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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Distribution of β -amyloid and pTau in brain cortex depending on age and mental state

Alexandra V. Sentyabreva^{1,2}  , Olyesya A. Vasyukova¹ , Yana A. Zorkina^{3,4} ,
Alisa V. Andryuschenko^{3,5} , Georgy P. Kostyuk^{3,6,7} ,
Irina Z. Eremina⁸ , Anna M. Kosyreva^{1,2} 

¹ Avtsyn Research Institute of Human Morphology of “Petrovsky National Research Centre of Surgery”, Moscow, Russian Federation

² Research Institute of Molecular and Cellular Medicine, RUDN University, Moscow, Russian Federation

³ Scientific and Clinical Research Center for Neuropsychiatry, Alekseev Psychiatric Clinical Hospital No. 1, Moscow, Russian Federation

⁴ Serbsky National Medical Research Center for Psychiatry and Narcology, Moscow, Russian Federation

⁵ Lomonosov Moscow State University, Moscow, Russian Federation

⁶ Russian Biotechnological University (ROSBIOTECH), Moscow, Russian Federation

⁷ Sklifosovsky Institute of Clinical Medicine, Sechenov University, Moscow, Russian Federation

⁸ Medical Institute, RUDN University Moscow, Russian Federation

 alexandraasentyabreva@gmail.com

Abstract: Relevance. Alzheimer’s disease (AD) is the most cause of disability and dementia, which is the 7th leading cause of death worldwide. Diagnosis of AD includes detection of amyloid plaques and hyperphosphorylated tau protein (pTau) in the brain. However, in recent years the amyloid hypothesis of AD development has been criticized and revised, and a growing pool of data emerges indicating more complex pathogenetic mechanisms leading to neurodegeneration in AD. The aim of our work was to evaluate the presence and distribution of amyloid plaques and pTau fragments in different regions of the cerebral

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cortex in patients > 60 years old with diagnosed dementia and without cognitive impairment, as well as in people < 60 years old. **Materials and Methods.** The amount of β -amyloid and pTau fragments in three groups of patients was measured on IHC stained histological sections in the regions of parahippocampal, temporal, and occipital cortex. **Results and Discussion.** Amyloid plaques were detected in all patients over 60 years of age (with and without dementia), while in younger individuals 60 years of age they were found in 66% of cases. The largest amyloid- β burden was observed in the occipital cortex. pTau was detected in all cortical areas in the three groups of patients. Also, the amount of pTau was higher in the occipital cortex in patients over 60 years of age both with and without dementia than in the group of people under 60 years of age. **Conclusion.** Thus, accumulation of pTau occurs earlier than β -amyloid. The amount of pTau was higher in patients over 60 years of age with clinically manifested dementia, while in some regions the amount of amyloid conglomerates is higher in cognitively intact patients. The findings point to much more complex mechanisms of the neurodegenerative diseases development with the formation of amyloid plaques being a consequence rather than cause of the disease.

Keywords: Alzheimer's disease, β -amyloid, tau-protein, age-related diseases

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Introduction

Alzheimer's disease (AD) is the most cause of disability and dementia, which is the 7th leading cause of death worldwide. [1]. AD is an age-related disease and usually occurs in older people >60—65 years of age. AD also refers to socially significant pathologies, which means that social support should be provided from the federal budget in accordance with Federal Law N 323-FZ “On the fundamentals of protecting

the health of citizens in the Russian Federation” [2]. Limited epidemiological studies and extrapolation of data obtained in other countries suggest that in 2020, in the Russian Federation there could live about 1.4 million patients with AD, while by 2035, their number will reach 2—3.6 million [3]. However, there is still no unified registry for patients with AD, as well as accessible and effective methods of intravital diagnostic approaches, especially early ones, which would allow validating the

diagnosis [4]. Only about 10% of all cases are taken into account in official morbidity statistics [5]. Current clinical guidelines indicate that the main part in the pathogenesis is violation of metabolism of amyloid precursor protein (APP) and the formation of insoluble β -amyloid conglomerates, as well as accumulation of hyperphosphorylated tau protein, which stabilizes the neuronal cytoskeleton microtubules. According to the amyloid theory, its hyperphosphorylation is initiated by already formed amyloid plaques. While the clinical manifestation and severity of the disease depends on the accumulation and distribution of these pathognomonic morphological AD signs [6, 7]. However, in recent years, the amyloid hypothesis of AD development has been criticized and revised, while a growing pool of data indicate much more complex pathogenetic mechanisms leading to neurodegeneration in AD. The aim of our work was to evaluate the presence of amyloid plaques and hyperphosphorylated tau protein fragments, as well as their distribution in different regions of the cerebral cortex, in patients >60 years old with diagnosed dementia and without cognitive impairment, as well as in people <60 years old.

