Традиционно около 90% всех случаев сахарного диабета (СД) у взрослых приходится на долю СД 2 типа, при этом, как правило, СД типа MODY (maturity-onset diabetes of the young – диабет взрослого типа у молодых лиц) остается вовремя не диагностированным, что, в свою очередь, приводит к выбору неправильной тактики лечения. Одной из наиболее распространенных моногенных форм СД является заболевание, обусловленное мутацией гена глюкокиназы (GCK) – СД типа MODY2. Знание особенностей клинической картины заболевания позволяет выделить пациентов с высоким риском наличия мутации гена GCK и направить их для верификации диагноза на молекулярно-генетическое исследование (МГИ). В настоящей работе отражены особенности клинической картины СД типа MODY2 и трудности его диагностики у взрослых. Представлен клинический случай пациентки с СД типа MODY2, который в полной мере демонстрирует все особенности данного типа СД.

КЛЮЧЕВЫЕ СЛОВА:
sахарный диабет; ген глюкокиназы (GCK); диабет взрослого типа у молодых лиц (MODY); СД типа MODY2; гестационный сахарный диабет; клинический случай

TITLE
MODY2 diagnostic issues in adults

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ABSTRACT
About 90% of all cases of diabetes mellitus in adults occur in type 2 diabetes, while MODY diabetes (maturity-onset diabetes of the young) remains undetermined in time, which leads to incorrect treatment tactics. One of the most common monogenic forms of diabetes is a disease caused by a mutation of the glucokinase gene – MODY2. Knowledge of the clinical features of the disease allows you to select patients with a high risk of the presence of a mutation of the glucokinase gene and to verify the diagnosis for molecular genetic research. This paper reflects the clinical features of MODY2 and the difficulties of
diabetes mellitus. This paper presents a clinical case of a patient with MODY2 which demonstrates all the features of this type of diabetes. The presence of a mutation in a gene in one of the family members allows us to predict the nature of carbohydrate metabolism disorders in the next of kin of relatives. A targeted study of only one part of the glucokinase gene in a molecular genetic research is sufficient to confirm the diagnosis in relatives.

KEYWORDS:

diabetes mellitus; GCK gene; maturity-onset diabetes of the young (MODY); MODY2; gestational diabetes; case report

BACKGROUND

In typical cases, an analysis of the clinical presentation of the disease is sufficient to determine the type of diabetes mellitus (DM) and the choice of further treatment approach. Additional immunological and genetic studies that allow differential diagnostics of various types of DM are rare. At the same time, a number of studies demonstrate that from 7 to 15% of DM cases are classified incorrectly [1]. With the expansion of the capabilities and accessibility of molecular genetic testing (MGT), it becomes apparent that the prevalence of DM monogenic forms is higher than it was previously considered. Previous studies have shown that in childhood and adolescence, the frequency of DM monogenic forms is 1.1–4.25% of all forms of DM, and the prevalence in the population is 2.1–4.6 per 100,000 [2]. Among Americans under the age of 20, about 10% of DM cases with residual insulin secretion and without antibodies to various pancreatic antigens are actually cases of monogenic DM [3]. According to other authors, the frequency of monogenic forms of DM in developed countries amounts to 1–2% [4]. Moreover, in 2010, S. Amed et al. [5] reported a minimum incidence of MODY (maturity onset diabetes in youth, option 1) in Canada among subjects under the age of 18 of 0.4 cases per 100,000. In 2012, T. Della Manna et al. [6] noted that the prevalence of MODY in Brazil ranged from 0.3% to 2.4% of DM cases, and approximately 70% of them are MODY3 and MODY2. The relative prevalence of MODY subtypes varies. In the Czech Republic, S. Pruhova et al. [7] demonstrated a multi-year study (from 1999 to 2009), where MGT was conducted in 959 probands from 292 families, which demonstrated the detection rate of monogenic forms of DM of 35% for MODY2, 10.6% for MODY3, and 4.5% for MODY1. In 2007, a study of 59 Israeli MODY patients [8] revealed a relative frequency of MODY (10.1% for MODY3, 8.5% for MODY2, 1.7% for MODY1).

