Infant critical head injury could be a remote cause of middle-aged cerebral amyloid angiopathy

Keisuke Tachiyama
Suiseikai Kajikawa Hospital https://orcid.org/0000-0001-8897-1845
Masahiro Nakamori (mnakamori1@gmail.com)
Yuki Hayashi
Suiseikai Kajikawa Hospital
Hayato Matsushima
Suiseikai Kajikawa Hospital
Eiji Imamura
Suiseikai Kajikawa Hospital
Shinichi Wakabayashi
Suiseikai Kajikawa Hospital
Katsuya Urakami
Tottori University

Case report

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Abstract

Background Cerebral amyloid angiopathy (CAA) is a sporadic condition in the elderly and is associated with Alzheimer's disease. The younger cases, however, may have a history of traumatic brain injury (TBI) during infancy. Case Presentation We present a case of a 37-year-old man who had cerebral lobar hemorrhage. Magnetic resonance imaging revealed several lobar microbleeds, which along with the asymptomatic, lobar hemorrhages increased every year. At the age of 40 years, he developed mild cognitive impairment. Cerebrospinal fluid (CSF) analysis revealed a markedly decreased level of amyloid β42. Moreover, he had a subdural hematoma during infancy. Thus, we diagnosed him with CAA, which was related to the TBI at infancy. Conclusion TBI at infancy can be a remote cause of middle-aged CAA and dementia. This was supported by the low Aβ42 level in the CSF analysis.

Background

Cerebral amyloid angiopathy (CAA) is characterized by amyloid deposition in the walls of the leptomeningeal and cortical arteries and arterioles. CAA is usually a sporadic condition in the elderly and is associated with Alzheimer's disease (AD) [1]. According to the modified Boston criteria, an age of ≥55 years is the typical cut-off for the diagnosis of probable CAA [2].

However, there are several reports of younger CAA cases with a history of traumatic brain injury (TBI) during infancy [3]. It is often reported that TBI contributes to AD during adulthood [4], and mainly promotes tau phosphorylation and not amyloid deposition. Pathological diagnosis of the neurodegenerative disease is difficult, and thus, amyloid β (Aβ) and phosphorylated tau in cerebrospinal fluid (CSF) serve as useful biomarkers for the diagnosis [5].

We present a case of CAA who was younger as per the modified Boston criteria and had a history of TBI during infancy. We measured the levels of Aβ and phosphorylated tau in his CSF.

Case Presentation

A 37-year-old man was admitted to our hospital owing to convulsions on January 15, 2016. Head computed tomography showed a left frontal lobar hemorrhage (Figure 1A). Magnetic resonance imaging (MRI), T2* weighted imaging (T2*WI) and susceptibility weighted imaging (SWI) revealed spot-like low-intensity diffusely distributed signals particularly in the left occipital lobe, some of which indicated previous subcortical hemorrhage (Figure 1B). These findings were suggestive of lobar type microbleeds. Other abnormalities including atrophy and sclerosis of hippocampus were not observed. Contrast effect was absent, and vessel abnormalities were not detected on magnetic resonance angiography and magnetic resonance venography (Figure 1C, D). Electroencephalography findings did not indicate any abnormalities and epileptic discharge was not observed. The patient's convulsions disappeared spontaneously in a few minutes and did not recur. Thus, he was diagnosed as having acute symptomatic seizure caused by cerebral hemorrhage. Neurological deficits were absent; hence, he was discharged on

the 11th hospital day. After the discharge, despite the strict control of the blood pressure, non-symptomatic lobar hemorrhage occurred several times and spot-like low-intensity signals on T2*WI increased every year.

At the age of 40 years, the patient had slight cognitive impairment and recent memory impairment was found. In addition, he could not design and execute a plan efficiently. Aphasia was not detected, and repetition and designation were normal. Although auditory comprehension was almost normal, the content of his speech was unorganized. His visuospatial cognition was normal and topographical agnosia was not observed. The Mini-Mental State Examination score was 28, and the Montreal Cognitive Assessment score was 22, which was less than the cut-off score of 25 [6]. The patient mainly missed items on the delayed recall. Blood examinations, mainly involving autoantibody, blood coagulation, complement, and vitamin levels, and endocrine hormones including the thyroid hormone, did not reveal particular abnormalities. On CSF examination, no elevation was observed in the cell number and protein levels. However, further examination revealed that the Aβ42 level in CSF was 184 pg/mL, which was less than the cut-off point mentioned in a previous report [5]. The Aβ42 level in CSF was markedly decreased, whereas the phosphorylated tau level was within the reference range. Furthermore, the ApoE genotype analysis of this patient revealed a genotype of ε3/ε2. To confirm the diagnosis, pathological evaluation including cerebral biopsy was considered, but the patient refused.