Materials and Methods

Patients

Autopsy material for a retrospective study and anamnesis data from the medical records of patients >60 years old with diagnosed dementia were provided by the pathology department of Alekseev Psychiatric Clinical Hospital No. 1. Autopsy material and medical history data from patients >60 years of age without diagnosed dementia and patients <60 years of age were provided by the pathology department of the City Clinical Hospital No. 31 of the Moscow Department of Health (Table). Pathoanatomical autopsies were carried out in accordance with the order of the Ministry of Health of the Russian Federation No. 354n dated 06.06.2013 "On the procedure for conducting pathological autopsies". The study was approved by the local ethics committee of Alekseev Psychiatric Clinical Hospital No. 1 (Protocol No. 2 of October 28, 2020).

Immunohistochemical and morphometric study

After fixing brain tissue samples (fragments 1x1x0.5cm) in 10% buffered formalin (BioVitrum, Russia), they were processed through alcohols of increasing concentration and poured into histomix according to the standard protocol, after which histological sections 5 μ m thick were prepared. Immunohistochemical staining, morphological and morphometric assessment of histological preparations of the brain were carried out. Primary antibodies used: anti-A β 1—42 1:1000 (ab201060, Rabbit); anti-TAU-2 1:1000 (sigma5530, Mouse); secondary antibodies: Donkey-anti-Rabbit HRP 1:500 (Novex lifetechnologies A16035); Goat-anti-Mouse HRP 1:500 (ab6789). The average number of amyloid plaques was assessed at a magnification of x100 (standard field of view 96,000 μ m²), and fragments of phosphorylated tau protein (pTau) — at a magnification of x400 (field of view 25,000 μ m²). Counting was carried out in the areas of the parahippocampal, temporal and occipital cortex. The areas were recommended by the National Institute on Aging — Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease [8].

Statistical analysis

The morphometric study data were statistically processed using GraphPad Prism 8.1 software. Statistical differences between groups were assessed by multiple comparisons using the nonparametric Kruskal — Wallis test with the Dwass — Steele — Crichlow — Fligner post-hoc test. $p < 0.05$ differences between groups were considered significant.

Results and Discussion

In the group of patients with clinically confirmed dementia, β -amyloid deposits were detected in 100% of cases, while the size of amyloid plaques and the intensity of their staining varied significantly both between cortical regions in one patient and between patients in the corresponding cortical regions. In the occipital and temporal regions of the cortex, these structures were observed in 100% of cases, while in the parahippocampal region of the cortex they were found only in 66% (4/6) of patients (Fig. 1).

Table

Data from medical records of patients included in the study

Patient	Age	Sex	Major disease	Age-related diseases
Patients > 60 years with diagnosed dementia				
N1	84	F	Diffuse small-focal cardiosclerosis. Stenosing atherosclerosis of the coronary arteries	Hypertension, atherosclerosis
N2	86	F	Diffuse small-focal cardiosclerosis. Stenosing atherosclerosis of the coronary arteries	Hypertension, atherosclerosis
N3	74	F	Diffuse small-focal cardiosclerosis. Stenosing atherosclerosis of the coronary arteries	Hypertension, diabetes mellitus type 2, atherosclerosis
N4	75	F	Diffuse small-focal cardiosclerosis. Stenosing atherosclerosis of the coronary arteries	Hypertension, atherosclerosis
N5	89	F	Cardiac arrhythmia, unspecified	No data
N6	82	F	Postinfarction cardiosclerosis	No data
Patients > 60 years without diagnosed dementia				
N7	94	F	Postinfarction cardiosclerosis	Hypertension, atherosclerosis
N8	72	F	Chronic cerebral ischemia with encephalopathy	Hypertension, atherosclerosis
N9	98	F	Ischemic cardiomyopathy, atherosclerosis of the coronary arteries	Diabetes mellitus type 2, Hypertension, atherosclerosis
N10	76	F	Ovarian adenocarcinoma	Atherosclerosis
Patients < 60 years				
N11	52	F	Neuroendocrine tumor of the pancreas tail	Hypertension, atherosclerosis
N12	48	F	Child-Pugh C alcoholic liver cirrhosis	Hypertension, atherosclerosis
N13	58	M	Adenocarcinoma of the colon splenic flexure	Hypertension, atherosclerosis
N14	47	M	Child-Pugh C liver cirrhosis of mixed origin (HCV + toxic)	None
N15	48	M	Adenocarcinoma of the sigmoid colon	None
N16	39	M	Pancreatic necrosis	None

