Семейный случай инсулинзависимого сахарного диабета с мутацией в гене *PTF1A*

© Г.Н. Светлова[1], Т.Л. Кураева[1,2], Е.А. Сечко[1]*, В.А. Петеркова[1,2]

[1]ФГБУ «Национальный медицинский исследовательский центр эндокринологии» Минздрава России, Москва, Россия; [2]ФГБОУ ВО «Первый МГМУ им. И.М. Сеченова» Минздрава России, Москва, Россия

Сахарный диабет (СД) — генетически гетерогенное заболевание, и часть случаев СД 1-го типа (СД1) обусловлены мутацией одного гена.

Ребенок болен СД с 1 года, получает инсулин, течение СД лабильное. HbA_{1c} 9,9—11,4%. Обследован в 14 лет, длительность заболевания 13 лет. Суточная доза инсулина 1,15—1,35 ед/кг. Из осложнений СД начальные проявления дистальной диабетической полинейропатии, хайропатия. СД1 с множественными осложнениями у матери (39 лет) и у бабушки (74 года). При генетическом исследовании у всех трех членов семьи выявлена гетерозиготная замена в гене *PTF1A* p.P274, патологическая значимость которой неизвестна.

В настоящее время нельзя утверждать, что выявленная мутация является этиологическим фактором СД в описанном случае. Не исключен СД1 у данного ребенка, поскольку специфичные АТ не исследовались. Однако мутация выявлена у всех трех членов одной семьи с СД, что не исключает обнаружение новой, ранее не описанной формы MODY.

Ключевые слова: моногенный сахарный диабет, клинический случай, MODY, PTF1A.

A familial case of insulin-dependent diabetes mellitus with a mutation in the *PTF1A* gene

© Galina N. Svetlova[1], Tamara L. Kuraeva[1,2], Elena A. Sechko[1]*,Valentina A. Peterkova[1,2]

[1]Endocrinology Research Centre, Moscow, Russia; [2]I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Diabetes mellitus (DM) is a genetically heterogeneous disease, and some cases of type 1 diabetes mellitus (T1DM) are caused by a mutation of one gene. The child has suffered from brittle diabetes since the age of 1 year and received insulin. The HbA_{1c} level is 9.9—11.4%. The patient was examined at the age of 14 years; the disease duration is 13 years. The daily dose of insulin is 1.15—1.35 U/kg. DM complications include initial manifestations of distal diabetic polyneuropathy as well as cheiropathy. The mother (39 years) and grandmother (74 years) have T1DM with multiple complications. A genetic study revealed that all three family members had a heterozygous substitution p.P274 in the *PTF1A* gene with an unknown pathological significance.

At present, it can not be asserted that the identified mutation is the etiologic factor of diabetes in the described case. We can not exclude T1DM in this child because specific antibodies have not been tested. However, the mutation is detected in all three members of the same family with diabetes, which does not exclude the discovery of a new form of MODY, not described earlier.

Keywords: monogenic diabetes mellitus, clinical case, MODY, PTF1A.

Topicality

Type 1 diabetes mellitus (T1DM) is the most common form of diabetes mellitus (DM) in childhood and accounts for 90% of all diabetes cases in children [1]. The progress in molecular genetics has made it obvious that diabetes is a genetically heterogeneous disease, and some of diabetes cases that clinically present as T1DM are caused not by immune destruction of β-cells, but by a single gene mutation, i.e. they are monogenic diseases. These include, in particular, MODY, APS-1, and neonatal DM.

Monogenic DM (MDM) is a group of non-immune disorders of carbohydrate metabolism, which are associated with mutations in various genes responsible for the development or function of β-cells. Usually, MDM refers to maturity-onset diabetes of the young (MODY) that is characterized by a mild course, onset in adolescence or early adulthood (up to 25 years), and autosomal dominant inheritance. However, the course of MDM may be similar to that of T1DM [2, 3]. To date, mutations in 13 genes are known to lead to MODY. The most common mutations detected in patients with the MODY phenotype are those in the *GCK* and *HNF1A* genes. Also, MDM includes neonatal DM associated with recessive mutations in more than 10 genes that are involved in development of the pancreas and formation of the islet apparatus or control the function of β-cells; most often, mutations are detected in the *KCNJ11*, *ABCC8*, and *INS* genes. Homozygous mutations in these genes cause neonatal DM, and heterozygous mutations are associated with MODY [4].

