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CASE REPORT
Vascular Neurology 2010;2:26-30
ISSN 2092-6855

Cerebral Amyloid Angiopathy Presenting as Alzheimer's Disease: Four Case Reports

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Received February 26, 2010
Revised April 2, 2010
Accepted April 13, 2010

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Cerebral amyloid angiopathy (CAA) is well known to present with lobar intracerebral hemorrhage, dementia or transient neurological events. CAA is a microangiopathy that frequently co-occurs with Alzheimer's disease (AD) and appears to increase with age. In AD, CAA is due to the deposition of amyloid alpha protein (Abeta) within the adventitia and media of leptomeningeal and brain parenchymal arteries. We present 4 cases with rapidly progressive dementia in whom magnetic resonance imaging brain showed multiple microbleed in the whole cerebral lobe, mainly parieto-occipital lobe. Brain positron emission tomography revealed symmetrical hypometabolism in temporal and parietal cortex as features of AD. Apolipoprotein E (ApoE) genotype revealed Apo e3/e3. The presence of one or two ApoE E4 alleles is considered to be a risk factor for AD. Evidence suggests that the ApoE4 isoform promotes fibril formation of the amyloid b protein (Ab). ApoE2, on the other hand, may play an opposite role, protecting against Ab deposition and the development of AD. The role of ApoE in the genetics and pathogenesis of AD has been well established. As with AD, the 4 allele of ApoE is a risk factor for developing CAA, whereas the 2 allele is a risk factor for developing hemorrhage associated with CAA. We found ApoE3 in 4 patients, and we can't prospect AD accompanied with CAA in ApoE genotype.

Vascular Neurology 2010;2:26-30

Key Words Cerebral amyloid angiopathy, Alzheimer's disease, ApoE genotype.

Introduction

Cerebral amyloid angiopathy (CAA) commonly presents with lobar intracerebral hemorrhage in the elderly. Other manifestations such as cerebellar hematomas, dementia, transient ischemic attack, seizures and cerebral vasculitis have been described although they are unusual.[1,2] Dementia can result from the recurrent lobar hemorrhage or can occur due to a coexistent Alzheimer's disease (AD) in 80% of cases. CAA consists of deposition of amyloid in brain arterioles, capillaries, and leptomeningeal vessels. In AD, CAA is due to the deposition of amyloid alpha protein (Abeta) within the adventitia and media of leptomeningeal and brain parenchymal arteries.[3] The most common form of CAA results from deposition of the amyloid-(A) peptide in the walls of cerebral vessels, gradually replacing the smooth muscle cell layer. The vast majority of patients diagnosed with AD also have CAA.[4] A major consequence of CAA is fatal lobar cerebral hemorrhage, and it also appears to play a role in ischemic brain lesions and leukoariaosis. The role of Apolipoprotein E (ApoE) in the genetics and pathogenesis of AD has been well established. As with AD, the 4 allele of ApoE is a risk factor for developing CAA, whereas the 2 allele is a risk factor for developing hemorrhage associated with CAA. ApoE2 may play protecting against Ab deposition and the development of AD.[5-7] Our case differs from the case recently published.

Case Report

There were five patients, two female and three male, with age range from 56 years old to 69 years old and mean age of 61.3 years old. All patients underwent neuropsychological test and brain magnetic resonance imaging (MRI) and brain positron emission tomography (PET) (Fig. 1)(Table 1, 2 and 3).

Case 1

A 56-year-old man was admitted with an 3-week history of rapidly progressive change in personality, memory impairment and apathy. She had episodes of numbness spreading from Lt. hand to arm and face, mild memory loss. There were no depressive symptoms. There was no past history of diabetes, hypertension, renal failure, exposure to toxic chemicals, radiation, or drugs. There was no family history. She was a non-smoker and drank little alcohol. Neurologic, ophthalmologic and general examination, were otherwise normal. She scored 23/30 on her mini men-