MODY combines forms of DM with an autosomal dominant type of inheritance, which are based on mutations of genes associated with dysfunction of beta cells. More than 80% of MODY cases remain undiagnosed, and it often takes more than 10 years before the diagnosis can be verified [9].

Currently, 14 genes are known, that lead to the development of various types of MODY [10], while the two most common forms are MODY2 and MODY3 induced by mutations in the genes of glucokinase (GCK) and hepatocyte nuclear factor (HNF1a), respectively [2, 10].

With MODY2, there are usually no clinical symptoms of the disease; and carbohydrate metabolism disorders are often detected randomly (during preventive examination or for a concomitant disease, as well as during screening during pregnancy). Patients do not require the prescription of insulin therapy, as normoglycemia can be maintained with a diet. The exception is pregnant women with MODY2 type DM, when insulin therapy prevents the development of fetal macrosomia in the absence of a similar mutation [11–14].

A homozygous inactivating mutation in GCK can lead to a complete glucokinase deficiency and cause permanent neonatal DM [12]. If there are activating mutations in the GCK gene, a unique form of congenital hyperinsulinism develops [15].

Knowledge of the major clinical aspects of MODY2 enables to suggest the presence of this form of DM at the history taking stage, to conduct the necessary examination and refer the patient to MGT. The detection of a mutation in the GCK gene enables to verify unambiguously the MODY2 diagnosis.

CLINICAL CASE DESCRIPTION

The use of MGT methods in the Department of Diabetes Therapy of the Institute of Diabetes, National Medical Research Center of Endocrinology, during 2017–2018, enabled to diagnose 12 cases of MODY2. Molecular genetic analysis was performed in the laboratory of the department of hereditary endocrinopathies of the National Medical Research Center of Endocrinology (Head of the Department, A.N. Tyulpakov, MD, PhD). Genomic DNA was isolated from peripheral blood leukocytes by a standard method (Pure Link kit, Genomic DNA Mini Kit, Life Technologies, USA). For molecular genetic analysis, the NGS method was used. We used a primer panel for multiplex PCR and sequencing using the
Ion Ampliseq™ Custom DNA Panel technology (Life Technologies, USA), developed in the Department of hereditary endocrinopathies of the National Medical Research Center of Endocrinology. Sequencing was conducted on a PGM semiconductor sequencer (Ion Torrent, Life Technologies, USA). Bioinformatic processing of sequencing results was performed using the Torrent Suite 4.2.1 software module (Ion Torrent, Life Technologies, USA) and the Annovar software package (version 2014Nov12). Genbank references were used as reference cDNA sequences of candidate genes. Interpretation of the research results and assessment of the pathogenicity of nucleotide changes were performed in accordance with international recommendations. All single nucleotide variants with a minor allele frequency of more than 0.001 were excluded from the subsequent analysis. Mutations were designated in accordance with the recommendations of den Dunnen and Antonarakis. Subsequently, similar mutations were searched in the relatives on the Genetic Analyzer Model 3130 sequencer (Life Technologies, USA).

The median age of patients at the time of the examination was 28 [22; 34.25] years (18 to 48 years). At the same time, only one examined patient underwent a genetic study confirming the diagnosis, immediately after initial detection of carbohydrate metabolism disorders. The onset of carbohydrate metabolism disorders was at the age of 9–19. The median disease duration was 10 [2; 21] years. All the patients were hospitalized to clarify the type of DM, while in three of them, previously identified disorders of carbohydrate metabolism met the criteria for impaired glucose tolerance (IGT), two patients were diagnosed with DM2 and one with DM1. At the time of MGT, 6 patients were on a diet with a restriction of easily digestible carbohydrates, 2 patients received insulin therapy, 3 patients took vildagliptin (2 in combination with metformin), and 1 patient took metformin.

