Donepezil Abolishes Anticholinergic Activity in a Patient with Amnesia

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Key Words

Alzheimer's disease • Serum anticholinergic activity • Antidementia agent • Acetylcholine • Mental stress

Abstract

We report the case of a 74-year-old woman who presented with amnesia and positive serum anticholinergic activity (SAA), which disappeared after treatment with the cholinesterase inhibitor donepezil for 1 year. Her only other regular medications were topical glaucoma preparations. We suggest that mental stress, mild cognitive impairment and Alzheimer's disease pathology combined to generate SAA in this patient. We also consider that SAA may have subsequently become negative because of upregulation of acetylcholine production by donepezil, and because the patient's other medications and physical condition (including glaucoma) remained unchanged during the 1-year period.

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Introduction

We previously reported that anticholinergic activity (AA) can occur endogenously in patients with Alzheimer's disease (AD) [1], and that AA accelerates AD-associated pathological changes (amyloid plaques and tau protein) [2]. Accordingly, endogenous AA should be investigated in a longitudinal study. It is also important to establish adequate treatment measures for abolishing AA. We also reported previously that downregulation of acetylcholine (ACh) production leads to an increase in inflammation and AA [3]. We report the case of a 74-year-old woman with amnesia and visual hallucinations who was positive for serum AA (SAA) on presentation at our hospital. SAA became undetectable after 1 year of treatment with donepezil, which is a cholinesterase inhibitor (ChEI) that enhances ACh activity. Her other medications were unaltered during this period and her physical condition remained stable. We also discuss the reasons for initial detection and

subsequent disappearance of SAA after 1 year of donepezil treatment. Both the patient and her husband gave written informed consent for the publication of this case report.

Case Presentation

A 74-year-old woman presented at the memory clinic of our hospital with a complaint of memory disturbances over the previous 2 years. She had moved to a new residence 3 months before visiting our clinic and this shift had caused her excessive stress. Ever since the move, she had been troubled by visual hallucinations, apathy and irritability. She told us that 'I can see someone here, but he soon disappears, and my husband says there is no one there'. She also complained of blurred vision for 3 months before the first visit to our hospital. On initial examination, her Mini-Mental State Examination (MMSE) [4] score was 26, and SAA was 4.28 nmol/l. Magnetic resonance imaging (MRI) revealed atrophy of the frontal and temporal lobes. Although the hippocampus was also somewhat atrophied, it was relatively intact. We diagnosed mild cognitive impairment (MCI) because her cognitive function was relatively spared, although she and her husband had noted memory disturbances. We prescribed donepezil (5 mg daily) and soon after starting this treatment her visual hallucinations, blurred vision and apathy resolved. Her MMSE score decreased to 24 after 1 year of treatment and, in addition, SAA was undetectable (<1.95 nmol/l). During this year she was also using latanoprost and carteolol hydrochloride eye drops for glaucoma. She also received other eye drops (levofloxacin hydrate and fluorometholone), and afloqualone and loxoprofen sodium hydrate were temporarily prescribed for headache. Consequently, her glaucoma remained stable during this period.

Patient information was kept confidential at sample submission and SAA was assayed according to the receptor-binding assay protocol of Tune and Coyle [5] at Mitsubishi Chemical Medicine Corp. (Kumamoto, Japan). Briefly, SAA was measured by a receptor-binding assay using rat forebrain muscarinic receptor. The assay assessed the inhibition of quinuclidinyl benzilate, L-[benzyl-4, 4' 3 H], (3 H)-QNB binding to the rat brain receptors. A standard displacement curve was created for each assay run by adding various concentrations of atropine to the serum of healthy young volunteers who were not taking any medications. The level of SAA was expressed as atropine equivalents (picomoles of atropine equivalents per milliliter of serum, nmol/l) on the basis of 3 H]-QNB counts in the patient's serum sample [5].

Discussion

We report the case of a 74-year-old woman with an MMSE score of 26 on presentation. Her MRI findings suggested mild atrophy. Therefore, we considered that her cognitive function was relatively intact. However, Spalletta et al. [6] reported that cognition and behavior are independent in patients with AD, and that heterogeneous symptoms can occur. Apathy and irritability are

considered to be frequent symptoms in patients with AD [7–10] and the onset of apathy is thought to predict cognitive or functional decline in such patients [7, 9, 10]. Therefore, we considered that this patient suffered from AD with MCI [11] because she not only had amnesia but also apathy and irritability. Moreover, her 3-month history of visual hallucinations and blurred vision indicated that AA had been elevated for those 3 months [12]. Because of the patient's visual hallucinations, we considered delirium and Lewy body disease (LBD) [13] as differential diagnoses. We also considered the possibility that AA elevation was related to delirium [14] and LBD [15].

