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Early diagnosis of Alzheimer's disease: potential of ^{18}F-FDG PET as a biomarker of neurodegeneration

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ABSTRACT

BACKGROUND: Dementia is considered one of the most actual medical problems of our time, being one of the main causes of disability among the elderly, and its prevalence will only increase in the coming years. The first place among conditions leading to dementia is given to Alzheimer's disease (up to 70%). The effectiveness of Alzheimer's disease therapy largely depends on the timeliness of diagnosis, which leads to the need to search for diagnostic markers that allow to detect the disease at the earliest stages.

AIM: To evaluate the possibilities of using ^{18}F-FDG PET for the early diagnosis of Alzheimer's disease.

MATERIALS AND METHODS: Cerebral metabolism was assessed using positron emission tomography with ^{18}F-FDG. A total of 183 patients were divided into groups depending on their diagnosis and the severity of cognitive impairment.

RESULTS: A characteristic pattern of cerebral metabolic disorders has been established in patients with Alzheimer's disease. It can be detected in the early pre-dementia stages and has developmental features as the disease progresses. The pattern was characterized by bilateral hypometabolism in the parietal and temporal cortex with a predominance in its mediobasal sections. An important marker of the development of the neurodegenerative process was a metabolic disorder of the cingulate gyrus, the posterior sections of which are affected already at the earliest stages of the disease, while the involvement of its anterior sections reflects the transition to the stage of severe dementia. Described metabolic disorders prevailed in the dominant (left) brain hemisphere at all stages of the disease.

CONCLUSION: Currently ^{18}F-FDG PET can be considered the most informative of the available methods for the early diagnosis of Alzheimer's disease which have a fairly high degree of accuracy.

Keywords: Alzheimer's disease; cerebral metabolism; cognitive disorders; dementia; neuroimaging; positron emission tomography; mild cognitive impairment.

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Ранняя диагностика болезни Альцгеймера: возможности ПЭТ с ^{18}F-ФДГ как биомаркера нейродегенерации

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АННОТАЦИЯ

Актуальность. Деменция — это одна из самых важных и актуальных медицинских проблем современности, поскольку очень часто является причиной инвалидизации лиц пожилого возраста, а ее распространенность в ближайшие годы будет только увеличиваться. Первое место среди состояний, приводящих к деменции, занимает болезнь Альцгеймера (до 70 % всех деменций). Эффективность ее терапии во многом зависит от своевременности постановки диагноза, что приводит к необходимости поиска диагностических маркеров, позволяющих выявлять заболевание на максимально ранних стадиях.

Цель исследования: оценить возможности применения позитронно-эмиссионной томографии с ^{18}F-ФДГ в диагностике заболеваний, сопровождающихся развитием расстройств высших корковых функций, и целесообразность использования метода в целях ранней диагностики болезни Альцгеймера.

Материалы и методы. Проведено комплексное обследование 183 пациентов с разной нозологией и степенью тяжести когнитивного дефицита. Метаболизм разных отделов головного мозга изучался посредством позитронно-эмиссионной томографии с ^{18}F-ФДГ, совмещенной с компьютерной томографией.

Результаты. Установлено, что у пациентов с болезнью Альцгеймера имеется характерный паттерн нарушения церебрального метаболизма, выявляемый уже на додементных стадиях, который имеет определенные закономерности развития по мере прогрессирования заболевания. Данный паттерн характеризуется билатеральным гипометаболизмом в области теменной и височной коры с преобладанием в медиобазальных ее отделах. Важным маркером развития нейродегенеративного процесса является нарушение метаболизма поясной извилины, задние отделы которой страдают уже на самых ранних стадиях заболевания, тогда как вовлечение передних ее отделов отражает переход на уровень более тяжелого когнитивного дефицита. Кроме того, в динамике развития заболевания дополнительно регистрируется вторичный гипометаболизм в затылочной коре, поясной извилине (все отделы) и лобной коре. Отмечена тенденция к преобладанию описанных метаболических нарушений в доминантном (левом) полушарии головного мозга на всех стадиях заболевания.