The median body mass index (BMI) at the time of the examination was 20.65 [19.4; 21.85] kg/m². One patient who was first diagnosed with carbohydrate metabolism disorders at the age of 41 years old had II degree obesity (BMI 35.1 kg/m²). The median level of glycated hemoglobin (HbA1c) of the subjects was 6.4 [5.85; 6.6] %. Only 4 out of 13 patients had the HbA1c level which met the criteria for DM (≥6.5%) at the time of the examination (6.6 – 6.7%). In 3 patients, the level of HbA1c, with the disease duration of more than 20 years was 6.4%, 6.3%, 6.0%, respectively. An oral glucose tolerance test (OGTT) was performed to 7 patients (Table 1). According to the OGTT results, carbohydrate metabolism disorders were classified as DM in 3 patients and as IGT in 4.

Table 1. Indicators of the oral glucose tolerance test in MODY type DM patients (n=7, Me [Q1; Q3])

<table>
<thead>
<tr>
<th>OGGT, min</th>
<th>Plasma glucose, mmol/L</th>
<th>C-peptide, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of the patients showed microvascular complications of DM, which is especially important, given the duration of the carbohydrate metabolism disorder.

The key clinical characteristics of the presented group of patients with MODY2 type DM are presented in Table 2.

Table 2. Clinical characteristics of patients with diabetes mellitus type MODY2 (Me [Q1; Q3]).

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (m/f), n</td>
<td></td>
</tr>
<tr>
<td>Age at the time of examination, years</td>
<td></td>
</tr>
<tr>
<td>Age of the onset of carbohydrate metabolism disorders, years</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td></td>
</tr>
<tr>
<td>HbA1c ≥6.5%, n</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td></td>
</tr>
<tr>
<td>Diagnosis at admission (set earlier), n:</td>
<td></td>
</tr>
<tr>
<td>- type 1 DM</td>
<td></td>
</tr>
<tr>
<td>- DM2</td>
<td></td>
</tr>
<tr>
<td>- unspecified DM</td>
<td></td>
</tr>
<tr>
<td>- IGT</td>
<td></td>
</tr>
<tr>
<td>Therapy before diagnosis verification, n:</td>
<td></td>
</tr>
<tr>
<td>- diet</td>
<td></td>
</tr>
</tbody>
</table>
The following is a clinical case of a patient with MODY2 type DM, which fully demonstrates the special aspects of this type of DM.

Patient I., 35 years old, was admitted to the department, with complains about an increase in fasting plasma glucose to 7.3 mmol/L.

The anamnesis indicates that a carbohydrate metabolism disorder was first detected at the age of 14 years (with normal body weight) during prophylactic medical examination. The patient has been monitored for 2 years was observed in a primary care facility with a diagnosis of IGT; she followed a diet with restricted easily digestible carbohydrates. With self-control, an increase in fasting glycemia was periodically noted. Since 16 years old, she has not been examined. Fluctuations in body weight during 19 years of the monitoring did not exceed 7 kg (minimum 56 kg, maximum 63 kg).

At the age of 23 years old, there was an inevitable miscarriage at a term of 10 weeks. At the age of 33 years, during the second pregnancy, gestational DM was diagnosed at week 11. Intensified insulin therapy was prescribed, which helped to achieve the target glycemic indicators (before delivery, Levemir 16 units before bed, NovoRapid 9-10 units before main meals: 0.65 units/kg/day). Weight before pregnancy was 62.5 kg, and before childbirth, it was 71 kg (total weight gain 8.5 kg). Term birth (week 38 of gestation) was by cesarean section, the baby’s weight at birth was 2560 g. 2 months after delivery, OGTT was performed, which revealed fasting glycemia of 6.6 mmol/l, after 2 hours it was 11.0 mmol/l; fasting C-peptide was 262 pmol/L (0.79 ng/ml), and 1478 pmol/L after 2 hours, thyroid-stimulating hormone (TSH) was 0.46 mlU/L. Low carbohydrate diet was recommended.

Changes in time of HbA1c after childbirth were 6.4% after 3 months and 5.6% in a year. Due to the increase in fasting glycemia to 6.4–6.5 mmol/L, metformin was prescribed by the endocrinologist with a gradual increase in the dose to 1700 mg/day. Due to the lack of effect, the drug was withdrawn independently by the patient. The patient was hospitalized to clarify the diagnosis.

