INTRODUCTION

Congenital hyperinsulinism (CHI) is a disease characterized by persistent hypoglycemia due to increased insulin secretion by β-pancreatic cells. CHI is associated with high risk of complications of chronic hypoglycemia, and therefore timely diagnosis of the disease and immediate initiation of therapy is a top-priority task. The choice of treatment tactics largely depends on the morphological form of the disease. Morphological form cannot be established based on clinical and laboratory presentation of the disease, ultrasound, MRI, computed and positron emission tomography (PET) with [18F]-fluorodeoxyglucose. Calcium stimulation test and percutaneous transhepatic blood sampling from the portal vein were previously used for differential diagnosis, but the results provided by these invasive studies are imprecise. At present, preoperative differential diagnosis of diffuse and focal forms of CHI is based on the data of genetic testing and radionuclide diagnosis ([18F]-DOPA PET). The article presents the first results of the use of [18F]-DOPA PET in CHI patients in the Russian Federation. Radionuclide study was performed in 17 patients with pharmacoresistant CHI followed by comparative analysis of the results of 18F-FDG PET/CT and histological picture of intraoperative pancreatic tissue samples, which is known as the gold standard for the differential diagnosis of HI histological forms.

Keywords: congenital hyperinsulinism, [18F]-DOPA, positron emission tomography.
subtotal pancreatectomy (resection of 95—98% of the pancreas) is required [4].

Focal CHI develops sporadically and is associated with a pathological mutation on the paternal allele in the \textit{ABCC8} or \textit{KCNJ11} genes in combination with a specific loss of the maternal allele in the 11p15.15 imprinting region [5]. Insulin hypersecretion in patients with focal CHI occurs in a limited adenomatous region. The medically unresponsive disease is observed in 96.2% of patients with focal CHI [6]. The optimal treatment for these patients is resection of the lesion with preservation of the remaining intact pancreatic tissue [7].

Given the differences in surgical tactics, a high risk of diabetes due to subtotal pancreatectomy [8], and the possibility of complete recovery of patients with focal CHI after resection of an adenomatous lesion, the preoperative differential diagnosis of a morphological CHI form is extremely important.

The morphological form of medically unresponsive disease can not be identified based only on clinical laboratory findings. A CHI form may be determined using molecular genetic testing. Such techniques as ultrasound, MRI, CT, and [18F]-fluorodeoxyglucose PET do not enable visualization of an adenomatous lesion. A calcium stimulation test and percutaneous transhepatic blood sampling from the portal vein were previously used to differentiate the diagnosis; however, high invasiveness and a low accuracy of these techniques initiated the search for other ways to diagnose the histological form of CHI [9].

Currently, the most accurate technique for differential diagnosis of diffuse and focal forms of CHI is [18F]-fluoroDOPA PET (sensitivity, 89%; specificity, 98%) [10].

The diagnostic efficacy of this technique is based on high uptake of [18F]-fluoroDOPA by \(\beta\)-cells overproducing insulin. During [18F]-fluoroDOPA PET, the uniformity of radiopharmaceutical (RP) uptake in the pancreatic tissue is visually evaluated, and the pancreatic index (PI) is calculated, whose value is used to differentiate between diffuse and focal forms of CHI in the examined patient [11, 12]. According to the international guidelines, [18F]-fluoroDOPA PET/CT findings are interpreted as diffuse CHI at PI of less than 1.30 and as focal CHI at PI of more than 1.50 [13].

A series of clinical cases

\textit{Examination standards and patient group description}

Seventeen CHI patients (11 females and 6 males) underwent [18F]-fluoroDOPA PET/CT at the Almazov National Medical Research Center. The diagnosis of CHI in all patients was established at the Endocrinology Research Center, based on hypoketotic hypoglycemia that persisted since the first days of life without reducing insulin levels. At the hospital, the patients also underwent molecular genetic testing to identify mutations responsible for the development of the disease. Despite ongoing insulinostatic therapy (diazoxide, somatostatin, glucagon), all patients experienced frequent episodes of hypoglycemia, which indicated the medically unresponsive form of CHI.

