NEUROD1 Mutation in an Italian Patient With Maturity Onset Diabetes of the Young 6: a Case Report

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Short report

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Abstract

Background and Aims: maturity onset diabetes of the young (MODY) is a monogenic, autosomal, dominant disease characterized by a single genetic mutation that results in beta-cells dysfunction with consequent hyperglycemia. It represents a rare form of diabetes (1-2% of all the cases).

Sulphonylureas (SU) represent the first line treatment for this form of diabetic disease.

NEUROD1 is a transcription factor expressed by pancreatic and nervous tissues that is necessary for a proper development of beta cells. A mutation of NEUROD1 gene has been found to cause beta-cells dysfunction, inadequate insulin secretion, and hyperglycemia (MODY 6).

A recent case report has documented for the first time a new missense mutation (p.Met114Leu c.340A>C), of the NEUROD1 gene pathogenetic for diabetes mellitus.

Methods and Results: We report the case of a 50 years-old man who presented the same mutation, and who was able to suspend rapid insulin after the diagnosis and treatment with SU.

Interestingly, our patient had an early onset [dilated cardiomyopathy](#) but no other data about cardiac diseases in patients with MODY 6 are available.

Conclusions: Diagnostic criteria for MODY can overlap with other kinds of diabetes and most cases are still misdiagnosed as diabetes type 1 or 2. The disease should be suspected in patients with a strong family history of diabetes, normal BMI, early onset and no autoimmunity.

Introduction

Diabetes mellitus comprises a group of heterogeneous disorders characterized by increased blood glucose concentration. Type 1 (immune-mediated) and type 2 (due to insulin-resistance and overweight) are the most common forms of diabetic disease and both environmental and genetic factors play a crucial role in their onset.

Type 1 diabetes results from cellular-mediated autoimmune destruction of the pancreatic β -cells and it usually affects children and adolescents. Patients diagnosed with type 1 diabetes are dependent on insulin administration.

Type 2 diabetes, which accounts for 90–95% of the cases, is characterized by insulin resistance and relative insulin deficiency. At least initially, these individuals do not need insulin treatment to survive, but they can be treated with oral hypoglycemic agents [1].

Maturity onset diabetes of the young (MODY) is a genetic form of diabetes caused by a mutation of a single gene that impairs beta cells function and development [2]. It usually affects people aged under 25 and it is characterized by the following clinical features [3, 4]:

- impaired insulin secretion
- early hyperglycemia onset
- negative beta-cells antibodies

MODY represents 1–2% of all cases of diabetes, but this condition is often underdiagnosed or misdiagnosed as diabetes type 1 or 2 because of some similar clinical features. Especially in adults, it remains very difficult to distinguish between these forms of diabetic disease and the clinical diagnosis is still very challenging [5].

In the last few years, thanks to the development of genetic techniques, some of the molecular mechanisms that lead to MODY have been cleared up. More specifically, at least fourteen different forms of MODY and their respective genetic mutations have been identified [6].

Like many genetic disorders, MODY is transmitted in an autosomal dominant mode. Each form of MODY is characterized by unique genetic, clinical and metabolic features according to the tissues in which the responsible genes are expressed. The most common forms are caused by mutations in HNF4A, GCK and HNF1A [7].

Monogenic diabetes should be suspected in non-obese young patients with no insulin-resistance, an important family history of diabetes and negative beta cells antibodies (even if a few cases of MODY with positive autoimmunity are reported). In this kind of patients the possibility of MODY should be always kept in mind and a genetic investigation should be performed as soon as possible [8, 9].

Nowadays Next Generation Sequencing (NGS) allows the simultaneous sequencing of the genes that are linked to MODY. In this way, very rapid results are obtained at a lower cost [10, 11, 12]. However, even today genetic testing is not affordable in many hospitals all over the world, and it should be requested only in case of very strong clinical suspect [13]. Genetic testing and the detection of the mutation at the basis of the disease are necessary in order to provide proper prognostic information and set up the best clinical management and pharmacological therapy for the patient [14, 15]. In addition, family counseling should be provided for all patients diagnosed with MODY because of the autosomal dominant inheritance that characterizes this condition [16].

The therapeutic approach differs among the various forms of MODY according to their clinical characteristics and molecular causes. In some case, insulin administration is necessary to obtain a better glucose control, but some patients with MODY simply benefit from a treatment with OHA (eg, sulfonylureas) without using insulin [17]. The cause of this phenotypical heterogeneity is not clear yet, but it can suggest that not only genetic but also environmental parameters play an important role in the trend of the diabetic illness. The aim of the therapy is to improve the quality of life and prevent the complications of diabetes [18].

Neuronal differentiation 1 (NEUROD1) is a transcription factor expressed by pancreatic endocrine and neuronal cells that plays a crucial role in the normal development and maintenance of these tissues.

More specifically, in the pancreatic tissue, this factor is involved in the regulation of insulin synthesis and secretion. NEUROD1 binds another transcription factor (E47) to form a heterodimer that promotes the transcription of the insulin gene by reaching the Ebox of its promoter [17].