Заключение. Выявление определенного паттерна гипометаболизма с помощью позитронно-эмиссионной томографии с ^{18}F-ФДГ, совмещенной с компьютерной томографией, дает возможность осуществлять раннюю дифференциальную диагностику болезни Альцгеймера с достаточно высокой точностью, при этом позитронно-эмиссионная томография с ^{18}F-ФДГ является наиболее информативной из доступных для практического использования методик, отражающих начальный этап нейродегенеративных изменений.

Ключевые слова: болезнь Альцгеймера; деменция; когнитивные расстройства; нейровизуализация; позитронно-эмиссионная томография; церебральный метаболизм; умеренное когнитивное расстройство.

Как цитировать

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阿尔茨海默病的早期诊断：^{18}F–FDG PET作为神经退行性标志物的应用潜力

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摘要

背景。痴呆症是当今最重要和紧迫的医学问题之一，因为它是导致老年人残疾的主要原因之一，且其发病率在未来几年内将继续增加。阿尔茨海默病是导致痴呆的主要原因，占所有痴呆病例的70%。治疗效果在很大程度上依赖于及时诊断，因此需要找到能够在早期阶段检测疾病的诊断标志物。

研究目的。评估^{18}F–FDG PET在诊断伴随高级皮层功能障碍的疾病中的应用潜力，并验证该方法在阿尔茨海默病早期诊断中的有效性。

材料和方法。对183名具有不同疾病类型和认知缺陷程度的患者进行了综合检查。利用^{18}F–FDG PET结合CT分析不同脑区的代谢状况。

结果。发现阿尔茨海默病患者在痴呆前阶段即存在特征性的脑代谢异常模式，且随着疾病进展呈现一定规律性。该模式表现为双侧顶叶和颞叶皮层区域的低代谢，尤其在内侧基底部区域更为显著。扣带回的代谢异常是神经退行性过程的重要标志，后部区域在疾病最早期即受到影响，而前部区域受累则标志着更严重的认知缺陷。此外，随着疾病的进展，还观察到枕叶皮层、全扣带回以及额叶皮层的继发性低代谢。代谢异常在大脑优势半球（左半球）更为显著。

结论。通过^{18}F–FDG PET结合CT检测特定的低代谢模式，可以实现阿尔茨海默病的早期鉴别诊断，并具有较高的准确性。^{18}F–FDG PET是目前临床实践中识别神经退行性变化早期阶段的最具信息量的方法之一。

关键词：阿尔茨海默病；痴呆；认知障碍；神经影像学；正电子发射断层扫描；脑代谢；轻度认知障碍。

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BACKGROUND

The growing prevalence of dementia-causing diseases is one of the most urgent medical challenges nowadays. According to the World Health Organization, there are 55 million patients with dementia worldwide, with approximately 10 million new cases reported each year. At the same time, the older and senile population is steadily growing, which will undoubtedly increase the incidence and prevalence of dementia. This is supported by existing data on the incidence of dementia, accounting for 1 per 100 cases per year in patients aged 65–70 years and 4 per 100 cases per year in patients over 80 years [1]. The incidence of predementia syndromes in patients over 65 years is approximately 20% [2].

According to numerous epidemiology studies, Alzheimer's disease (AD) account for 60%–70% of all cases of dementia in older patients. The mean predicted risk of AD in patients over 85 years is 10%–11% for males and 14%–17% for females.

AD is typically defined as a chronic neurodegenerative disease with a gradual, concealed onset in the presenile or senile age and progressive deterioration of memory and other cognitive functions, resulting in dementia with a distinct complex of neuropathological, neuroimaging, and biochemical signs [3].

The criteria proposed in 1984 by the National Institute of Neurological Disorders and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (NINCDS-ADRDA) are currently used for the diagnosis of AD [4]. These criteria provide for making a "possible" or "probable" diagnosis of BA. A definite diagnosis can only be made after a neuropathological assessment with the determination of typical disease markers.

When applying these criteria, the presence of dementia syndrome is critical, which does not take into account the early stages of AD. At the same time, characteristic pathology findings have been identified, which can be detected during all stages of the disease, including predementia and even presymptomatic stages. These include amyloid beta (Aβ) accumulation and abnormal tau changes with the formation of neurofibrillary tangles, resulting in impaired synaptic transmission and subsequent neuronal death.