Upon examination, the weight was 56.5 kg, the height was 165 cm, and the BMI was 20.8 kg/m2. During the examination, HbA1c was 6.0%, fasting insulin was 7.92 μE/ml (2.3–26.4), and antibodies to beta-cell antigens were not detected. During OGTT, IGT was detected along with intact secretion of insulin (plasma glucose was 6.46–10.67–9.93 mmol/L, C-peptide was 1.68–7.39–8.24 ng/ml). The increase in glycemia during the test (after 2 hours) was less than 4.6 mmol/L [16–19]. With the usual diet, fasting glycemia ranged from 6.3 to 7.3 mmol/L, after meals it was up to a maximum of 8.7 mmol/L. When examining the signs of diabetic retinopathy, nephropathy was not detected.

Family history (Fig. 1):

father of proband (II.2): 65 years old, had a slight increase in glycemia to 7.0 mmol/l for 40 years, does not receive treatment;

half-sister (III.7): 9 years 4 months (height 131 cm; weight 27.5 kg), asymptomatic non-progressive fasting hyperglycemia of up to 6.5 mmol/L was registered at the age of 2.5 years old. When examined at the age of 8 years, 7 months: HbA1c – 6.1%, insulin – 3.6 μU/ml (2.6–24.9), C-peptide – 293 pmol/L (370–1470), antibodies to beta-cell antigens negative;

cousin sister (III.9): 35 years old, BMI 17.2 kg/m2. An increase in fasting glycemia of 7.0 mmol/L was actively revealed. During OGTT, fasting glycemia of 6.0 mmol/L was found, and after 2 hours, it was 12.3 mmol/L;

cousin once removed (IV.6): 10 years 8 months (height 134 cm, weight 27 kg), BMI 15.0 kg/m2 (+1.3 SD). An increase in fasting glycemia to 6.3 mmol/l was detected by chance for the first time at the age of 9 years 2 months, with HbA1c of 6.2%. A diet with a restriction of easily digestible carbohydrates was recommended. When examined at the National Medical Research Center of Endocrinology at the age of 10 years and 3 months, HbA1c was 6.7%. No specific pancreatic antibodies were detected. During OGTT, IGT (plasma glucose 6.12–8.0 mmol/L) was detected, with preserved basal and stimulated secretion of insulin (insulin 4.45–14.68 μE/ml; C-peptide 1.0–2.86 ng/ml). Fasting glycemia is maximum up to 7.3 mmol/L, and after meals it is up to 10.9 mmol/L.

Given the particular course of the disease, the hereditary nature of carbohydrate metabolism disorder, MGT was performed for the patient. A heterozygous variant c.449T>A:p.F150Y was revealed in the GCK gene, described as pathogenic in MODY2 type DM. Similar mutations were found in a half-sister and a cousin once removed. A normal-calorie balanced diet with restriction of easily digestible carbohydrates was recommended to the patient, as well as controlled physical activity, self-monitoring of glycemia 1–2 times a week at different times of the day.
Fig. 1. Family tree of the patient I. Notes: CMD – carbohydrate metabolism disorder. MGT – molecular genetic testing.

<table>
<thead>
<tr>
<th>Roman numerals (I, II, etc.)</th>
<th>Generation of a family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabic numerals (1, 2, etc.)</td>
<td>Representatives of one generation</td>
</tr>
</tbody>
</table>

**Designations:**

- Female
- Male
- Marriage
- Children
- Male relatives with impaired carbohydrate metabolism (HVO) and mutation F150Y in gene GCK
- Male relatives with HVO, no genetic testing performed
- Male relatives without HVO, according to the patient
**DISCUSSION**

The glucokinase gene (*GCK*) is located on chromosome 7, has 10 coding exons and a coding sequence of 1398 base pairs. *GCK* is the first verified MODY candidate gene (1992) [20]. The main function of glucokinase is encoding of a protein of the hexokinase family (IV isotype). This protein is mainly expressed in hepatocytes and pancreatic cells and catalyzes the phosphorylation of glucose to form glucose-6-phosphate, which is the first step in most glucose metabolism pathways [21]. The activity of this enzyme is not inhibited by its product, glucose-6-phosphate, so it retains its activity even with an excess of glucose. In pancreatic beta cells, glucokinase acts as a sensor when the concentration of glucose in the blood changes (a kind of sensor), and the rate of insulin secretion depends on its enzymatic activity, which explains hyperglycemia during the inactivating mutation of the *GCK* gene (the body perceives hyperglycemia as normal). In the liver, glucokinase plays an important role in the absorption of glucose and its conversion to glycogen. It was determined that mutations causing the development of MODY2 type DM are distributed disproportionately in exons from 2 to 10 [22]. By 2018, 745 mutations in the *GCK* gene have been described [23]. No frequent mutations in the *GCK* gene were detected; each of them was determined mainly in one family [2, 23, 24].