Currently, there is an active search for candidate genes that may cause MDM.

Different MDM forms significantly differ in the hyperglycemia level, therapeutic approach, and risk of complications and concomitant extra-pancreatic pathology. Identification of DM etiologies enables predicting the clinical course of the disease, assessing the risk of potential complications, and personalizing the therapeutic approach as well as genetic counseling and molecular-genetic testing of other family members.

Case Report

A boy *M.*, a first pregnancy child, pregnancy in the setting of decompensated insulin-dependent DM in the

doi: 10.14341/probl8635

 DOI: http://dx.doi.org/10.14341/probl8635

mother. Timely delivery by Cesarean section. At birth, the body weight was 3,800 g (SDS 0.52); the body length was 53 cm (SDS 1.25). The child cried normally after birth; pulmonary arrest occurred at the 5th min; the child was transferred to the Critical Care Department where he stayed on the ventilator for 3 days. The early psychomotor development was normal.

Disease history. The child has suffered from T1DM since the age of 1 year 3 months. The disease manifested as polyuria, sticky urine, and weight loss. Glycemia was 15 mmol/L, no ketosis. During the first month of the disease, stable glycemic parameters were achieved by means of a non-carbohydrate diet. A less restricted diet required intensive insulin therapy.

The child has been followed-up since the age of 2.5 years at the Department of Diabetes Mellitus of the Institute of Pediatric Endocrinology of the Endocrinology Research Center (ERC). At the same age of 2.5 years, the child was diagnosed with subclinical hypothyroidism; therapy with L-thyroxine at a dose of 37.5 μg was provided. During 13-year follow-up, DM was brittle, without severe ketoacidosis. At the age of 4 years, he had hypoglycemia (glycemia 0.6 mmol/L), which was managed by intake of easily assimilated carbohydrates. HLA-typing revealed two predisposing haplotypes. Specific pancreatic antibodies (Abs) were not tested. At the age of 12 years, the boy was diagnosed with grade I to II cheiropathy. At the age of 13 years, he started insulin pump therapy. On intensive insulin therapy, fluctuations in the HbA1c level amounted to 9.9—11.4%; 3 months after the onset of insulin pump therapy, the HbA1c level was 7.4%.

The boy had the latest examination at the age of 14 years at the ERC. He was on insulin pump therapy; the daily dose of insulin was 60—70 units (1.15—1.35 U/kg).

Physical examination. The height was 155 cm (SDS −0.85); the body weight was 52 kg; the BMI was 21.6 kg/m^2 (SDS BMI 0.63). The constitution was normosthenic. The skin was of normal color, moderately dry, and clean. The subcutaneous fat was moderately developed and evenly distributed. The thyroid gland was unenlarged, dense, and mobile upon swallowing. The heart rate was 80 beats per minute; blood pressure was 100/60 mm Hg. The liver was not enlarged. Sexual development: Tanner stage 3; the testicular volume was d=l=15 mL.

Laboratory tests. The HbA1c level was 8.9%. Complete blood count was normal. Common urine analysis revealed glycosuria. A blood chemistry panel revealed hypercholesterolemia and dyslipidemia (a total cholesterol level of 6.1 mmol/L; an LDL cholesterol level was 3.8 mmol/L). A trace level of endogenous insulin secretion was detected: the C-peptide level was 0.1 ng/mL. According to the hormonal profile, the child had drug-induced euthyroidism (on treatment with L-thyroxine, 37.5 μg): TSH, 2.4 mIU/L (0.53—5.27); fT4, 12.3 pmol/L (10—17.7). Spot urine biochemistry showed moderate albuminuria (47—50 mg/L); a 24-hour urinary albumin level was within the normal range.

Instrumental findings. ECG was normal. Abdominal ultrasound revealed signs of diffuse changes in pancreatic tissue. There were no echographic signs of kidney disease.