The age of children at the time of [18F]-fluoroDOPA PET/CT examination ranged from 2 months to 2 years 9 months (median, 3.45 months). All patients were under inpatient follow-up before and after the study. According to the international recommendations [13], pharmacological therapy with insulinostatic agents was discontinued in all patients 48—72 h before [18F]-fluoroDOPA PET. Normal blood glucose indicators were maintained by intravenous infusion of a glucose solution with glycemic control every 20 min. Given the need for general anesthesia, the patients had a hungry interval of 5 to 6 h: a peripheral intravenous catheter was placed for RP administration. The drug Propofol was used for general anesthesia. The drug dose was calculated based on the patient’s body weight. During PET, patients occurred in the supine position and were immobilized. The examination was conducted using a combined Discovery 710 PET/CT system (General Electric). The drug [18F]-fluoroDOPA was synthesized at the Department of Radiopharmaceutical Agent Production of the Almazov National Medical Research Center. [18F]-fluoroDOPA was administered as an intravenous bolus at a dose of 4 MBq per 1 kg body weight. CT was performed in a low-dose mode (40 mA, 80 kV) to correct photon energy absorption. PET data was acquired in a static mode: 10-minute scans were also recorded 10, 30, 40, 50, and 60 min after injection. After study completion, the children were followed-up at the Therapeutic Department.

PET images were evaluated in three planes: axial, frontal and, sagittal, as well as in a 3D reconstruction mode. In the presence of an [18F]-fluoroDOPA hyperfixation focus in the pancreas, the pancreatic index was calculated using a 10-minute scan acquired 50—60 min after RP administration: the ratio of the maximum standardized RP uptake index (SUV\textsubscript{max}) value in the [18F]-fluoroDOPA hyperfixation focus to the next lower SUV\textsubscript{max} value in apparently intact pancreatic parenchyma. In the case of a uniform RP distribution in the pancreatic parenchyma, SUV\textsubscript{max} was evaluated in the pancreatic head, body, and tail. According to the PET/CT [18F]-fluoroDOPA findings, the conclusion on the morphological form of CHI was made based on the visual data and PI index.

After surgery, pancreatic tissue morphology was studied in 16 children. One patient with suspected diffuse CHI did not undergo surgical treatment and morphological study due to relatively stable glucose indicators during treatment with a long-acting somatostatin analog and frequent feeding.

\textit{Examination findings}

According to the molecular genetic analysis, diffuse CHI was suggested in 7 children: homozygous, compound heterozygous, and dominant mutations in the \textit{ABCC8}, \textit{KCNJ11}, and \textit{HNF4a} genes were found in these patients (Table 1). Focal CHI was suspected in 10 patients in whom
heterozygous mutations were found on the paternal allele in genes encoding ATP-dependent potassium channels. On the basis of the [18F]-fluoroDOPA PET/CT findings, 7 out of 17 patients were diagnosed with diffuse CHI, and the remaining 10 patients were diagnosed with focal CHI. Physiological RP uptake was observed in the pancreas, liver, gallbladder, kidneys, and urinary tract. During the study, all children had increased RP uptake in the pancreatic head, which was considered as a norm, given the differences in β-cell density in different parts of the organ.

In patients with focal CHI (n=10), the median PI at the 50th—60th minutes of the examination amounted to 1.64 (1.14—3.51), and a significant increase in local RP uptake on PET images was also visually detected (Fig. 1A). A single focus of elevated RP uptake was detected in all patients of this group: in the pancreatic head (7 patients); in the body (1 patient); in the tail (1 patient); in one patient, the focus was located between the head and the body of the pancreas. The minimum and maximum scintigraphic size of the detected [18F]-fluoroDOPA hyperfixation focus was 1.32 and 22.00 mm, respectively.

In patients with diffuse CHI (n=7), the median PI at the 50th—60th minutes of [18F]-fluoroDOPA PET was 1.15 (1.02—1.42) (Fig. 1B). Except the pancreas, no other pathological RP uptake localizations were found in the examined patients.

**Discussion**

The issue of differential diagnosis of morphological CHI forms is particularly important in patients with the medically unresponsive disease. The first step in identification of the CHI form is molecular genetic testing due to its informativeness and minimal risks to the patient’s health. Despite the fact that a CHI form suggested in our patients based on molecular genetic testing fully coincided with the final histological diagnosis, this method may provide erroneous results. For example, a pathological heterozygous mutation on the paternal allele in patient 12 (Table 1) was detected only after repeated molecular genetic testing. Furthermore, according to the international literature, genetic mutations are not detected in 21% of patients based on molecular genetic testing fully coincided with the final histological diagnosis, this method may provide erroneous results. For example, a pathological heterozygous mutation on the paternal allele in patient 12 (Table 1) was detected only after repeated molecular genetic testing. Furthermore, according to the international literature, genetic mutations are not detected in 21% of patients based on molecular genetic testing fully coincided with the final histological diagnosis, this method may provide erroneous results. For example, a pathological heterozygous mutation on the paternal allele in patient 12 (Table 1) was detected only after repeated molecular genetic testing.

