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Difficulty for Early Diagnosis of Alzheimer's Disease: Especially MCI Level

Koji Hori*, Chiaki Hashimoto, Ouga Sasaki, Masanori Tadokoro, Sachiko Tsukahara and Michiho Sodenaga

Department of Neuropsychiatry, St. Marianna University School of Medicine, Kawasaki, Japan

***Corresponding author:** Koji Hori, Department of Neuropsychiatry, St. Marianna University School of Medicine, Kawasaki, Japan, Tel: +81-44-977-8111, Fax: +81-44-976-3341; E-mail: kojihori@marianna-u.ac.jp

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Abstract

Early diagnosis of Alzheimer's disease (AD) is very difficult. The main characteristic of neuro-image in AD is the atrophy of hippocampus and the main symptoms of AD is memory disturbance. However, we speculate these two sticks cause overdiagnosis or underdiagnoses of AD because the atrophy of hippocampus is not specific to AD and memory disturbance is not the first symptom in AD. As for memory disturbance, this symptom is not only unspecific to AD but also not the first symptom in AD. Moreover, we speculate that there two situations when the pathological symptoms occur at MCI in AD.On situation is when patients with AD at the MCI stage relax, at which time these patients show apathy. The other situation is when they are more stressed than usual. In this situation, these patients will be upset or panic. Therefore, the most important is hearing family of caregiver whether the patient shows apathy when he or she is relax (e.g., when they watch television, they fall asleep) and whether he or she is confused or panic when he or she is more stressed than usual.

Keywords: Acetylcholine; Alzheimer's disease (AD); Apathy; Early diagnosis

Abbreviations: Ach: Acetylcholine; AD: Alzheimer's Disease; ChAT: Choline Acetyltransferase; MCI: Mild Cognitive Impairment

Introduction

Early diagnosis of Alzheimer's disease (AD) is very difficult. The main characteristic of neuro-image in AD is the atrophy of hippocampus [1,2] and the main symptoms of AD is memory disturbance [3,4]. However, we speculate these two sticks cause overdiagnosis or underdiagnosis of AD. If we stick to the atrophy of hippocampus, we overdiagnose AD and if we stick to memory disturbance, we underdiagnose AD. When the underdiagnosis is occurred, the chance of early time intervention is failed. When the overdiagnosis is occurred, the unnecessary prescription of antidementia agents, especially cholinesterase inhibitor, is caused and existant depressive symptom is exaggerated [5,6]. Therefore, exact early diagnosis of AD is important.

In this short commentary, firstly we comment the memory disturbance and hippocampal atrophy in AD. Then we show the important points for the early diagnosis of AD.

The Atrophy of Hippocampus and Memory Disturbance in Alzheimer's Disease

The main characteristic of neuro-image in AD is the atrophy of hippocampus and the main symptoms of AD is memory disturbance. However, the atrophy of hippocampus is not specific to AD and memory disturbance is not the first symptom in AD.

As for the atrophy of hippocampus, depression is also accompany with this, which causes the short-time memory disruption in depression [7]. Catani et al. commented that emotion, memories and behavior occur from common pathway related with limbic system and proposed the revised limbic system model for those conducts [8]. As the result patients with depression showed deteriorated learning and memory skills relative to normal controls even in remission [9]. Moreover, in Nun Study, there were patients with AD pathology who had not showed demented state during their lifetimes [7]. From these results the atrophy of hippocampus, amyloid pathology and memory disturbance are not specific to AD.

As for memory disturbance, this symptom is not only unspecific to AD but also not the first symptom in AD. Needless to say in AD, there appears the downregulation of acetylcholine (ACh) [10,11], which occurs in hippocampus included in limbic system. This is why memory disturbance occurs in AD. However, motivation is also related this system [11]. Therefore, apathy is also related with AD [12,13]. The dysfunction of hippocampus causes apathy and this limbic circuit not to work. As the result, emotion did not occur, which cause memory dysfunction [14]. Therefore, we consider that the fist symptom in AD is not memory disturbance but apathy. We should pay more attention to apathy.

We previously reconsidered the stages of AD (mild cognitive impairment (MCI), mild, moderate) [15]. As mentioned before, AD pathology causes the degeneration of cholinergic neurons. However, although the activity of choline acetyltransferase (ChAT, an enzyme that produces ACh) is downregulated in the mild to moderate stages of AD, there were some reported that in patients with MCI or early AD, ChAT activity shows a compensatory increase so that ACh activity remains normal [16-19]. According to this speculation, at moderate stage ChAT activity in AD patients could have been high, which could account for the fact that her ACh level was relatively normal and in ordinal situations, cognitive functions in AD patients were relatively intact. This compensatory reaction to the onset of AD may be attributable to hyperactivity of presynaptic cholinergic neurons. If this compensatory mechanism works, then the cholinergic system is intact, rather than deteriorated. This means that when clinical symptoms occur, the cholinergic system is burdened, but still intact. Therefore, we speculate that when clinical symptoms occur, neurons are intact (i.e.

not degenerated) in MCI stage. When AD pathology causes clinical symptoms, such as memory disturbance, disorientations, etc., then neurons are degenerated. From these speculations, we hypothesize that in the MCI stage, AD pathology burdens the brain in AD patients, but ChAT activity is upregulated, resulting in normal ACh levels. Moreover, we also propose that in mild-stage AD, ACh gradually decreases because hyperactivity of presynaptic neurons may cause early and rapid neuronal degeneration, consequently downregulating ChAT activity (Figures 1 and 2) [15]. From these speculations, we consider that at MCI stage in AD, there might be no serious atrophy in AD in view of neuroimaging study.