An ophthalmologist examination revealed a high degree of myopia, divergent concomitant strabismus, and no diabetic retinopathy signs. Neurologist opinion: signs of early distal diabetic polyneuropathy.

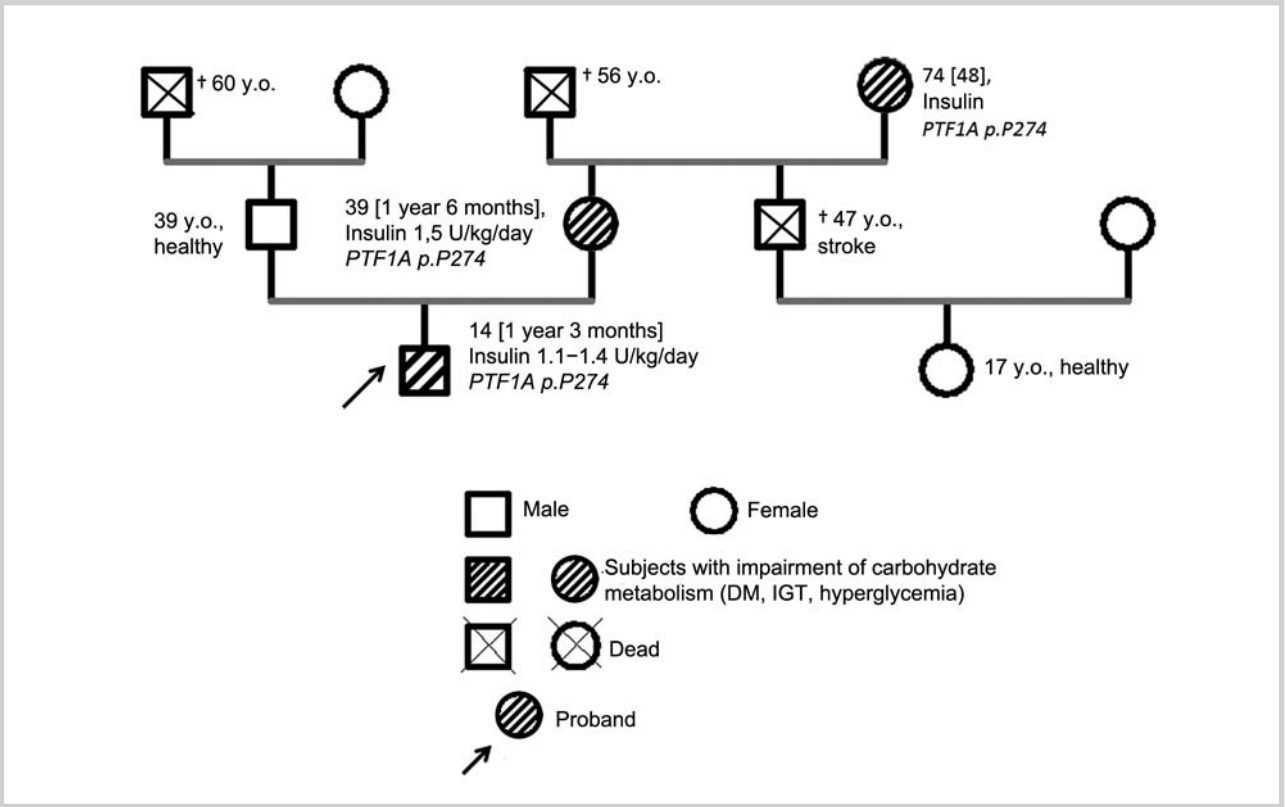
Hereditary history. The mother, 39-year-old, was diagnosed with T1DM at the age of 1.5 years; manifestation was acute, without ketosis. She received insulin since the onset of the disease. On the latest examination at the age of 39 years, the insulin dose was 1.5 U/kg, the level of HbA1c was 9.8%. Self-control was irregular; there was no carbohydrate metabolism compensation throughout the disease. At the age of 13 years, she was diagnosed with diabetic retinopathy; at the age of 31 years, she underwent laser coagulation of the retina. At the age of 39 years, she was diagnosed with maculopathy and initial cataract. At the age of 20 years, she was diagnosed with proteinuria in the setting of acute pyelonephritis. At the age of 39 years, microalbuminuria was detected; ACE inhibitors were prescribed. At the age of 13 years, there were complaints of numb and cold feet. At the age of 31 years, she had difficulty in walking and instability in standing position; at the age of 34 years, she developed gait impairment (dragging of the left leg). At the age of 34 years, a wound defect was detected on the first finger of the left foot; at the age of 38 years, she underwent an amputation of the first finger of the left foot due to osteomyelitis. On examination, osteoarthropathy as well as microangiopathy and macroangiopathy of the lower extremities were diagnosed.