In 2011, an expert panel from the National Institute on Aging (NIA) and the Alzheimer's Association (AA) proposed a clearer demarcation between clinical manifestations and underlying pathomorphological and pathophysiological mechanisms of the disease [5]. A concept of early biomarker-based diagnosis of AD has been developed, allowing for intravital detection of typical pathophysiological signs reflecting pathology findings characteristic of AD. The diagnostic criteria were reviewed in 2018, supporting the neurobiological approach to AD classification based on existing biomarkers [6].

The most valuable biomarkers for early AD diagnosis have been identified. These include the following main categories (ATN algorithm): 1) A: signs of amyloidosis (amyloid deposits in the brain on positron emission tomography (PET) with corresponding ligands and decreased Aβ42 levels in the cerebrospinal fluid (CSF); 2) T: signs of impaired tau protein structure (tau protein accumulation on PET with corresponding ligands and increased phosphorylated tau levels in the CSF); 3) N: signs of neurodegeneration (increased total tau levels in the CSF and regional hypometabolism on 18F-fluorodeoxyglucose PET [^{18}F-FDG PET]) and signs of brain atrophy on MRI [6]. It was proposed to make the diagnosis of AD if amyloidosis and taupathy markers are detected, even in the absence of clinical signs. Moreover, the potential for expanding these categories is considered, as well as the introduction of new biomarker groups: inflammation, synuclein, and vascular (I, S, and V, respectively).

The International Working Group (IWG) also presented new criteria in 2007, which were subsequently reviewed in 2010, 2014, and 2021. In contrast to the NIA-AA criteria, the diagnostic value of a biomarker should be interpreted only in the presence of a corresponding clinical phenotype (phenotype positive AD) [7].

These innovations modified the understanding of AD, shifting the concept from a clinical pathomorphological to neurobiological condition, which allows the disease to be confirmed during the mild cognitive impairment (MCI) stage.

Predementia stages are currently gaining greater attention due to the high risk of progression during early stages of AD, as well as the potential higher efficacy of therapy prior to the onset of dementia. In real-world clinical practice, the annual rate of MCI progression to dementia is 5%–20% [8]. Amnestic MCI has the least favorable prognosis, with a progression rate up to 40% within 5 years. The polyfunctional damage (episodic memory impairment with a concomitant deficiency in another domain, with frequent visuospatial, regulatory, or speech impairments) has an additional impact [9]. The presence of positive biomarkers can increase the risk of progression by 11 times compared to the absence of positive biomarkers [10].

The findings of the long-term observational study Alzheimer's Disease Neuroimaging Initiative (ADNI) allowed identifying the most valuable biomarkers in each category (ATN). These include the following: A: Aβ 42/40 ration in the CSF; T: tau protein accumulation on PET with tau ligands; N: hypometabolism on ^{18}F-FDG PET [11].

Unfortunately, only a few facilities in Russia currently have the capacity to detect CSF biomarkers, and PET with amyloid and tau ligands is expensive. Thus, ^{18}F-FDG PET, which allows for minimally invasive assessment of metabolic activity in various brain structures, can be considered the most available neurodegeneration marker, which is of both scientific and practical interest [12, 13].

Researchers of the Department of Nervous Diseases of the Military Medical Academy performed a series of studies to assess the efficacy of ^{18}F-FDG PET in the early differential diagnosis of cognitive impairments of various origin [14–16].

Study aim: to assess the efficacy of ^{18}F-FDG PET in the differential diagnosis of various conditions associated with cognitive impairments. Based on the preliminary findings, the study aim was expanded to include an assessment of the method's potential application in the early diagnosis of AD.

MATERIALS AND METHODS

A total of 183 patients were included in the study at various stages. Of these, 55 had AD, 58 had various phenotypes of vascular dementia, 21 had mixed dementia, 25 had amnestic MCI, and 24 had dysregulatory MCI.

The criteria proposed by Petersen (2005) were used for the diagnosis of MCI. Dementia syndrome was confirmed using the criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD10) [17]. The type of dementia was determined using the NINCDS-ADRDA criteria for Alzheimer-type dementia and the NINDS-AIREN criteria for vascular dementia [4, 18]. The severity of cognitive impairment was assessed using the Clinical Dementia Rating (CDR).