[18F]-fluoroDOPA PET/CT enables more accurate identification of the pathological CHI form and acquisition of visual data. The main calculated parameter in this examination is PI; if its value is less than 1.3, diffuse CHI is most likely; if the PI value is more than 1.5, the focal form is most likely. In our study, diffuse CHI was suspected in a patient with PI greater than 1.30. This child had increased RP uptake in the pancreatic head region (patient 3, PI=1.42), which may be associated with increased physiological uptake of [18F]-fluoroDOPA in this area. The absence of pathological mutations in the genes encoding ATP-dependent K+ channels also suggested the diffuse form of CHI.

Upon [18F]-fluoroDOPA PET/CT, the focal form of CHI was detected not only in patients with PI of more than 1.50 at the 50th—60th minutes of the examination but also in patients with PI of 1.15 (patient 6), 1.14 (patient 7), and 1.40 (patient 12). This conclusion was based on increased RP uptake in certain pancreatic regions (assessed visually) and the presence of mutations in the paternal ABCC8 and KCNJ11 genes, respectively. We think that the reduced PI is associated with increased RP uptake in the pancreatic head; the ratio of SUVmax in the pathological focus to SUVmax in the head area gave a lower value. In these examples, the ratio of SUVmax in the pathological focus and in the pancreatic tail region (PI) exceeded 1.50. Furthermore, upon calculating PI at the 10th min of examination in patients 6 and 7, this index was 1.60 and 1.83, respectively, which was associated with a smaller SUV value in the pancreatic head region in the specified time interval. The results of [18F]-fluoroDOPA PET/CT were confirmed by histological examination of surgical material. The obtained data indicate the need for complex use of both visual and calculated [18F]-fluoroDOPA PET data together with results of molecular genetic testing.

The [18F]-fluoroDOPA PET/CT data enabled preoperative assessment of the surgical intervention amount in patients with medically unresponsive CHI and identification of adenomatosis localization in the pancreas in focal CHI. According to several studies, [18F]-fluoroDOPA PET/CT have been recognized as a fairly accurate and effective technique in the differential diagnosis of histological CHI forms [10, 17—19]. We suggest conducting [18F]-fluoroDOPA PET/CT in the following categories of CHI patients: patients with medically unresponsive CHI and suspected focal CHI (inherited from the father or de novo heterozygous mutation in the KCNJ11 or ABCC8 gene); patients with medically unresponsive CHI and without identified pathological mutations in the genes characteristic of CHI; patients with medically unresponsive CHI and the presence of compound heterozygous mutations in the KCNJ11 or ABCC8 gene, as well as in the case of persistent hyperinsulinemic hypoglycemia in children with CHI after partial resection of the pancreas or subtotal pancreatectomy.