The grandmother, 74-year-old, was diagnosed with T1DM at the age of 48 years and received intensive insulin therapy since the onset of manifestations. The history of T1DM and complications was absent. The family tree is shown in **Figure 1**.

Given the hereditary history of DM in three generations, monogenic DM was suspected; blood samples of the child, mother, and grandmother were sent for molecular genetic tests for a panel of genes *GCG*, *GLUD1*, *WFS1*, *HNF1A*, *GCK*, *INS*, *HNF1B*, *ABCC8*, *HNF4A*, *RFX6*, *PTF1A*, *NEUROD1*, AKT2, *ZFP57*, *INSR*, *EIF2AK3*, *PPARG*, *PAX4*, *PDX1*, *GLIS3*, *KCNJ11*, *SLC16A1*, *FOXP3*, *BLK*, *CEL*, KLF11, *SCHAD*, and *GCGR* using parallel sequencing on an Ion Torrent platform with a custom DM_HI Ampliseq panel (Laboratory of Hereditary Endocrinopathies of the ERC; head of the laboratory is A.N. Tiulpakov, DMSc). A heterozygous substitution p.P274 in the *PTF1A* gene was revealed; the pathological significance of this mutation is unknown.

Discussion

t1DM is characterized by chronic immune-mediated destruction of pancreatic β-cells, which leads to absolute



Proband's family tree.

insulin deficiency [5]. The disease is characterized by multifactorial etiology and underlied by the genetic predisposition and influence of environmental factors. Markers for T1DM include specific pancreatic antibodies (GAD, IA2, ZnT8) [6] and specific combinations of HLA alleles [7]. A high familial concentration is not typical of T1DM; family aggregation of diabetes occurs in about 10% of cases [8].

Autosomal dominant inheritance of DM is most likely associated with the presence of MODY, the clinical course of which is quite diverse (from mild hyperglycemia to insulin-dependent DM). MODY is characterized by the absence of specific Abs and the onset of DM before the age of 25 years.

In the described case, specific antibodies were not studied in the proband at the disease onset, and their testing at a disease duration of 13 years is not informative because their diagnostic significance is sharply reduced 7—11 years after the onset of T1DM [10]. At present, autoimmune destruction of β-cells can not be excluded. A study of HLA-haplotypes revealed a high-risk T1DM genotype. However, autosomal dominant inheritance in the family (DM in three generations) with the same DM phenotype in the proband and the mother was the reason to suspect the monogenic form of diabetes and to send blood samples of the proband, his mother, and grandmother for molecular genetic tesing by high-throughput parallel sequencing. All three had a heterozygous mutation in the *PTF1A* gene.

The *PTF1A* gene encodes a transcription factor and is expressed at the early stages in pancreatic duct precursors as well as pancreatic exocrine and endocrine cells [11—13]. Therefore, *PTF1A* is involved in the pancreas development. Studies conducted in mice revealed an important role of *PTF1A* in the cerebellum development. In 2004, homozygous mutations in the *PTF1A* gene were shown to cause neonatal DM with pancreatic agenesis, cerebellar hypoplasia, and central respiratory dysfunction [14].