In our group of patients, the following mutations in the glucokinase gene were revealed (Table 3).

**Table 3. Range of nucleotide changes detected in the GCK gene**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heredity</th>
<th>Nucleotide substitution</th>
<th>Amino acid substitution</th>
<th>Exon</th>
<th>gnomAD</th>
<th>HGMD</th>
<th>Pathogenicity</th>
</tr>
</thead>
</table>

Most cases of DM in the age category up to 40 years with normal body weight are classified as type 1 DM, less commonly as type 2 DM and are rarely reviewed. The absence of autoantibodies as a marker of DM1 is an extremely important component in the differential diagnostics of DM monogenic forms in young patients. The absence of antibodies to beta cell antigens, especially in the presence of a familial nature of the disease, is typical for monogenic forms of DM, but can be registered in less than 5% of patients with DM1. Long-lasting endogenous insulin secretion (with the disease duration of more than 3–5 years) is not typical for DM1 and is noted in MODY type DM. In all patients of the study group, specific pancreatic antibodies tests were negative.

The presence in several generations of family members with characteristic disorders of carbohydrate metabolism enables to suspect the monogenic nature of the disease with great probability, but this is also characteristic of DM2. Among the patients examined by us, in most cases, the disease was of a family nature, as in 10 patients, the first degree relatives had metabolic disorders of various severity. Due to the disease asymptomatic course, carbohydrate metabolism disorders remain undiagnosed for a long time, and only an active, purposeful examination of the next of kin enables to identify carbohydrate metabolism disorders in them. Thus, in the relatives of six patients of our group with impaired carbohydrate metabolism, similar mutations were found by the Sanger direct sequencing method.

The absence of signs of metabolic syndrome, obesity is one of the characteristic signs of MODY type DM and, in some cases, distinguishes it from DM2.

Carbohydrate metabolism disorders typical for MODY2 can be detected at any age. Moderate non-progressive hyperglycemia due to mutations in the GCK gene occurs from birth, but, remaining asymptomatic for a long time, it can be first detected after 18 years of age. In a comparative study by T.L. Kuraeva et al. of MODY2 and MODY3 in pediatric patients in Russia [2], it was shown that with MODY2, hyperglycemia is determined already since birth (in 13.4% under the age of 1 year, the minimum age is 1 month), in contrast to MODY3 (the minimum age for diagnosing the disease is 8 years). A situation is possible when young patients with an unspecified type of carbohydrate metabolism disorder or with an atypical course of DM1 become under the supervision of adult endocrinologists. In our group, in 7 out of 12 patients, carbohydrate metabolism disorders were detected before the age of 18 years. Of these, one patient was diagnosed with DM1 and insulin therapy was prescribed, the other was diagnosed with DM2, the DM type was not diagnosed in three patients, and two patients were diagnosed with IGT. Often, in patients with MODY type DM, the results of OGTT and HbA1c values do not meet the criteria for DM, which causes difficulties in formulating the diagnosis. IGT or impaired fasting glycemia do not contradict the diagnosis of MODY type DM, being its distinguishing characteristic. At different periods of the patient’s life, the OGTT and HbA1c results may vary slightly [25].