Similar morphological changes were observed in a group of elderly patients without diagnosed dementia. Conglomerates of β -amyloid were also detected in all samples of the occipital and temporal cortical regions, while in the parahippocampal region were visualized in 75 % (3/4) of patients (Fig. 1).

At the same time, in the group of patients < 60 years old, amyloid plaques were detected in only 66 % (4/6). In the occipital, temporal and parahippocampal regions of the cortex, a positive

immunohistochemical reaction with antibodies to β -amyloid was recorded only in 16 % (1/6), 33 % (2/6) and 16 % (1/6) of cases, respectively (Fig. 1).

At the same time, pTau fragments were detected in 100 % of patients in each group in all studied regions of the cerebral cortex (Fig. 2).

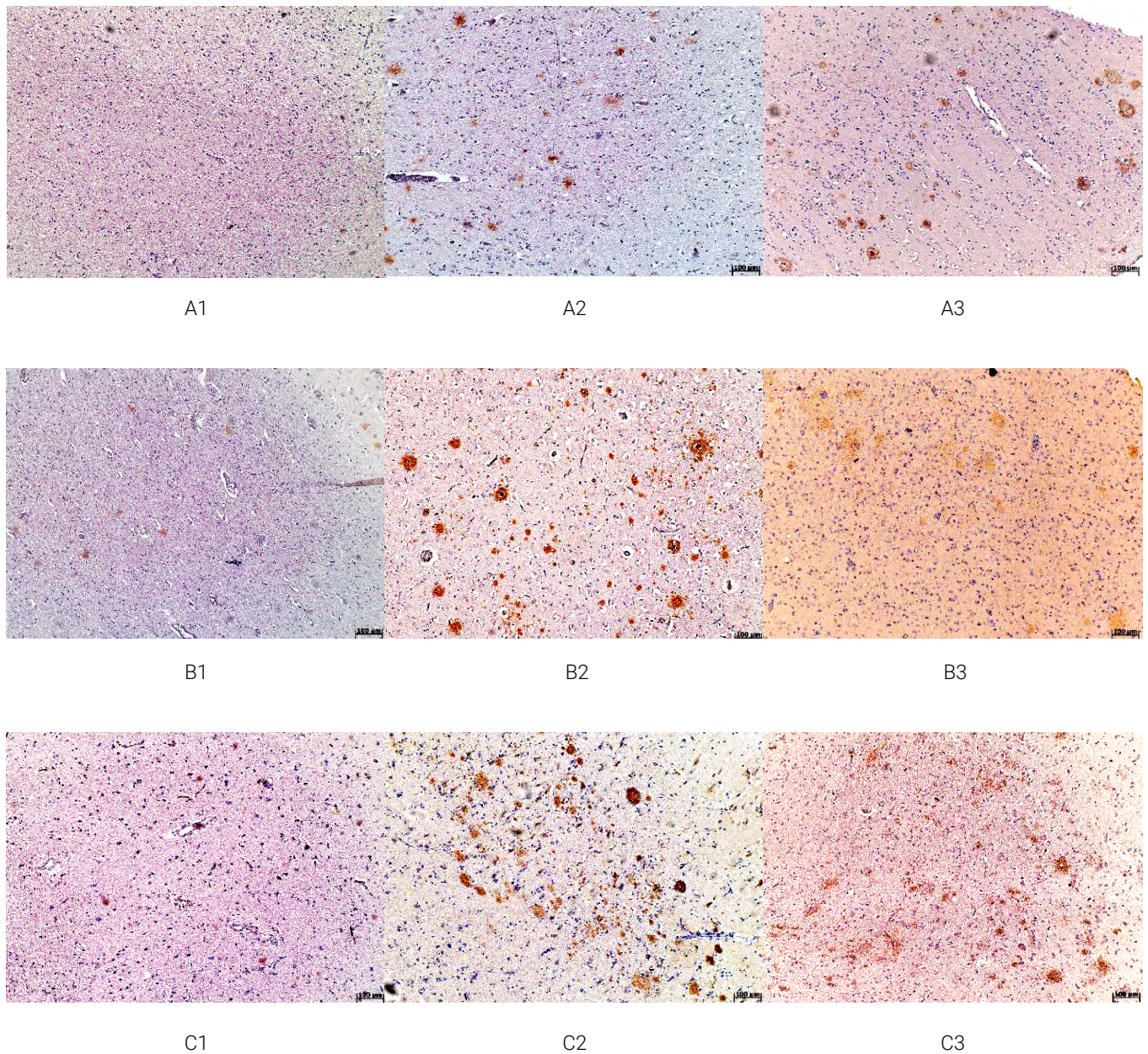


Figure 1. Distribution of amyloid plaques in the occipital (1), temporal (2), and parahippocampal (3) regions of the cerebral cortex in patients >60 years old with diagnosed dementia (A1, A2, A3), patients >60 years old without diagnosed dementia (B1, B2, B3) and patients <60 years old (C1, C2, C3). Immunohistochemical staining, primary antibodies anti-A β 1–42 (Rb) + secondary antibodies Donkey-anti-Rabbit HRP, staining with hematoxylin, magnification x100