Table 1. Clinical charcteristics of patients

Patient number	Age	Sex	Years (education)	Vascular risk factor	Clinical presentation	Evidence for CAA
1	56	M	12	None	Episodes of numbness spreading from Lt. hand to arm and face, mild memory loss	Multiple small cortical hemorrhages on MRI including previous subsequent Rt. frontoparietal with negative angiogram and CT
2	59	F	6	Hyperlipidemia	Episodes of paresthesias spreading from Lt. shoulder to hand	Multiple small cortical hemorrhages and Previous subsequent Rt. parietooccipital hemorrhage with negative angiogram
3	69	F	16	None	Episodes of visual hallucinations and misperceptions	Multiple small cortical hemorrhages on MRI, including hemorrhage near Rt. central sulcus
4	61	M	16	None	Profound dementia, progressive over 2 years;	Multiple lobar hemorrhages including subsequent hemorrhages of L pons

CAA: cerebral amyloid angiopathy, MRI: magnetic resonance imaging, CT: computed tomography.

Table 2. Results of ApoE genotype

	Case 1	Case 2	Case 3	Case 4
ApoE genotype	ε3/ ε3	ε3/ ε3	ε3/ ε4	ε3/ ε3

ApoE: apolipoprotein E.

tal status examination (MMSE). Routine blood exam, metabolic and endocrine work up, thyroid function, serum B_{12} and red cell folate, venereal disease research laboratory test (VDRL), rheumatic arthritis (RA) factor, chest X-ray, electrocardiography (ECG), electroencephalography (EEG) were normal. MRI brain showed multiple microbleed subsequent Rt. basal ganglia hemorrhage with negative follow-up MRI. So this patient is diagnosed as probable CAA according to boston criteria.[8] Brain PET revealed symmetrical hypometabolism in temporal and parietal cortex as features of AD. ApoE genotype revealed Apo e3/e3.

Case 3

A 69-year-old woman was admitted with an 8-week history of rapidly progressive change in personality, memory impairment and apathy. She had increasing difficulty in getting dressed, cooking and coordinating household tasks and wandered aimlessly around the house. There were no depressive symptoms.

There was no past history of diabetes, hypertension, renal failure, exposure to toxic chemicals, radiation, or drugs. There was no family history. She was a non-smoker and drank little alcohol. Neurologic, ophthalmologic and general examination, were otherwise normal. She scored 25/30 on her MMSE. Routine blood exam, metabolic and endocrine work up, thyroid function, serum B_{12} and red cell folate, VDRL, RA factor, chest X-ray, ECG, EEG were normal. MRI brain showed multiple microbleed in the whole cerebral lobe, mainly parieto-occipital lobe. So this patient is diagnosed as probable CAA according to boston criteria.[8] Brain PET revealed symmetrical hypometabolism in temporal and parietal cortex as features of AD. ApoE genotype revealed Apo e3/e3.

Discussion

CAA is characterized by cerebrovascular amyloid deposition. Mild CAA is not associated with clinical manifestations, while severe CAA may cause cerebrovascular disorders such as lobar cerebral hemorrhage and leukoencephalopathy, and may present with dementia.[4,9] CAA is found in the leptomeningeal and cortical vessels of the cerebral lobes. As for the distribution of CAA in the brain, the occipital lobe is most frequently and severely affected with CAA. CAA is also found in the cerebellum.[10] In contrast, CAA is uncommon in the basal ganglia, thalamus, brainstem, and white matter.[4] Development of CAA is not correlated with the presence of common cerebrovascular risk factors including hypertension, diabetes mellitus, and hyperlipidemia, or with severity of atherosclerosis of the cerebral arteries.[10] Progressive dementia is frequently found in patients with CAA.