During pregnancy, glycemia rates in MODY2 patients are slightly increased and, as a rule, meet the criteria for overt DM. Intensified insulin therapy was prescribed to four patients of our group during pregnancy, followed by its withdrawal after delivery (N4, N7, N11, N12). One patient (N6) continued to follow a diet during pregnancy. Since MODY2 is inherited in an autosomal dominant manner, the risk of transmitting this mutation to a child is 50%. The choice of the treatment approach of MODY2 during pregnancy should be based on the fetus genotype, as only infants without mutations in the GCK gene are at risk of developing macrosomia under the influence of maternal hyperglycemia [26]. In the case when the mother and the child have mutations in the GCK gene, hyperglycemia does not require correction by insulin, and the child is born with normal weight [16, 27]. Children who inherit the mutation have the same homeostatic glucose level as their mothers, and perceive a higher glucose level as normal. In this case, hyperglycemia does not affect adversely the weight of the child. The risk of complications with the invasive method of prenatal screening to determine the fetus genotype (unless amniocentesis or chorionic biopsy is performed for more significant reasons) is the rationale for finding ways of non-invasive prenatal diagnostics (at present, pregnant women can undergo ultrasound with dopplerometry, a genetic testing of parents, cardiotocography, blood test for serum markers). An alternative to prenatal screening can be ultrasound fetometry every 2 weeks, starting from the week 26 of pregnancy. At the same time, accelerated fetal growth indicates indirectly the absence of an inactivating mutation in the fetal GCK gene, which is an indication for initiation of insulin therapy [28].

In 2012, A.T. Hattersley et al. [29] developed a simple MODY prediction model (using logistic regression) that can help identify cases suitable for further genetic testing. The model improved sensitivity from 72% to 91% and specificity from 91% to 94% to determine MODY compared to standard criteria. The ease of use of this development is the most attractive (Fig. 2). For our patient, the Positive Predictive Value of this method (PPV) is 75.5%, which suggests with high reliability that she has MODY. However, this online calculator can only be used in patients with manifestations of carbohydrate metabolism disorders under the age of 35 years and, therefore, is formally not applicable for patients with newly diagnosed carbohydrate metabolism disorders aged 35 years and older. For example, in our group, a male patient with second-degree obesity was first diagnosed with carbohydrate metabolism disorders at the age of 41 years (N10). This calculator is being finalized and modified [10, 29]. In pregnant women, other
criteria for diagnosing carbohydrate metabolism disorders are used, and therefore this calculator has limitations in this group of patients.

1. Возраст на момент постановки диагноза

2. Пол

3. В настоящее время лечение инсулином или ПССП?

4. Время до назначения инсулинотерапии

(если в настоящее время лечится инсулином)

5. ИМТ

6. HbA1c

7. Возраст на текущий момент

8. У кого-то из родителей есть диабет?

Fig. 2. The MODY calculator [5, 23]. Adapted from [30].
Confirmation of the inactivating mutation in the \textit{GCK} gene (MODY2), unlike other types of MODY, enables to refuse from insulin therapy or oral sugar-lowering therapy that is ineffective in typical cases. Thus, in our group, insulin therapy was canceled for 2 patients, and oral sugar-lowering drugs were withdrawn for 4 patients. During hospitalization, all patients reached their target glycemic levels with a low carbohydrate diet.

\textbf{CONCLUSION}

Clinical characteristics of the disease, such as borderline disorders of carbohydrate metabolism (impaired fasting glycemia, IGT), non-progressive for a long time, the absence of specific autoantibodies, and the absence of the effect of oral sugar-lowering therapy in young patients with normal body weight, especially in the presence of the family nature of the disease, require MGT to rule out MODY2 type DM.

\textbf{ADDITIONAL INFORMATION}

\textbf{Patient consent.} Upon admission to the hospital, the patient gave her consent to processing of personal data. Informed consent for the publication of the medical data presented in the article (in anonymized form) in the journal Diabetes Mellitus was received from the patient.

\textbf{Conflict of interest.} The authors declare no apparent or potential conflicts of interest related to the publication of this article.

\textbf{Contribution of authors.} A.A. Glibka was involved in the material processing, literature review, text writing, and design of the figures; I.V. Kononenko created the study concept and design, collected the material, and edited the text; N.A. Zubkova performed analysis of the MGT results, edited the text; A.Yu. Mayorov received final approval of the manuscript for publication; A.N. Tyulpakov performed MGT, was involved in final approval of the manuscript for publication; O.M. Schmidt typed the material. All authors made a significant contribution to the study and preparation of the article, read and approved the final version before its publication.

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