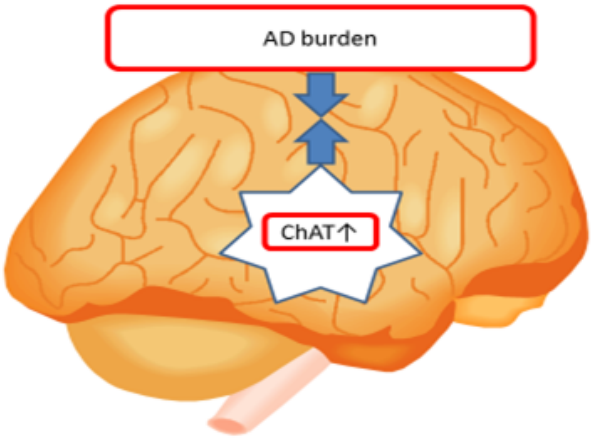

Figure 1: MCI stage: AD pathology causes a burden in the brains of patients with AD; however, ChAT activity is upregulated and ACh is maintained at a normal level.

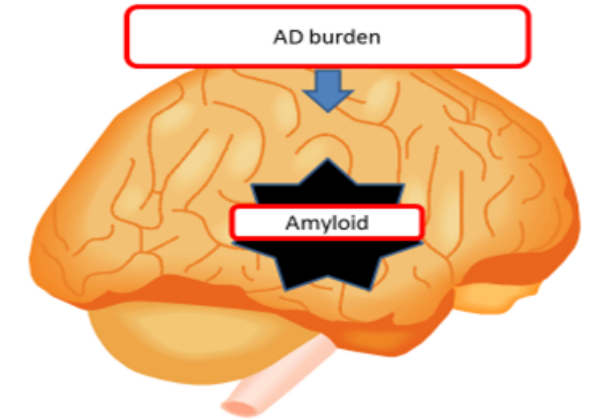

Figure 2: Mild stage: ACh gradually decreases because hyperactivity of presynaptic neurons may cause early and rapid neuronal degeneration with a consequent downregulation of ChAT activity.

These figures are reproduced from Konishi, et al. [15], with the permission of Karger, Basel, Switzerland.

Moreover, we should recognize when the symptom occur. In addition to these, we speculate that there two situations when the pathological symptoms occur in AD [20].As we mentioned before that apathy occurs when patients with AD at the MCI stage relax, at which time the ACh level is lower than normal. In this situation, these patients show apathy (e.g., when they watch television, they fall asleep). The other situation is when they are more stressed than usual. In this situation, their cholinergic system cannot be up regulated any further because ChAT is already activated and does not permit further upregulation [20].

Concerns for Diagnose Alzheimer's Disease

From these points of views, when we diagnose the patients as AD, we should keep in mind that atrophy of hippocampus and memory disturbance are not always seen in MCI. Therefore, we should not diagnose AD only using cognitive tests and neuroimaging. The most important is hearing family of caregiver whether the patient shows apathy when he or she is relax (e.g., when they watch television, they fall asleep) and whether he or she is confused or panic when he or she is more stressed than usual. If this situation is yes, we should diagnose the patient who is affected by AD even though cognitive function and neuroimaging study are normal.

In clinical settings or epidemiological survey, there is substantial misdiagnosis we pointed out before. At least we should diagnose AD exactly as much as possible in order to beneficial for patients.

Conflict of Interest

Koji Hori received lecture fees from Eisai Co. Ltd., Pfizer Japan Inc., Novartis Pharma KK, Daiichi Sankyo Inc., Ono Pharmaceutical Co. Ltd., Janssen Pharmaceutical KK, Yoshitomi Yakuhin Co. Meiji Seika Pharma Co. Ltd., Mitsubishi Tanabe Pharma Co. and Otsuka Pharma Co. However, the sponsors had no role in study design, data collection and analysis including our before presented articles, decision to publish, or preparation of this manuscript.

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Author Contributions

Koji Hori mainly coordinates the study regarding to this article and wrote the manuscript with the cooperation of mainly Michiho Sodenaga. Chiaki Hashimoto, Ouga Sasaki, Masanori Tadokoro, Sachiko Tsukahara and Michiho Sodenaga are member of in study group of geropsychiatry in St. Mariana University School of Medicine, Department of Neuropsychiatry and work as physicians and psychologist according to policies in this manuscript and checked the manuscript.

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