We previously reported a positive relationship between SAA and the symptoms of patients with AD [1, 2]. Among 76 patients with AD, 26 were positive for SAA (SAA+) while the remaining 50 were negative (SAA–). The mean SAA level in the SAA+ group was 4.14 ± 2.70 nmol/l. However, this group was taking a significantly larger number of psychotropic medications and had significantly lower cognitive function, particularly in the memory domains (registration and recall domains). Moreover, dementia was significantly more severe in the SAA+ group. We suggest that AA not only disturbs cognitive function but also accelerates the pathophysiological process of AD because the SAA+ patients reported above show memory disturbances [2] that are related to AD symptoms [16]. In addition, these patients not only had impaired higher cognitive function but also more severe dementia. In fact, Fisher [17] and Jones et al. [18] have reported that a muscarinic 1 receptor agonist processes amyloid precursor protein to non-amyloid protein (α -processing), thus preventing amyloidosis. Therefore, antagonism of the muscarinic 1 receptor (i.e. AA) may increase the processing of amyloid precursor protein to amyloid protein. Moreover, Perry et al. [19] reported that the amyloid plaque density was more than 2.5-fold higher in patients who had received long-term antimuscarinic therapy (>2 years) than in those who had received short-term antimuscarinic therapy (<2 years) or those who did not receive any such therapy. Similarly, Lu and Tune [20] reported that chronic exposure to anticholinergic medications accelerates the clinical course of AD. Because SAA shows a correlation with AA in the cerebrospinal fluid [21, 22], we propose that the SAA level may be a useful peripheral marker in patients with rapidly progressing AD pathology. Positive SAA suggests more rapid progression of AD [3]. Alternatively, if SAA becomes negative, progression of AD can be expected to become slower. In fact, no significant difference was observed in the age at dementia onset or age at the time of

study entry between the SAA+ group and the SAA- group. However, the dementia stage was more severe and cognitive function was worse in the SAA+ group than in the SAA- group, indicating more rapid progression of dementia in the former group. Accordingly, we should further elucidate the relationship between AD severity (normal, MCI, mild, moderate and severe) and SAA, and we are currently studying longitudinal SAA changes in patients with AD at the MCI and mild stages.

The origin of SAA in our patient is unknown. SAA (AA) was once thought to be induced chiefly by prescription medications, particularly those associated with high AA, and polypharmacy [14]. In our patient, AA was not caused by medications because her medications were unaltered at the time when SAA became negative. In contrast, the number of medications had actually increased (eye drops and temporary oral medications), which should not have led to an improvement in SAA. It has been suggested that AA may have not only an exogenous origin but also an endogenous origin, and that its onset is mediated by inflammation [23]. From this perspective, we reviewed why endogenous SAA could occur in AD patients [3]. ACh is not only involved in cognitive function but also related with the regulation of inflammation in both peripheral tissues and the nervous system [24, 25]. Moreover, a decrease in ACh may lead to activation of inflammatory processes and failure in suppression of inflammation, which in turn produces an increase in SAA. Therefore, we speculate that downregulation of ACh is one of the factors that increases AA, and that deficiency of cholinergic activity yields AA via inflammatory processes [3]. AD is well known as a disease with degeneration of cholinergic neuronal activity in the brain [26]. These deficiencies in cholinergic neuronal activity cause a decrease in anti-inflammatory activity; this process is called the cholinergic anti-inflammatory pathway [27]. Following this, the inflammatory process is upregulated. Therefore, the downregulation of ACh, a characteristic feature in AD, causes hyperactivity of inflammation, endogenous appearance of AA and acceleration of AD pathology. Of course, as AD pathology progresses, cholinergic neuronal activity will decrease further. We refer to this process "as the endogenous anticholinergic cascade in AD" [3]. Alternatively, upregulation of ACh may prevent the appearance of AA or abolish AA in patients treated with ChEIs such as donepezil. The exact molecular mechanisms underlying the production of AA in relation to ACh downregulation have not been fully elucidated. Because ACh is involved not only in cognitive function but also in suppression of inflammation via nicotinic ACh receptors [28] as previously mentioned, it can be suggested that AD progres-

sion and related ACh downregulation leads to activation of inflammation in both the central and peripheral nervous systems. Various cytokines such as tumor necrosis factor, C-reactive protein (CRP) and interleukin-6 or inflammatory substances in peripheral tissue and inflammation-related substances in the central nervous system are induced during inflammation [28], and some of these have anticholinergic properties. In fact, Nazarov et al. [29] reported that CRP, which increases during inflammatory states, may result in AA by capturing ACh or binding to the ACh receptor, whereas Tsuruta et al. [30] reported that plasma AA was related to CRP in critically ill and injured patients. Furthermore, Horiuchi et al. [31] reported that an endogenous immunologically active peptide (apelin) inhibited cholinergic activity by binding to the ACh receptor, and Jadcherla [32] found that inflammation inhibited muscarinic receptor-mediated signaling. Therefore, the downregulation of ACh in the central nervous system causes AA in both the central and peripheral systems by way of inflammation. Therefore, SAA has been shown to correlate with AA in the cerebrospinal fluid [21, 22] regardless of whether substances those have AA can permit blood brain barrier or not.