Isolated pancreatic agenesis with homozygous mutations in the *PTF1A* gene was described in 10 probands and 4 siblings. In all probands, DM manifested in the neonatal period. In 3 out of the 4 siblings, DM was diagnosed at the age of 8, 10, and 22 years, respectively [15]. All they had exocrine pancreatic insufficiency. There were reports of neonatal DM combined with microcephaly [14]; in some cases, optic nerve dystrophy was observed [16].

Polymorphism of the clinical DM course caused by homozygous mutations in the *PTF1A* gene manifests even within the same family. A family was reported where DM manifested as pronounced reduced secretion of insulin in the first month of life, which required insulin therapy since the diagnosis of diabetes; simultaneously,

pronounced exocrine pancreatic insufficiency was revealed. In the elder sister, insulin-dependent diabetes mellitus was diagnosed at the age of 9.5 years; exocrine pancreatic insufficiency was absent [17].

In the available literature, we did not find cases of autosomal dominant diabetes caused by heterozygous mutations in the *PTF1A* gene. Now, we can not claim that the identified mutation is the etiologic factor of DM in the described case. Type 1 diabetes mellitus can not be excluded in this child because specific Abs have not been studied. However, the mutation was detected in all three members of the same family with diabetes, which does not exclude the discovery of a new MODY form that has not been reported yet.

The progress in genetics makes it increasingly evident that DM, including an insulin-dependent form, is a genetically extremely heterogeneous disease. Identification of etiologic factors enables prediction of the disease course, genetic counseling, and even modification of the therapeutic approach. The identification of a heterozygous mutation in the *PNF1A* gene in three members of the same family with the T1DM phenotype indirectly confirms potential involvement of this mutation in the development of DM. The presented data expand our knowledge of the genetic basis of DM, but elucidating the role of heterozygous mutations in the *PNF1A* gene in the development of diabetes requires further research. Identification of repeated cases of this mutation with a similar phenotype could confirm our hypothesis of a new monogenic form of insulin-dependent diabetes.

Conclusion

the identification of a heterozygous mutation in the *PNF1A* gene in three members of the same family with the T1DM phenotype indirectly confirms involvement of this mutation in the development of DM. This clinical case expands our knowledge of the genetic basis of DM, but elucidating the role of heterozygous mutations in the *PNF1A* gene in the development of diabetes requires further investigation. Identification of repeated cases of this mutation with a similar phenotype could confirm our hypothesis of a new monogenic form of insulin-dependent diabetes mellitus.

Additional information

Consent of the patient. The patient provided written consent for publication of personal medical information.

Conflict of interests. The authors declare no obvious and potential conflicts of interest related to the publication of this article.