**Conclusion**

Patients with medically unresponsive forms of CHI need a timely differential diagnosis of the morphological form of disease, which further enables choosing the approach and extent of surgical intervention. [18F]-fluoroDOPA PET/CT is a rather sensitive and specific technique for solving the challenge. Both visual and calculated parameters should be considered in analysis of [18F]-fluoroDOPA PET/CT data. The development of a single protocol for [18F]-fluoroDOPA PET/CT in patients with CHI will increase the accuracy of this technique.
### Results of [18F]-fluoroDOPA PET in CHI patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age of manifestation, days</th>
<th>Age of diagnosis, months</th>
<th>Age of PET, months</th>
<th>Therapy before surgery</th>
<th>Genetics</th>
<th>SUV max</th>
<th>SUV pre-max</th>
<th>PI</th>
<th>PET findings</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1</td>
<td>0.7</td>
<td>2.87</td>
<td>gluc + oct</td>
<td>ABC8c.T259C:p.C87R, homozygous</td>
<td>2.22</td>
<td>2.17</td>
<td>1.02</td>
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<tr>
<td>2</td>
<td>F</td>
<td>1</td>
<td>0.24</td>
<td>7.39</td>
<td>diaz + oct</td>
<td>ABC8c.C2113T:p.R705X, heterozyg, on pat. allele</td>
<td>3.17</td>
<td>1.99</td>
<td>1.59</td>
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<tr>
<td>3</td>
<td>F</td>
<td>1</td>
<td>0.57</td>
<td>2.06</td>
<td>gluc + oct + glucagon</td>
<td>hNF4a.c.C387T:p.1129A, heterozyg</td>
<td>4.32</td>
<td>3.04</td>
<td>1.42</td>
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<td>4</td>
<td>M</td>
<td>2</td>
<td>0.7</td>
<td>3.3</td>
<td>gluc + oct</td>
<td>ABC8c.C1332+1delG, heterozyg, on pat. allele</td>
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<td>1.70</td>
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<tr>
<td>5</td>
<td>M</td>
<td>1</td>
<td>0.25</td>
<td>3.45</td>
<td>gluc + oct</td>
<td>ABC8c.C454G:p.S138S, heterozyg, on mat. allele</td>
<td>2.32</td>
<td>1.91</td>
<td>1.21</td>
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<td>6</td>
<td>F</td>
<td>2</td>
<td>1</td>
<td>6.81</td>
<td>oct</td>
<td>ABC8c.C436G:p.R1436G, heterozyg, on pat. allele</td>
<td>2.59</td>
<td>2.24</td>
<td>1.15</td>
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<tr>
<td>7</td>
<td>M</td>
<td>3</td>
<td>0.5</td>
<td>8.15</td>
<td>oct</td>
<td>kCNJ11c.A680G:p.E227G, heterozyg, on pat. allel</td>
<td>4.7</td>
<td>4.18</td>
<td>1.14</td>
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<tr>
<td>8</td>
<td>F</td>
<td>3</td>
<td>0.2</td>
<td>2.86</td>
<td>oct + food</td>
<td>ABC8c.C2521C:p.T841X, heterozyg, on pat. allele</td>
<td>1.51</td>
<td>1.01</td>
<td>1.50</td>
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<tr>
<td>9</td>
<td>M</td>
<td>6</td>
<td>1</td>
<td>3.13</td>
<td>oct + diet</td>
<td>ABC8c.G1705C:p.A569P, heterozyg, on pat. allele</td>
<td>2.66</td>
<td>1.28</td>
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<td>12</td>
<td>F</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>oct + diet</td>
<td>ABC8c.C332dupC:M.1109fs, heterozyg, on pat. allele</td>
<td>1.75</td>
<td>1.25</td>
<td>1.40</td>
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<tr>
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<td>0.5</td>
<td>3.4</td>
<td>oct with/without gluc</td>
<td>kCNJ11c.G617A:p.R206H, heterozyg, on mat. allele</td>
<td>3.74</td>
<td>2.99</td>
<td>1.25</td>
<td></td>
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<tr>
<td>14</td>
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<td>2</td>
<td>2</td>
<td>5.46</td>
<td>oct</td>
<td>ABC8c.T3629C:p.LI210P, heterozyg, on pat. allele</td>
<td>3.34</td>
<td>1.78</td>
<td>1.88</td>
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<tr>
<td>15*</td>
<td>F</td>
<td>1</td>
<td>0.03</td>
<td>4.53</td>
<td>somatuline</td>
<td>kCNJ11c.C761T:p.254L, G368A:p.V290M, heterozyg, on pat. allele, dominant</td>
<td>3.02</td>
<td>2.81</td>
<td>1.07</td>
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<tr>
<td>16</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>3.3</td>
<td>gluc + oct</td>
<td>ABC8c.C1923+2T&gt;A, heterozyg, on pat. allele</td>
<td>4.96</td>
<td>1.67</td>
<td>2.97</td>
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<tr>
<td>17</td>
<td>F</td>
<td>2</td>
<td>0.5</td>
<td>4.39</td>
<td>oct + diet</td>
<td>kCNJ11c.C1327T:p.Q444H, heterozyg, on pat. allele</td>
<td>5.93</td>
<td>1.69</td>
<td>3.51</td>
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</tr>
</tbody>
</table>

**Notes:**
- [18F]-DOPA PET/CT was performed in 17 patients (median age at study was 3.9 months). On the basis of [18F]-DOPA PET findings, 10 out of 17 patients were diagnosed with focal CHI (foc), and 7 patients were detected with diffuse CHI (diff), which was confirmed by histological examination of postoperative material.
- This patient did not undergo histological examination due to the lack of sufficient indications for surgical treatment.
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ИНФОРМАЦИЯ

КАК ЦИТИРОВАТЬ:
Губаева Д. Н., Меликян М. А., Рыжкова Д. В., Митрофанова Л. Б., Никитина И. Л. Дифференциальная диагностика морфологических форм врожденного гиперинсулинизма методом ПЭТ/КТ с [18F]-фторДОФА. // Проблемы эндокринологии. — 2018. — Т. 64. — № 5. — С. 306-311. doi: https://doi.org/10.14341/probl9726

ТО СЦИТЕ THIS ARTICLE:

*Fig. 1, A.* Results of positron emission tomography with 18F-DOPA: a focal form of CHI.
A focus of increased RP uptake in the pancreatic body and head region in patient 7 with focal CHI. PI at the 50th—60th minutes of examination was 1.14, whereas it was 1.6 at the 10th—20th minutes.

*Fig. 1, B.* Results of positron emission tomography with 18F-DOPA: a diffuse form of CHI.
Uniform RP uptake in a patient with diffuse CHI. PI at the 50th—60th minutes of examination was 1.15.