Table 3. Results of neuropsychological test

	Case 1	Case 2	Case 3	Case 4
KMMSE				
Orientation to time	5	5	5	5
Orientation to place	4	4	4	4
Registration	3	3	3	3
Attention and calculation	2	0	3	3
Recall	0	1	1	1
Language	8	8	8	8
Drawing	1	1	1	1
Total score	23	22	25	25
Attention				
Digit span, forward	4 (12.30 %ile)	9 (97.06 %ile)	5 (16.35 %ile)	9 (93.70 %ile)
Digit span, backward	5 (84.38 %ile)	6 (98.67 %ile)	4 (67.36 %ile)	6 (92.36 %ile)
Language & related funtions				
K-BNT	58/60 (93.70 %ile)	48/60 (39.94 %ile)	45/60 (42.47 %ile)	53/60 (71.90 %ile)
Rt-Lt orientation	Normal	Normal	Normal	Normal
Calculation (+/-/×/÷)	Normal (3/3/3/3)	Normal (3/3/3/3)	Normal (3/3/3/3)	Normal (3/3/3/3)
Praxis	Normal	Normal	Normal	Normal
Visuospatial function and memory				
Reye complex figure, copy	34/36 (82.64 %ile)	35/36 (81.06 %ile)	35/36 (77.94 %ile)	36/36
Immediate recall	16.5/36 (76.11 %ile)	7.5/36 (14.92 %ile)	13.5/36 (27.43%)	6/36 (1.16 %ile)
Delayed recall	11/36 (38.59 %ile)	8/36 (7.78 %ile)	14/36 (29.12%)	6/36 (2.17 %ile)
Recogntion score	16 (3.75 %ile)	17 (14.92 %ile)	19 (28.77%)	18 (10.2 %ile)
Korean verbal learning test				
Immediate recall	4-5-7:16 (13.14 %ile)	3-4-4:11 (2.56 %ile)	5-5-9:19 (37.45 %ile)	6-6-9:21 (56,36 %ile)
Delayed recall	0	0	8 (62.55 %ile)	7 (46.41 %ile)
Recognition score	16 (1.92 %ile)	17 (17.36 %ile)	21 (54.38 %ile)	23 (79.39 %ile)
Frontal executive funtions				
Contrasting program	Abnormal	Normal	Normal	Normal
Go-no-go	Abnormal	Normal	Abnormal	Normal
Fist-edge-palm	Abnormal	Abnormal	Abnormal	Abnormal
Alternating hand movement	Abnormal	Abnormal	Abnormal	Abnormal
Alternating square & triangle	Normal	Normal	Abnormal	Normal
Luria loop	Normal	Normal	Normal	Normal
Phonemic word fluency	9 (1.58 %ile)	19 (97.2 %ile)	14 (22.66 %ile)	12 (10.75 %ile)
(animal/supermarket)	7 (5.59 %ile)	17 (79.10 %ile)	6 (4.01 %ile)	12 (6.06 %ile)
Semantic word fluency	3/3/3 (9)	8/4/3 (15)	8/6/5 (19)	11/11/8 (30)
(ㄱ/ㅇ/ㅅ/total)	(10.5 %ile)	(37.83 %ile)	(24.2%)	(24.2%)
Stroop test, word reading (correct/error)	112/0	112/0	112/0	112/0
Stroop test, color reading (correct/error)	86/3	63/0	64/6	77/3

KMMSE: Korean mini mental status examination, K-BNT: Korean-Boston Naming Test.

Pathomechanisms underlying the dementia are not uniform, including vascular dementia (VD) due to CAA, coexistence of AD, mixed dementia of VD and AD, and a vascular variant of AD.[11] In AD patients, soluble Ab and ApoE levels in the cerebrospinal fluid have been reported to be significantly lower in AD patients with CAA than in those without CAA.[12] A recently described genetic risk factor for AD is the e4 allele of the ApoE gene. The ApoE e4 allele is found at a frequency of approximately 0.4 in sporadic cases of late-onset AD, roughly three-fold its frequency in the general population. ApoE e4 is associated with an increased density of senile plaques in AD and a greater likelihood of Ab deposition following head trauma, raising the pos-

