with that family context of diabetes and prediabetes declared to childhood, insidious and modest hyperglycemia, and after excluding autoimmune and secondary diabetes, a monogenic diabetes type MODY-2 was strongly suspected. The search for the GCK mutation has been requested in the young diabetic girl. The method used was the high-speed sequencing Sanger, coming positive in favor of the mutation "DEL_CHR7_042577DC". It is a point mutation leading to a loss of function by a deletion mechanism, with a molecular size of 136 bp. Thus, the typing diagnosis is finally confirmed, in favor of GCK-MODY.

3. Discussion

Monogenic diabetes constitutes a heterogeneous entity of genetic diseases, leading to the appearance of diabetes in young people sometimes diagnosed in childhood, generally insidious and not very severe. Today there are 17 types of this condition with very different clinical and syndromes associated [1] (**Table 1**). The GCK-MODY or the MODY-2 is a preponderant subtype in terms of prevalence, which can constitute up to 57% of all types of Mody type diabetes (USA) [7], more than 56% in France [8], and up to 80% in the Spanish register [9]. On the other hand, the GCK-MODY is the most studied MODY subtype in the literature; On a meta-analysis using the Prisma guidelines and "PubMed Data Base", on more than 1600 articles about MODY, the GCK-MODY interested 423 publications, followed by HN1A with 360 quotes and HNF4A in 3rd position with only 82 quotes [10]. Within this variant, we can count more than 800 different mutations recorded on the Human Gene Mutation Database (HGMD), and relating to the entire gene introns and exons as well [7].

Table 1. Maturity-onset diabetes of the young (MODY) genes showing chromosomal location and pathophysiology by [1].

Genetic mutation	Biological function	Chromosomal location	MODY diabetes class	Clinical manifestations
HNF4A/ transcription factor	Hepatocyte nuclear factor-4 alpha	20q12	MODY 1	Causes progressive beta-cell dysfunction, leading to macrosomia and hyperinsulinemic hypoglycemia.
GCK/glycolytic enzyme	Glucokinase	7p15	MODY 2	Disrupts glucose sensing, leading to hyperglycemia.
HNFIA/ transcription factor	Hepatocyte nuclear factor-1 alpha	12q24.31	MODY 3	Causes gradual beta-cell dysfunction, leading to reduced insulin production and progressive hyperglycemia.
IPFI/PDX1/transcription factor	Insulin promoter factor/Pancreatic duodenal homeobox	13q27.92	MODY 4	Causes pancreatic agenesis, beta-cell developmental errors, and defective insulin secretion.
HNFIB/transcription factor	Hepatocyte nuclear factor 1B	17q12	MODY 5	Results in dysfunctional pancreatic embryonic development, the formation of kidney cyst, and suppresses cytokine signaling
NeURODI/transcription factor	Neurogenic differentiation 1	2q31.3	MODY 6	Impairs pancreatic morphogenesis and beta-cell differentiation.
KlFII/transcription factor	Krüppel-like factor 11	2p25.1	MODY 7	Disrupts the activation of some insulin promoters. It also suppresses the expression of certain free radical scavengers such as catalase and superoxide dismutase, disrupting pancreatic beta-cell function.
Cell/lipase	Carboxyl ester lipase	9q34	MODY 8	Alters C-terminal sequencing. It can also disrupt exocrine and endocrine functioning of pancreas.
PAX4/Transcription factor	Paired box 4	7q32.1	MODY 9	Truncates embryonic beta-cell development, inhibiting beta-cell differentiation.
INS/Insulin synthesis	Insulin hormone	11p15.5	MODY 10	Causes molecular defects in the β-cell and increases endoplasmic reticulum (eR) stress, resulting in the synthesis of structurally altered (pre) proinsulin molecules and low insulin biosynthesis.
BlK/B-cell receptor signaling and development, stimula	B-lymphocyte kinase	8p23.1	MODY 11	Suppresses MIN6 B-cells, disrupting beta-cell functions.
ABCC8/regulates insulin secretion	ATP binding cassette subfamily C member 8	11p15.1	MODY 12	Causes congenital hyperinsulinism, adversely affecting the biogenesis and insulin trafficking of KATP channels.
KCNJII/regulates insulin secretion	Inward-rectifyier potassium channel, subfamily J, member 11	11p15.1	MODY 13	Causes congenital hyperinsulinism, adversely affecting the biogenesis and insulin trafficking of KATP channels.
APPl1/regulates cell proliferation, cellular signaling pathways	Adaptor protein, Phosphotyrosine interacting with PH domain and leucine Zipper 1	3p14.3	MODY 14	Starts off the beta-cell structural abnormality and gradual death, leading to developmental delay. It can also suppress the insulin-uptake regulatory role of AKT2.