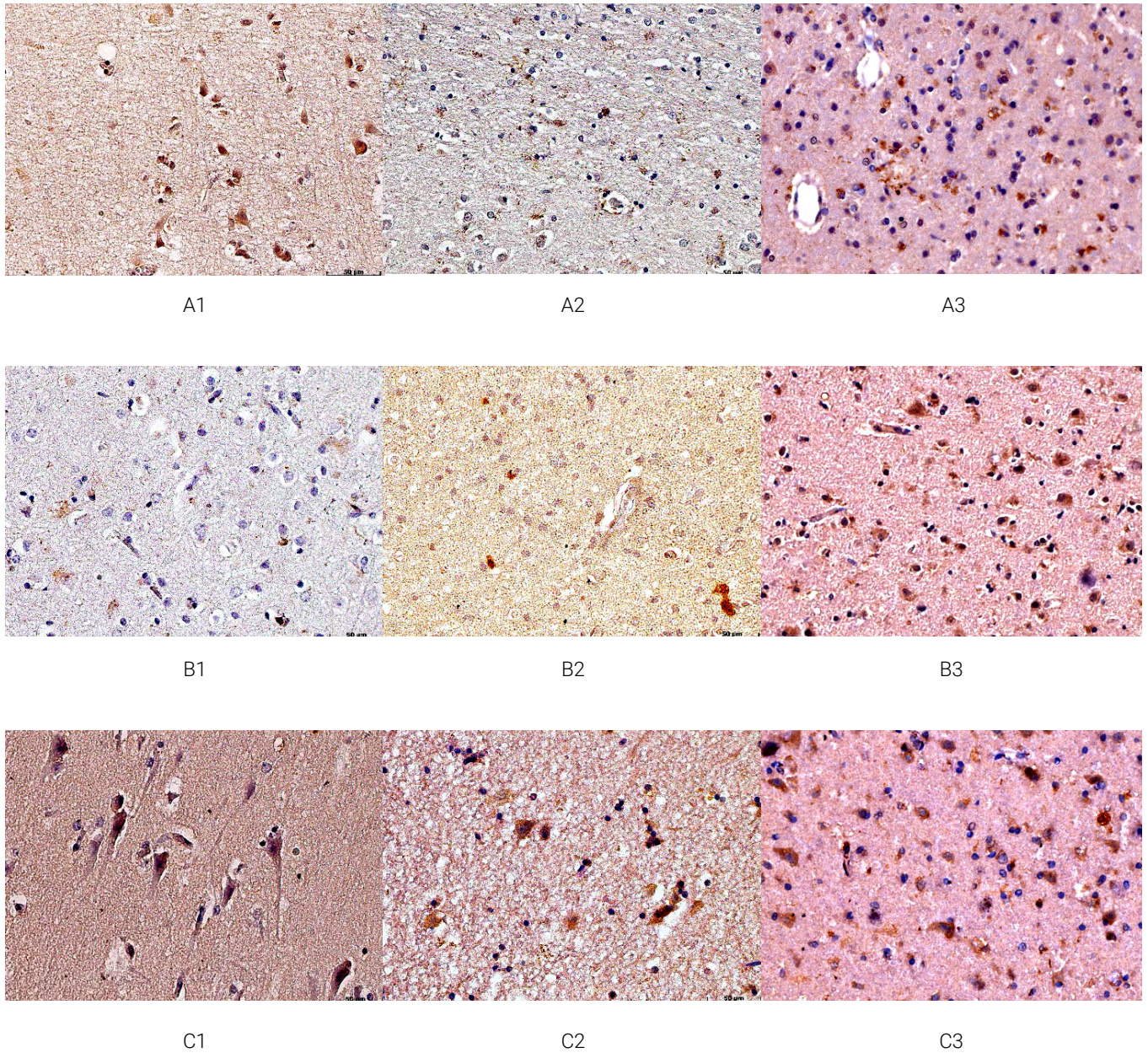


Figure 2. Distribution of fragments of phosphorylated tau protein (pTau) in the occipital (1), temporal (2) and parahippocampal (3) regions of the cerebral cortex in patients >60 years old with diagnosed dementia (A1, A2, A3), patients >60 years old without diagnosed dementia (B1, B2, B3) and patients <60 years old (C1, C2, C3). Immunohistochemical staining, primary antibodies anti-TAU-2 (Rb) + secondary antibodies Goat-anti-Mouse HRP, counterstaining with hematoxylin, magnification x400

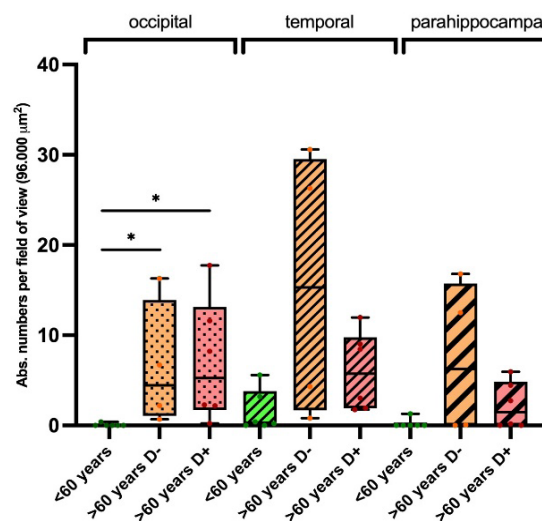
Analysis of the distribution of β -amyloid conglomerates revealed a significant increase in the mean number of amyloid plaques per standard visual field in the occipital region of the cerebral cortex in both elderly patients with and without diagnosed dementia compared with the group of patients <60 years of age. However, no differences were found for regions of the temporal and parahippocampal cortex, despite a trend towards an increase in the number of amyloid plaques in patients without dementia compared to patients with confirmed dementia (Fig. 3).

When assessing the distribution of pTau fragments in the occipital region of the cortex, an increase in the number of these structures was observed, similar to the distribution of β -amyloid deposits — in both groups of elderly patients it was significantly greater than in patients <60 years old. In the temporal and parahippocampal cortical regions, the number of pTau fragments was significantly higher in patients with dementia compared to the group of patients <60 years old, while no differences in this indicator were found between the groups of elderly patients without confirmed dementia and patients <60 years old (Fig. 3).

In accordance with the amyloid hypothesis of Alzheimer's disease [7], still dominant among researchers and clinicians, it is assumed that as the disease progresses, brain regions are affected in a certain order. Typically, the highest concentration of senile plaques, neurofibrillary tangles and neuronal death are detected in the mediobasal regions of the frontal and temporal lobes and the hippocampus; at the next stage, the posterior parts of the temporal and parietal lobes are involved in the pathological process, and the last ones are the frontal and occipital lobes of the brain [6]. However, recent studies using mathematical modeling have shown that amyloid plaques more likely form simultaneously in different cortical regions and subcortical structures than spread from primary affected areas to others [9]. In turn, neurofibrillary threads and tangles formed as a result of phosphorylation and subsequent misfolding of pTau manifest themselves in the entorhinal cortex, hippocampus and amygdala, and only then do they appear in various areas of the cortex. However, although it was previously believed that pTau fragments are formed after the formation of β -amyloid

deposits as a consequence of its toxic effects [10,11], it was later found that pTau is detected much earlier, including in young people aged <30 years [12, 13].