Our patient was in the MCI stage and only had mild disease. Although her MMSE score was 26 at presentation, her SAA value of 4.28 nmol/l was similar to that in the above-mentioned SAA+ group with a mean MMSE score of 8.89. Because we have already shown that SAA positivity is related to the severity of dementia and cognitive dysfunction, factors other than medications, inflammation and a decline in ACh caused by the progression of AD seemed to be related to the appearance of SAA in our patient. In this context, Plaschke et al. [33] have reported a correlation between circulating cortisol levels and SAA. They commented that elevated SAA is related not only to extrinsic factors such as medications and illnesses but also to intrinsic factors, and that stress was a plausible cause of increased SAA. In addition, stress is related to an exacerbation of inflammation [34]. Accordingly, our patient may have become SAA+ because of mental stress related to moving to a new residence combined with the burden of AD. However, the increase in SAA could also be attributed solely to intrinsic factors because she already had AD. Moreover, mental stress also promotes inflammation in both the central and peripheral nervous systems [35], and cytokines in peripheral tissues and inflammation-related substances in the central nervous system can also be induced by stress. Therefore, it is possible that there is a (final) common pathway for the generation of AA by downregulation of ACh, mental stress and inflammation.

Fig. 1. **a** The relationship between ChAT activity and cholinesterase (ChE) activity is balanced, therefore ACh level is normal. **b** In the MCI stage, the activity of ChAT is increased as a compensatory reaction to AD so that the activity of ACh remains normal. **c** Mental stress can lead to ACh downregulation in this situation. Because ChAT activity cannot become higher it would cause ACh downregulation. **d** If anti-dementia agents are prescribed in the MCI stage, the relationship between ChAT activity and ChE activity is balanced without upregulation of ChAT. In addition, the ACh level remains normal. **e** Although mental stress may lead to downregulation of ACh, ChAT activity can become higher and the ACh level can remain normal.

Why would stress and AD act together to elevate SAA? In addition, why would MCI be associated with reciprocal changes in AA and ACh? In the mild to moderate stages of AD, the activity of choline acetyltransferase (ChAT, an enzyme that produces ACh) is downregulated [36]. However, Gilmor et al. [37], DeKosky et al. [38] and Ikonovic et al. [39] reported that ChAT activity shows a compensatory increase so that ACh activity remains normal in patients with MCI or early AD. Accordingly, our patient's ChAT activity could have been high, because of which her ACh level was relatively normal and her cognitive function was relatively intact. This compensatory reaction to the onset of AD may be attributable to hyperactivity of presynaptic cholinergic neurons. Because hyperactivity of presynaptic neurons may cause their early and rapid degeneration and consequent downregulation of ChAT activity [40], we should probably prescribe ChEI to preserve these neurons. Alternatively, we considered that a ChEI such as donepezil would prevent presynaptic neuron and ChAT hyperactivity and protect the presynaptic

cholinergic neurons from early and rapid degeneration. Moreover, mental stress may lead to increased inflammation in this situation. If the patient had not been in an amnesic state, ChAT activity and ACh level could have been higher, which may have prevented upregulation of inflammation and the development of SAA. However, ChAT activity in her brain was already elevated; therefore, it could not become higher and ACh could not increase, which may have led to inflammation and SAA positivity. In this situation, if ChEI is prescribed in the absence of ChAT hyperactivity, ACh level would remain normal, and if stress causes ACh downregulation, ChAT activity would become higher, which would maintain a normal ACh level. We show this hypothesis in figure 1a-e. We consider that it is important to prescribe antidementia therapy to patients in the MCI stage in order to inhibit AA production in the brain and prevent rapid AD progression. We speculate that early antidementia therapy (at the MCI stage) prevents the early and rapid degeneration of cholinergic neurons, which is caused by AA (SAA) [1-3].

In conclusion, our case report demonstrates the possibility that endogenous SAA is detected in patients with AD, even at the MCI stage. Because AA is considered to accelerate AD progression, our patient's cognitive function

may have declined more rapidly if she had not received donepezil. We believe that it is important to treat patients with MCI with ChEI in order to abolish AA, regardless of the accuracy of the above-mentioned hypothesis.

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