The studies were performed in the Military Medical Academy using the Biograph PET/CT scanner (Siemens, Germany) and in the Russian Research Center of Radiology and Surgical Technologies using the Ecat Exact 47 and Ecat Exact HR+ scanners (Siemens, Germany). The brain metabolic activity was assessed using the 2-deoxy-2[18F]fluoro-D-glucose radioligand (half-life: 110 minutes; volume activity: 300–700 MBq/mL). Standard preparation for the study included a 6-hour fasting and control blood glucose measurement. The radioligand was administered intravenously at a dose of 100 MBq/m^2 body surface area. A PET/CT protocol with a total time of 10 minutes was used.

Data post-processing involved a quantitative measurement of the radioligand standardized uptake value (SUV). Data post-processing was performed according to the standard procedure and included the calculation of the ratios of radioactivity parameters in the examined area to the symmetrical area of the contralateral hemisphere and the mean cortical activity. The examined areas included the cerebral cortex, hippocampal formation, anterior cingulate gyrus, posterior cingulate gyrus, and subcortical structures, including the thalamus and basal ganglia. The resulting ratios were presented as percentages. Changes in the metabolic activity that exceeded 10% of the mean cortical metabolism were considered diagnostically significant.

RESULTS

The first stage of the study identified the basic pattern of metabolic disorders characteristic of AD, which includes three forms:

1) A symmetrical decrease in parietotemporal cortex metabolism in both hemispheres;

2) A symmetrical decrease in parietotemporal cortex metabolism in both hemispheres, most prominent in the hippocampal plane;

3) A diffuse decrease in cerebral cortex metabolism.

At all stages of the disease, the most severe hypometabolism was observed in mediobasal areas of the temporal lobes, as well as in the hippocampal formation. Significant differences were observed when assessing radiopharmaceutical uptake in the parietotemporal cortex relative to other brain structures, as well as when comparing with vascular cognitive impairments. The posterior cingulate gyrus was another diagnostically valuable area, with significant differences in metabolic disorders [16].

Moreover, the metabolic activity of various cingulate gyrus portions depending on the severity of cognitive impairments was assessed. Given a sufficient number of observations, several distinct patterns of metabolic changes in the cingulate gyrus were identified. It was found that mild and moderate Alzheimer-type dementia stages are associated with decreased radioligand uptake, primarily in the posterior portions, while severe dementia is characterized by hypometabolism in all portions of the cingulate gyrus [14].

In mild Alzheimer-type dementia, the most severe decrease in metabolism is observed in the hippocampal plane. The progression of cognitive deficiency was associated with a further decrease in parietotemporal cortex metabolism, which was symmetrical and relatively selective compared to other examined areas (Figure 1).

Decreased metabolic activity in the anterior cingulate gyrus was only observed in severe Alzheimer-type dementia, accompanied by hypometabolism in the occipital cortex, indicating further progression of neurodegeneration (Figure 2).

Thus, steady progression of neurodegeneration in AD patients causes a further bilateral decrease in parietotemporal cortex metabolism, a decrease in metabolic activity in the posterior cingulate gyrus, and the formation of new hypometabolism areas (anterior cingulate gyrus, frontal cortex, and occipital cortex) [14].

The first stage of the study confirmed the metabolic activity profile in patients with mild Alzheimer-type dementia, indicating the likelihood of similar changes already during the predementia stage.

The second stage of the study assessed metabolic activity in patients with amnestic MCI. It was found that this stage of cognitive deficiency is already associated with

decreased radioligand uptake in the hippocampal formation, temporal cortex, parietal cortex, frontal cortex, cingulate gyrus (bilaterally), or dominant hemisphere. The decrease in metabolic activity was more pronounced in the temporal lobes, particularly in hippocampal structures [16]. In contrast to the findings of metabolism assessment in patients with Alzheimer-type dementia, hypometabolism was more severe in the corresponding areas of the dominant (left) hemisphere (25%). Moreover, a unilateral (left-side) decrease in metabolic activity was relatively common (32%) [16].