It is also reported that NEUROD1 gene is involved in the transactivation of sulphonylurea receptor 1 gene [18].

Recent evidence has proven that the inactivation of NEUROD1 gene in human embryonic stem cells severely impairs their differentiation from pancreatic progenitors into insulin expressing cells and that a genetic mutation of NEUROD1 gene leads to hyperglycemia and diabetes (MODY6) [19].

The disease usually occurs at the age of 20–25 years in patients with a heterozygous mutation and often shows a familial distribution. The transmission pattern from mother is more often reported than that from father and it might contribute to an early onset of the disease probably due to the exposure to elevated blood glucose levels during pregnancy. These patients usually present a mild form of diabetes and are treated with oral hypoglycemic agents and no insulin. Very few cases of a homozygous mutation have been reported and this kind of condition usually leads to neonatal diabetes [18].

Recent findings have also shown a connection between NEUROD1 gene mutation and central nervous system abnormalities. More specifically, NEUROD1 expression is necessary for the correct development and function of cerebellum, inner ear and retina and an impairment of the gene can cause mental disability, hippocampal hypoplasia, hearing loss and epilepsy. It is reported that such abnormalities usually affect only patients with homozygous mutation, but some recent evidence suggests that they can occur even in heterozygous patients [18].

Although a few case-reports of MODY6 have been published in the last few years, this form of diabetes remains very rare and many details about the phenotypic traits and the correct pharmacological approach of the disease still have to be investigated.

Case Report

In this review we want to report a rare case of a 50 years-old man diagnosed with MODY6. An informed consent was obtained by the patient for the publication of his laboratoristic and clinical data.

The patient came for the first time to our clinic in 2017. His prior medical history included diabetes diagnosed in 1994 and classified as diabetes type II associated to a dilated cardiomyopathy treated with a pacemaker in 2011.

He had a family history of diabetes because his mother had been diagnosed with the disease, while his father was dead for natural causes. At the contrary his brother and sister were reported to be healthy, with no sign of hyperglycemia. He also had two children, in apparently very good health.

At the moment of our first medical control the patient had no signs of diabetic complications (nephropathy, neuropathy or retinopathy) and he was following a treatment with basal-bolus insulin associated to metformin. Patient's clinical features, blood parameters and therapy are summarized in Table 1 and Table 2, respectively.

Table 1
Patient's clinical features and blood parameters over time

	Visit 1	Visit 2	Visit 3
Arterial blood pressure systolic/diastolic (mmHg)	134/78	110/70	120/80
Body weight (kg)	68	66	67
BMI (kg/m ²)	21,7	21,1	21,4
Glycated hemoglobin (%)	8,6	10,7	7,5
Fructosamine (micromol/L)	341	missing data	264
Fasting blood glucose (mg/dL)	111	288	83
C-peptide (ng/mL)	0.4	0.8	0.6
Creatinine (mg/dL)	0,73	0,64	0,74
VFG (ml/min)	108	114	107
GOT (UI)	13	17	21
GPT (UI)	19	31	30
Total cholesterol (mg/dL)	140	115	105
Triglycerides (mg/dL)	72	71	79
LDL cholesterol (mg/dL)	74,2	47	38
HDL cholesterol (mg/dL)	52	54	51
Microalbuminuria (mg/L)	15	< 5	10
Urinary ketones	not detected	not detected	not detected
Fructosamine normal range (118–282 micromol/L); C-peptide normal range (0.9–7.1 ng/mL)			

Table 2
Patient's therapy over time

	Visit 1	Visit 2	Visit 3
Insulin glargine 100 U/ml	18–22 UI at 10.00 pm	.	16–18 UI at 10.00 pm
Insulin lispro 100 U/ml	5 UI before breakfast, 6 UI before lunch and 6 UI before dinner	.	.
Metformin	500 mg tid	=	=
Gliclazide 60 mg RM	.	1 tablet od	1 tablet od
Bisoprolol	5 mg od + 10 mg od	=	=
Ramipril	10 mg od	=	=
Simvastatin/ezetimibe	10/10 od (poor compliance)	10/10 od (good compliance)	=
Lansoprazole	15 mg od	=	=
=: continued without modification			

Due to the poor glycemic control we scheduled a medical examination after a month asking the patient to monitor capillary blood glucose at home in the morning and before every meal, writing the values on a diary. We also required the detection of beta-cells antibodies in order to investigate the possibility of an autoimmune etiology of diabetes.

When the patient came back in October 2017, blood test results were not significant for autoimmune diabetes (beta cells antibodies were negative) and the values of capillary blood glucose at home showed a good trend of diabetes (most of them were between 90 and 130 mg/dL in the morning and before meals). According to the good glycemic control, we modified the patient's treatment by removing Lispro insulin before meals and introducing an oral hypoglycemic agent of the SGLT2 inhibitors group (dapagliflozin) associated to metformin (dapagliflozin/metformin 5/1000 mg 2 tablets per day).