Distribution of A β plaques in various regions of cortex



Distribution of pTau fragments in various regions of cortex

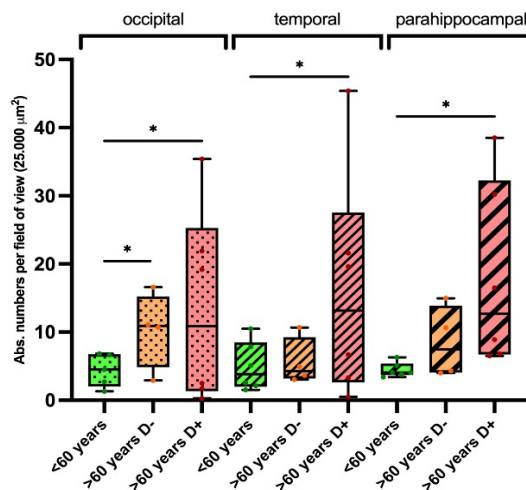


Figure 3. Distribution of amyloid plaques and fragments of phosphorylated tau protein (pTau) protein in the occipital, temporal, and parahippocampal cortex of the brain in patients <60 years old (<60 years, n = 6) patients >60 years old without diagnosed dementia (> 60 years D-, n = 4), and patients > 60 years old with diagnosed dementia (> 60 years D+, n = 6)

Note: * — p < 0.05. Multiple comparisons using the nonparametric Kruskal – Wallis test.

Our results confirm later literature data regarding the distribution and order of occurrence of pathognomonic morphological signs of AD: pTau fragments were identified in all patients, and their number was statistically significantly higher in all studied cortical areas in patients with diagnosed dementia compared to the group of patients <60 years. A significant increase in the number of amyloid plaques was recorded only in the temporal region of the cortex. At the same time, the localization and average number of amyloid plaques and pTau fragments in a standard visual field area did not correlate with the clinical manifestations of the disease, the rate of its progression and the severity of the course in patients included in this study.

These observations can be explained by the complex polyetiological nature of AD and the influence of a large number of modifiable and non-modifiable factors — for example, inflammation. As people age, cells inevitably age too, which is manifested by the acquisition of the senile pro-inflammatory secretory phenotype (SASP) and the formation of inflammaging — systemic chronic low-level inflammation [14]. It is important to note that the vast majority of patients included in the study had a history of concomitant somatic age-associated diseases, which were identified as risk factors for the development of dementia [15]. The most frequently mentioned disease was atherosclerosis, as well as type 2 diabetes mellitus, which are characterized by a systemic increase in the expression of inflammatory markers [16]. It is worth noting that some of the data from the medical records of patients with dementia was censored, and it was not possible to further clarify the presence or absence of age-associated diseases. Inflammatory responses, both systemic and limited to the central nervous system, are a debated risk factor not only for Alzheimer’s disease, but also for other mental illnesses such as schizophrenia [17]. However, it is AD that is an age-associated pathology with a high level of prevalence and a tendency to further increase; in addition, effective diagnosis and therapy for this neurodegenerative process have not yet been developed.

Conclusion

The presented data are evidence of the heterogeneous formation and distribution of pathognomonic signs of AD in the cerebral cortex — amyloid plaques and pTau fragments. It was noted that accumulation of pTau occurs earlier than β -amyloid. The average number of pTau fragments was significantly increased in patients with manifested dementia, while in some cortical regions the number of amyloid conglomerates was higher in cognitively intact elderly patients. Considering this, as well as the growing volume of data regarding more complex mechanisms underlying the pathogenesis of neurodegenerative diseases in general and AD in particular, it is advisable to continue experimental studies in the paradigm of non-amyloid hypotheses.

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Распределение β -амилоида и рТau в коре головного мозга в зависимости от возраста и психиатрического статуса

А.В. Сентябрева^{1, 2}  , О.А. Васюкова¹ , Я.А. Зоркина^{3, 4} , А.В. Андриющенко^{3, 5} ,
Г.П. Костюк^{3, 6, 7} , И.З. Еремина⁸ , А.М. Косырева^{1, 2, 8} 

¹ Научно-исследовательский институт морфологии человека имени академика А.П. Авцына, ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского», г. Москва, Российская Федерация

² Научно-исследовательский Институт молекулярной и клеточной медицины, Российский университет дружбы народов, г. Москва, Российская Федерация

³ Алексеевская психиатрическая клиническая больница № 1, г. Москва, Российская Федерация