Continued

ISl-1/transcription factor, INS enhancer	ISl lIM homeobox 1	5q11	-	Interferes with the expression of several genes, including insulin gene, also causes poor islet differentiation and proliferation.
RFX6/Regulatory factor (regulates the transcription factors involved in beta-cell maturation and function)	Regulatory factor X	6q22.1	-	Causes beta-cell dysfunction, leading to reduced insulin secretion and hyperglycemia.
NK6-1/transcription factor	NK6 homeobox 1	4q21.23	-	Beta-cell dysfunction.

Indeed, the mutation we found in our patient, as is common in GCK mutations, not a classical mutation in the genus encoding for the glucokinase this according to Gnomad site: (https://gnomad.broadinstitute.org/). For this platform, it occurred in just a single case of a non-Finnish European case, with an allele frequency of 0.00001694 [11].

Characteristics of dysglycemia in GCK MODY patients

This type of MODY is characterized by a very early start hyperglycemia, which can arise since birth [12], generally fortuitous discovery on systematic assessments, with fasting blood glucose around 5.5 - 8 mmol/L, and a modest glycemic increase After OGTT not exceeding 3 mmol/L, while A1C is also modest around 5.6% - 7.6% [13]. The causal link between GCK mutation and 'Maturity-onset Diabetes of the Young' was established in 1992 [10]. Since then, the studies of glycemic profiles of GCK-Mody patients have continued to progress. The comparison of blood sugar levels in GCK-Mudy patients versus those of type 2 diabetics shows significant differences for the same level of A1C. In fact, along the nychthemeral, indeed the MODY patients would have a slightly lower MBG than these with T2D = 6.73 ± 0.86 vs 6.85 ± 1.12 mmol/L with a significant P-Value < 0.001 [13]. But it is above all the variations in blood sugar which are much more modest in the MODY population: A CV of 20.99% ± 3% vs 28.63 ± 3.69 ($p < 0.001$) and a time-in-range equals 94.00 (90.95 - 97.75) in MODY vs 84.00 (78.00 - 92.15) in T2D ($p < 0.001$) [13]. This glycemic stability was observed on diurnal and nocturnal CGM recordings with a very low nocturnal variability delta for the MODY according to the MAGE which is 1.98 (1.77 - 2.21) versus 2.12 (1.70 - 3.03) in T2D [13]. This glycemic stability observed in patients diagnosed with GCK-MODY could explain the scarcity of complications in this entity of diabetic patients.

Degenerative profile and GCK-MODY management

Patients with a MODY-2 are most often stable without any pharmacological treatment, with the exception of specific circumstances, especially during pregnancy [14]. Apart from treatment, there is no significant impact on the occurrence of macro or microangiopathy complications [15]. Furthermore, the only best elucidated complication in the MODY diabetic patients is non -proliferating

retinopathy, with a median diagnostic age of 48.6 years [16]. The decision to start treatment in GCK-MODY patients also depends on the presence of obesity, dyslipidemia, or HTA [17]. The presence of these cardiovascular risk factors encourages the treatment of hyperglycemia with the aim of delaying the appearance of complications. When the decision to put under treatment is taken, sulfonylureas are the first-line treatment to choose, while treatment with SGLT-2 inhibitors is not in fact recommended for the risk of euglycemic diabetic ketosis [18].

4. Conclusion

The GCK-MODY is the most frequent subtype of MODY, with an excellent prognosis seen in its often-favorable evolution without treatment. Complications in the GCK-MODY are very rare. The positive diagnosis of MODY diabetes is not always easy. This requires clinical common sense, always starting by eliminating autoimmune diabetes and secondary diabetes. The clinical presumption scores are often of great help, they allow for a better sit diagnostic approach [19].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations and Acronyms

A1C:	hemoglobin 1C (glycated hemoglobin)
BLK:	B Lymphocyte Tyrosine Kinase
CEL:	Carboxyle ester lipase
CGM:	continuous glucose monitoring
CV:	coefficient of variation
GCK:	glucokinase
HNF1A:	hepatocyte nuclear factor
KCNJ11:	Potassium Inwardly Rectifying Channel Subfamily J Member 11
MODY:	Maturity-Onset Diabetes of the Young
NEUROD1:	Neuronal Differentiation 1
OGTT:	oral glucose tolerance test
PFG:	plasma fasting glucose
PQX 4:	Paired Box 4
T1D:	type-1 diabetes mellitus
T2D:	type-2 diabetes mellitus
TIR:	time-in-range