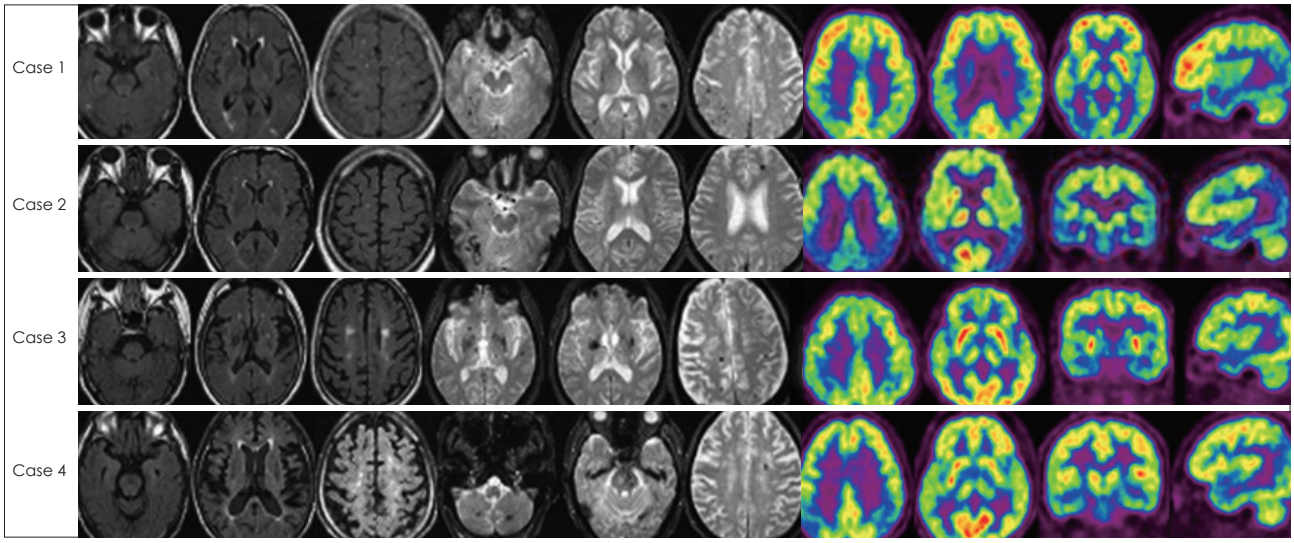

Figure 1. Axial fluid attenuated inversion recovery scan and gradient-recalled echo magnetic resonance imaging scan of the brain and positron emission tomography of the brain.

sibility that it may accelerate accumulation of Ab. Other potential roles for ApoE in the brain as well as a possible role in ischemic strok have also been described.[13] If ApoE e4 predisposes to AD by enhancement of AP deposition, it might also be expected to promote CAA. A relationship between ApoE e4 and increased CAA has been described. Recent evidence implicates the ApoE gene in the etiology of cerebral amyloid angiopathy-related hemorrhage.[14,15] someone previously hypothesized that whereas the ApoE e4 allele increases Ab deposition in the cerebral vasculature, ApoE e2 is associated with rupture of Ab-laden blood vessels, possibly by predisposing to the development of recognized vasculopathic complications of CAA. The role of ApoE in the genetics and pathogenesis of AD has been well established.[16] More than 40% of patients with CAA related hemorrhage have associated AD which may confound the analysis because ApoE4 is a well-established risk factor for AD whereas ApoE2 is protective. Whether ApoE4 is an independent risk factor for CAA-related hemorrhage or may be associated simply by its link with AD is unclear at present.[17] Generally, at an early stage, special features of AD are memory disturbane , visuoapatial function, naming disturbance and apraxia, calculation impairment. But special feature of our patients is frontal lobe dysfunction when AD is accompanied with CAA. It is known that ApoE e4 is related AD, and ApoE2 is related CAA. But we observed ApoE3 in 4 patients. So we think as follows. At first, ad accompanied with CAA is different from general AD and its special feature is frontal lobe dysfunction. So finding frontal lobe dysfunction in AD, you have to consider CAA. Next interesting point is that we found ApoE3 in 4 patients, and we can't prospect AD accompanied with CAA in ApoE genotype. On the contrary, MRI is more useful.

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