ЛИТЕРАТУРА | REFERENCES

1. International Diabetes F. *IDF Diabetes Atlas*. 6-th edn. Brussels, Belgium: International Diabetes F. 2013.
2. Fajans SS, Bell GI. Mody. *Diabetes Care*. 2011;34(8):1878-1884. doi: 10.2337/dc11-0035
3. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med*. 2001;345(13):971-980. doi: 10.1056/NEJMra002168
4. Kavvoura FK, Owen KR. Monogenic diabetes. *Medicine*. 2014;42(12):692-697. doi: 10.1016/j.mpmed.2014.09.009
5. Craig ME, Jefferies C, Dabelea D, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2014;15 Suppl 20:4-17. doi: 10.1111/pedi.12186.
6. Watkins RA, Evans-Molina C, Blum JS, DiMeglio LA. Established and emerging biomarkers for the prediction of type 1 diabetes: a systematic review. *Transl Res*. 2014;164(2):110-121. doi: 10.1016/j.trsl.2014.02.004
7. Nguyen C, Varney MD, Harrison LC, Morahan G. Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms. *Diabetes*. 2013;62(6):2135-2140. doi: 10.2337/db12-1398
8. Hemminki K, Li X, Sundquist J, Sundquist K. Familial association between type 1 diabetes and other autoimmune and related diseases. *Diabetologia*. 2009;52(9):1820-1828. doi: 10.1007/s00125-009-1427-3
9. Ellard S, Bellanne-Chantelot C, Hattersley AT, European Molecular Genetics Quality Network Mg. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. *Diabetologia*. 2008;51(4):546-553. doi: 10.1007/s00125-008-0942-y
10. Borg H, Marcus C, Sjöblad S, et al. Islet cell antibody frequency differs from that of glutamic acid decarboxylase antibodies/IA2 antibodies after diagnosis of diabetes. *Acta Paediatrica*. 2000;89(1):46-51. doi: 10.1111/j.1651-2227.2000.tb01186.x
11. Krapp A, Knofler M, Ledermann B, et al. The bHLH protein PTF1-p48 is essential for the formation of the exocrine and the correct spatial organization of the endocrine pancreas. *Genes & Development*. 1998;12(23):3752-3763. doi: 10.1101/gad.12.23.3752
12. Adell T, Gomez-Cuadrado A, Skoudy A, et al. Role of the basic helix-loop-helix transcription factor p48 in the differentiation phenotype of exocrine pancreas cancer cells. *Cell Growth Differ*. 2000;11(3):137-147.
13. Rose SD, Swift GH, Peyton MJ, et al. The role of PTF1-P48 in pancreatic acinar gene expression. *J Biol Chem*. 2001;276(47):44018-44026. doi: 10.1074/jbc.M106264200
14. Sellick GS, Barker KT, Stolte-Dijkstra I, et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. *Nat Genet*. 2004;36(12):1301-1305. doi: 10.1038/ng1475
15. Weedon MN, Cebola I, Patch AM, et al. Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nat Genet*. 2014;46(1):61-64. doi: 10.1038/ng.2826
16. Al-Shammari M, Al-Husain M, Al-Kharfy T, Alkuraya FS. A novel PTF1A mutation in a patient with severe pancreatic and cerebellar involvement. *Clin Genet*. 2011;80(2):196-198. doi: 10.1111/j.1399-0004.2010.01613.x
17. Gonc EN, Ozon A, Alikasifoglu A, et al. Variable Phenotype of Diabetes Mellitus in Siblings with a Homozygous PTF1A Enhancer Mutation.*Horm Res Paediatr*. 2015;84(3):206-211. doi: 10.1159/000435782

ИНФОРМАЦИЯ ОБ АВТОРАХ
***Сечко Елена Александровна** — к.м.н. [Elena A. Sechko, MD, PhD]; адрес: Россия, 117036 Москва, ул. Дм.Ульянова 11 [address: 11 Dm. Ulyanova street, Moscow 117036, Russia]; ORCID: http://orcid.org/0000-0002-8181-5572; eLibrary SPIN: 4608-5650; e-mail: elena.sechko@bk.ru
Петеркова Валентина Александровна — д.м.н., проф., акад. РАН [Valentina A. Peterkova, MD, PhD, Professor]; ORCID: http://orcid.org/0000-0002-5507-4627; e-mail: peterkovava@hotmail.com
Светлова Галина Николаевна — к.м.н. [Galina N. Svetlova, MD, PhD]; ORCID: http://orcid.org/0000-0002-4328-2090; eLibrary SPIN: 9356-2673; e-mail: g_svetlova@mail.ru
Кураева Тамара Леонидовна — д.м.н., проф. [Tamara L. Kuraeva, MD, PhD, Professor]; ORCID: http://orcid.org/0000-0003-4950-3920; eLibrary SPIN: 8206-0406; e-mail: diabetkuraeva@mail.ru

ИНФОРМАЦИЯ
Рукопись получена: 19.03.17. Одобрена к публикации: 20.06.17.

КАК ЦИТИРОВАТЬ:
Светлова Г.Н., Кураева Т.Л., Сечко Е.А., Петеркова В.А. Семейный случай инсулинзависимого сахарного диабета с мутацией в гене *PTF1A*. // *Проблемы эндокринологии*. — 2018. — Т. 64. — № 2. — С. 111-115. doi: 10.14341/probl8635

TO CITE THIS ARTICLE:
Svetlova GN, Kuraeva TL, Sechko EA, Peterkova VA. A familial case of insulin-dependent diabetes mellitus with a mutation in the *PTF1A* gene. *Problems of Endocrinology*. 2018;64(2):111-115. doi: 10.14341/probl8635