The patient had to interrupt the treatment with dapagliflozin/metformin about ten days later, due to the appearance of severe abdominal pain that spontaneously resolved at the suspension of the therapy. The symptoms were not attributed at the metformin component of the drug, that the patient was already taking since many months. On the contrary, we suspected an euglycemic ketoacidosis caused by the effect of dapagliflozin but unfortunately, we didn't have the chance to confirm it because the patient informed us by phone several days after.

We therefore chose to set up a therapy with only metformin (500 mg 3 tablets per day) and insulin glargine scheduling a new control after ten days. When the patient came back after monitoring capillary

blood glucose at home for ten days, the values were still very good (90–130 mg/dL) despite the reduction of the pharmacological therapy.

Six months later the medical condition of the patient was still very confounding because glycosylated hemoglobin had remained high at updated blood test, while glucose values at home before meals continued to be normal.

In consideration of the young age of the patient and of his clinical picture, we decided to plan a genetic test in order to investigate the possibility of a mutation of MODY genes.

Targeted NGS of the 14 MODY genes, as well as *WFS1* and *INSR* was performed by using amplicon-based libraries and Ion Gene Studio System S5, according to the manufacturer's instructions (Thermo Fisher Scientific Inc.). Variant classification was performed according to the American College of Medical Genetics and Genomics (ACMG) standards by using the VarSomeClinical platform (<https://varsome.com>) [20]. Possible pathogenic variants were confirmed by Sanger sequencing. Large rearrangements in MODY1, 2, 3 and 5 genes were excluded by MLPA (MRC-Holland, Amsterdam, NL).

The genetic test showed heterozygosity for the missense variant p.Met114Leu c.340A > C in *NEUROD1* (NM_002500.4), linked to MODY6. The variant was not found in GnomAD exomes and genomes, and resulted with pathogenic prediction from 10 computational analyses (DEGEN2, EIGEN, M-CAP, MVP, MutationAssessor, MutationTaster, PrimateAI, REVEL, PolyPhen-2 and SIFT) versus two benign predictions (DANN and FATHMM-MKL).

At the time of the molecular diagnosis, this variant was previously undescribed and we classified it as variant of uncertain significant (VUS).

Since MODY is characterized by an autosomal dominant inheritance, family counseling was provided for the patient. His brother and sister didn't show hyperglycemia and no evidence of this *NEUROD1* variant was found at genetic testing on them. We therefore report that the patient's mother had been diagnosed with diabetes type 2 since many years but, because of her old age and immobility, genetic testing has never been performed on her.

More recently, Bouillet et al. described the same *NEUROD1* variant associated to MODY6 in a French family and classified it as mutation [21].

International guidelines report sulfonylureas as the first-line treatment for monogenic diabetes, so the patient started a treatment with gliclazide RM (60 mg) and no basal insulin.

Unfortunately glycemic values didn't benefit from the treatment with sulfonylureas and at the following medical examination the patient showed a very bad glycemic control (glycosylated hemoglobin 93 mmol/mol, fasting glucose 288 mg/dL). We therefore decided to restore the therapy with basal insulin, also in consideration of a very low c-peptide value in addition to gliclazide and metformin. With this kind of therapy the patient obtained a very good glycemic control, practising only one injection, and without

the necessity to measure sugar after every meal. He referred us that his quality of life has improved, although this data was not measured with specific questionnaires.

Discussion

MODY diabetes is often misdiagnosed as diabetes type 1 or 2, with patients being wrongly treated with multiple insulin injections from an early age. It is well known how insulin therapy not only increases the risk of hypoglycemia, but it also brings a lot of psychological issues that deeply affect patients' quality of life. Since very young, patients treated with insulin have to measure blood glucose level multiple times per day, undergo regular medical examination and organize the injection even when they go out for meals.

For this reason, a selection of the patient based on their clinical features, would enable an early diagnosis of MODY, improving patients' quality of life and containing the health-care costs.

We decided to report the case of our 50 years-old patient diagnosed with MODY6. His heterozygous mutation of *NEUROD1* (p.Met114Leu c.340A > C) was recently also detected in a French family, confirming the association to MODY6 [21]. As this variant was not found in population databases (GnomAD exomes and genomes), we cannot exclude that it could arise from a common ancestor, or in alternative, it could be a mutational hot spot.

However, data about MODY 6 are still lacking and further studies are needed in order to identify a larger number of cases and point out which are the most important clinical features that characterize the disease. In particular, more evidence is necessary to clarify a possible connection between MODY6 and cardiac disease and to establish the best pharmacological treatment for patients.

Declarations

Ethics approval:

not applicable

Consent to participate:

A written informed consent was obtained by the patient for the publication of his laboratory and clinical data.

Consent for publication:

All authors approved the final version of the manuscript and they consented to publication.

Availability of data and materials:

The Corresponding Author is available to share the data for future researches, concerning privacy policy.

Competing interests:

None.

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Authors' contributions:

Lucia Brodosi and Bianca Baracco took care of the patient, collected data, drafted the manuscript; Vilma Mantovani performed the genetic analysis, provided an update in literature, and drafted the manuscript; Loris Pironi drafted the manuscript.

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