Thus, the comparative analysis revealed characteristic features of the progression of neurodegenerative changes in AD. During the predementia stage (MCI stage), metabolic activity decreases in the hippocampal formation, temporal cortex, and posterior cingulate gyrus, with more pronounced changes in the dominant hemisphere. The progression of cognitive impairments is associated with increased hypometabolism in the aforementioned structures, as well as the development of metabolic disorders in the anterior cingulate gyrus, parietal cortex, and frontal cortex [16].

DISCUSSION

There have been significant advancements in the differential diagnosis of cognitive impairments. A comprehensive approach involving various examination methods (clinical, neuropsycological, laboratory, imaging, and neuroimaging) makes it possible to determine the type of cognitive impairment already in the early stages. Functional neuroimaging is of special interest, because this method allows detecting perfusion and metabolism disorders in various brain structures during the cognitive deficiency stages, where conventional techniques (CT and MRI) have lower sensitivity and specificity [15]. Intravital assessment of the brain metabolic activity has recently become available. It is performed using proton magnetic resonance spectroscopy, providing for a quantitative measurement of the key metabolite levels in various brain structures, and PET/CT to assess changes in the ^{18}F-FDG radioligand uptake. According to the literature and our own experience, ^{18}F-FDG PET is currently the most effective intravital imaging technique in terms of critical biological and physiological responses, as well

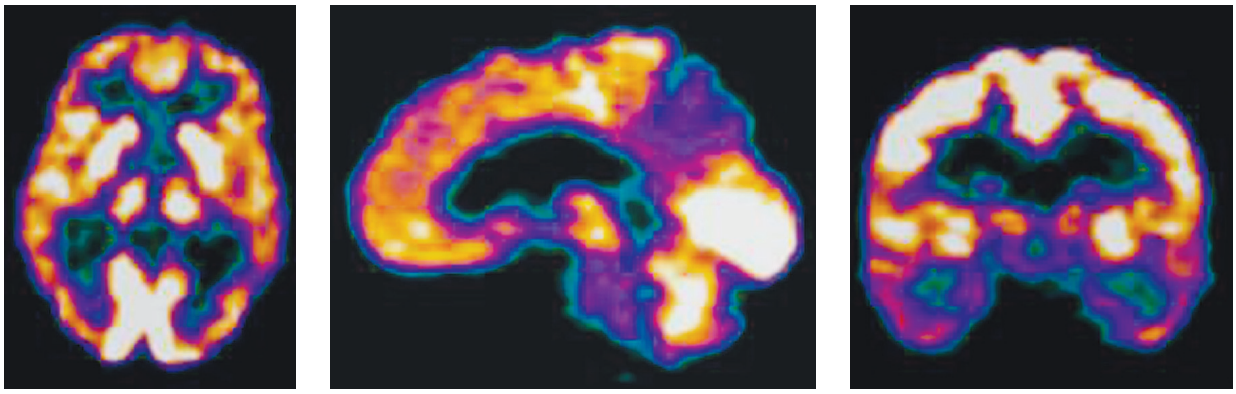

Fig. 1. Alzheimer's disease, mild dementia: impaired accumulation of ^{18}F-FDG in the projection of the parietal, temporal lobes, hippocampus, posterior cingulate gyrus
Рис. 1. БА, легкая деменция: нарушение накопления ^{18}F-ФДГ в проекции теменных, височных долей, гиппокампов, заднего отдела поясной извилины