⁴ Национальный медицинский исследовательский центр психиатрии и наркологии им. В.П. Сербского, г. Москва, Российская Федерация

⁵ МГУ им. М.В. Ломоносова, г. Москва, Российская Федерация

⁶ Российский биотехнологический университет (РОСБИОТЕХ), г. Москва, Российская Федерация

⁷ Сеченовский университет, г. Москва, Российская Федерация

⁸ Медицинский институт, Российский университет дружбы народов, г. Москва, Российская Федерация

 alexandraasentyabreva@gmail.com

Аннотация: Актуальность. Болезнь Альцгеймера (БА) является одной из наиболее распространенных причин инвалидности и основной причиной развития деменции и находится на 7-м месте среди ведущих причин смерти во всем мире. Диагностика БА включает определение амилоидных бляшек и гиперфосфорилированного тау-протеина (рТau) в головном мозге. Однако в последние годы амилоидная гипотеза развития БА подвергается критике и пересмотру, и появляется все больше данных, свидетельствующих о более сложных патогенетических механизмах, приводящих к нейродегенерации при БА. Целью нашей работы было оценить присутствие и распределением амилоидных бляшек и фрагментов рТau в разных регионах коры головного мозга у пациентов >60 лет с диагностированной деменцией

и без когнитивных нарушений, а также у людей <60 лет. Материалы и методы. На иммуногистохимически окрашенных гистологических срезах в зонах парагиппокампальной, височной и затылочной коры оценивали количество β -амилоида и фрагментов pTau в трех группах пациентов с БА. *Результаты и обсуждение.* Амилоидные бляшки выявлялись у всех пациентов старше 60 лет (с и без деменции), тогда как у лиц младше 60 лет они встречались в 66 % случаев. Причем наибольшая плотность β -амилоида наблюдалась в затылочной зоне коры. pTau обнаруживался во всех зонах коры у трех групп пациентов, однако в затылочной зоне коры у пациентов старше 60 лет с и без деменции количество pTau было значительно выше, чем в группе лиц младше 60 лет. *Выводы.* Таким образом, накопление pTau происходит раньше, чем β -амилоида. Кроме того, количество pTau выше у пациентов старше 60 лет с манифестировавшей деменцией, тогда как в некоторых регионах коры количество конгломератов амилоида выше у когнитивно сохранных пожилых пациентов. Полученные данные указывают на более сложный механизм развития нейродегенеративных заболеваний, при которых образование амилоидных бляшек может являться следствием, а не причиной заболевания.

Ключевые слова: болезнь Альцгеймера, β -амилоид, тау-белок, возрастные заболевания

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Corresponding author: Alexandra Vladislavovna Sentyabreva — junior researcher of the Laboratory of Neuromorphology Avtsyn Research Institute of Human Morphology of “Petrovsky National Research Centre of Surgery”, 117218, Tsyurupy st., 3, Moscow, Russian Federation. E-mail: alexandraasentyabreva@gmail.com

Sentyabreva A.V. ORCID 0000-0001-5064-219X

Vasyukova O.A. ORCID 0000-0001-6068-7009

Zorkina Ya.A. ORCID 0000-0003-0247-2717

Andryuschenko A.V. ORCID 0000-0002-7702-6343

Kostyuk G.P. ORCID 0000-0002-3073-6305

Eremina I.Z. ORCID 0000-0002-5093-6232

Kosyreva A.M. ORCID 0000-0002-6182-1799

Ответственный за переписку: Сентябрева Александра Владиславовна — младший научный сотрудник лаборатории нейроморфологии НИИ морфологии человека имени Авцына, ФГБУ «Российский научный центр хирургии им. Петровского», Российская Федерация, 117218, г. Москва, ул. Цюрупы, д. 3. E-mail: alexandraasentyabreva@gmail.com

Сентябрева А.В. SPIN 6966-9959, ORCID 0000-0001-5064-219X

Васюкова О.А. SPIN 2242-0958, ORCID 0000-0001-6068-7009

Зоркина Я.А. SPIN 3017-3328, ORCID 0000-0003-0247-2717

Андрющенко А.В. SPIN 8864-3341, ORCID 0000-0002-7702-6343

Костюк Г.П. SPIN 3424-4544, ORCID 0000-0002-3073-6305

Еремина И.З. SPIN 5819-6159, ORCID 0000-0002-5093-6232

Косырева А.М. SPIN 5421-5520, ORCID 0000-0002-6182-1799