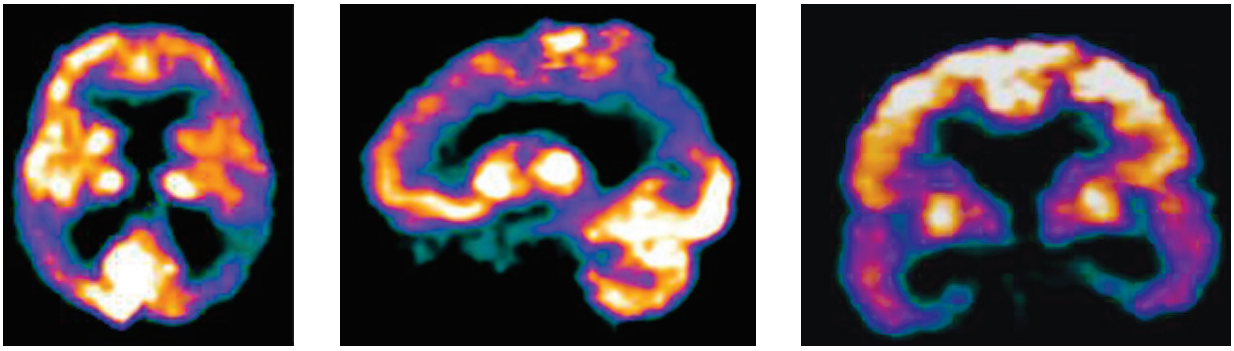

Fig. 2. Alzheimer's disease, severe dementia: pronounced metabolic disorders in the parietal, temporal lobes, hippocampus on both sides, anterior and posterior cingulate gyrus
Рис. 2. БА, тяжелая деменция: выраженное нарушение метаболизма в теменных, височных долях, гиппокампах с обеих сторон, переднем и заднем отделах поясной извилины

as pathophysiological processes in the brain, such as metabolic activity, substance transport, ligand-receptor interactions, gene expression, etc. [19].

Post-processing of ^{18}F-FDG PET findings revealed several patterns of brain metabolic activity changes during various cognitive deficiency stages in Alzheimer-type dementia, which is consistent with the findings of other studies. According to several foreign authors, a decrease in metabolic activity in the hippocampal formation and posterior cingulate gyrus can serve as an AD biomarker with sufficient sensitivity and specificity [20, 21]. Bilateral temporal and parietal hypometabolism was the predominant pattern of metabolic disorders. Metabolic activity disorders observed during the predementia stage (amnestic MCI) generally corresponded to changes characteristic of AD during the dementia stage. Moreover, a clear relationship was discovered based on the comparative assessment of metabolic activity parameters in brain structures most significant for Alzheimer-type dementia (mediobasal areas of the temporal lobes, including the hippocampus) and neuropsycological examination findings with a detailed assessment of memory functions. The discovery of metabolic disorders in the posterior cingulate gyrus during the early AD stages, including predementia stages, was both intriguing and clinically relevant. Many authors consider this phenomenon a sufficiently specific sign of AD [22].

Moreover, according to the literature, ^{18}F-FDG PET detects functional changes in brain metabolism in patients at high risk of AD, even in the presymptomatic stage. Metabolic disorders similar to those in AD were observed in asymptomatic carriers of mutations in the amyloid precursor protein gene, presenilin gene, and APOE-ε4 allele, as well as in patients with a family history of AD [23–25]. Changes in metabolic activity can be detected more than 15 years before the onset of first clinical symptoms [26].

Thus, a decrease in glucose metabolism in mediobasal areas of the temporal lobes, including the hippocampus, and the posterior cingulate gyrus can be considered an early clinically significant sign. The severity of hypometabolism corresponds to the severity of memory impairment. The course and progression of metabolic disorders can reflect the progression of neurodegeneration in AD, which starts in posterior brain structures and gradually involves anterior structures.

A decrease in metabolism according to ^{18}F-FDG PET findings in the most accurate and early sign among neurodegeneration biomarkers. Thus, it may be reasonable to create an individual biomarker category for these changes, indicated as M (metabolism), and expand the ATN classification to ATMN.

CONCLUSION

Based on the literature review and the analysis of our own study findings, we can conclude that ^{18}F-FDG PET is a promising method for the early diagnosis of Alzheimer-type cognitive impairments, including during the MCI stage. Glucose hypometabolism (predominantly bilateral) in the hippocampus, posterior cingulate gyrus, and parietal cortex is the primary biomarker of brain metabolic activity in AD during the predementia stages. The detection of a specific hypometabolism pattern using ^{18}F-FDG PET/CT allows for the early differential diagnosis of AD with sufficient accuracy. Moreover, ^{18}F-FDG PET is the most informative technique available in clinical practice, reflecting the initial stage of neurodegenerative changes.

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