The patient was a university graduate and had never played contact sports during his school days. He worked as a high school teacher; however, he resigned at the age of 36 years owing to his inefficiency in planning lectures. He had no past medical history except a TBI that occurred at the age of 9 months, which resulted in a subdural hematoma in the left temporal lobe. He underwent craniotomy and evacuation of the hematoma. Epidural transplantation was not performed. He had no particular familial history including dementia, and there was no consanguineous marriage in his family.

Discussion And Conclusions

Based on the present findings, the patient was diagnosed with CAA, which was associated with the TBI that occurred at infancy. Nakayama et al. reported a case similar to the present case in which the patient was a 32-year-old man with a history of TBI at the age of 1 year. He had a subdural hematoma in the left frontal lobe for which he underwent craniotomy and evacuation of the hematoma. He was admitted due to severe headache at the age of 32 years. The SWI revealed multifocal subcortical hemorrhage. Following a biopsy of the cerebral vessels, CAA was diagnosed using immunohistochemistry with anti Aβ antibodies and electron microscopy.

Through a literature review, several pathologically diagnosed cases of CAA involving patients younger than 55 years were identified. All these patients were men and most of them had a history of TBI at infancy [3]. In most cases, the ApoE genotype was ε3/ε3. In contrast, there were no cases of the ε4 genotype. The present case was similar to the aforementioned cases. Particularly, the injured lesion was strongly burdened with CAA and cerebral hemorrhage, which indicated the association between TBI at

infancy and middle-aged CAA. Moreover, in the present case, the Aβ42 level in CSF was decreased, strongly suggesting amyloid pathology. Thus, TBI at infancy might be considered to promote amyloid pathology. However, there are no previous reports that measured the levels of Aβ42 and phosphorylated tau in CSF among such cases. Thus, these results provide insights into the pathophysiological characteristics of CAA patients who have a history of TBI.

There are several speculated mechanisms for such cases. It is often reported that TBI contributes to AD during adulthood [4], and mainly promotes tau phosphorylation and not amyloid deposition. However, Aβ plaques and intra-axonal Aβ deposits have been observed in patients with fatal TBI [7]; hence, TBI may promote Aβ production. Aβ is produced by the cleavage of amyloid-beta precursor protein (APP), which is essential for nerve growth through degradation [8]. At infancy, because neuronal growth and APP metabolism are active, axonal damage caused by TBI may promote APP decomposition to compensate for the neuronal loss, thus leading to amyloid deposition. It is reported that Aβ plaques prevent the transport of soluble Aβ42 from the brain to the CSF [9]; TBI may also prevent this transportation. Thus, the decrease in Aβ42 levels in CSF directly reflects the presence/amount of cerebral Aβ deposits. Furthermore, decreased CSF Aβ42 is an early biomarker for MCI due to AD and indicates a high likelihood of progression to AD in patients with mild cognitive impairment (MCI) [10].

Two Aβ drainage pathways have been reported, namely the “perivascular drainage pathway” and “glymphatic pathway.” In the perivascular drainage pathway arterial pulsations promote the drainage of interstitial fluid containing Aβ [11]. In the glymphatic pathway, the exchange of solutes between CSF and interstitial fluid is driven primarily by arterial pulsations and astrocytic aquaporin 4 water channels [12]. The function of these pathways may be reduced due to trauma, surgical stress, and aging.

In this case, the patient experienced repeated asymptomatic subcortical hemorrhage due to which, large amounts of hydroxyl radicals can be generated. The hydroxyl radical has strong cytotoxicity and may inactivate intracellular metabolic activity [13]. Furthermore, cytotoxicity by iron may reduce the function of Aβ decomposition.

However, because there are no reports of MRI findings at a younger age in such patients, the onset age of amyloid deposition remains unclear, which is a limitation. In addition, CAA rarely occurs in patients with a history of severe TBI at infancy and other overlapping factors may induce the amyloid deposition in CAA. Although the underlying mechanism remains unclear, critical head injury at infancy could be a remote cause of middle-aged CAA. Further study involving a larger sample of CAA patients is needed to clarify the mechanism. Nevertheless, this case report shows that patients with a history of critical head injury at infancy should be repetitively evaluated using MRI to prevent stroke and dementia.

Abbreviations

CAA: Cerebral amyloid angiopathy; AD: Alzheimer’s disease ; CSF:cerebrospinal fluid; Aβ42: amyloid β42; TBI: traumatic brain injury; MRI: magnetic resonance imaging; T2* WI: T2* weighted imaging; SWI:susceptibility weighted imaging; APP: amyloid-beta precursor protein; MCI: mild cognitive impairment

Declarations

Ethical approval and consent to participate

All procedures performed in studies involving human participants were approved by the Ethical Committee of Suiseikai Kajikawa Hospital, and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All the data supporting our findings are provided within the manuscript.

Competing interests

None.

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Authors' contributions

KT examined, evaluated the patient. KT is a member of physicians and drafting manuscript. MN is a clinical supervisor and finalizing manuscript. YH, HM, and EI are members of physicians and examiners. SW and KU are clinical supervisors. All authors read and approved the final manuscript.

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Figures

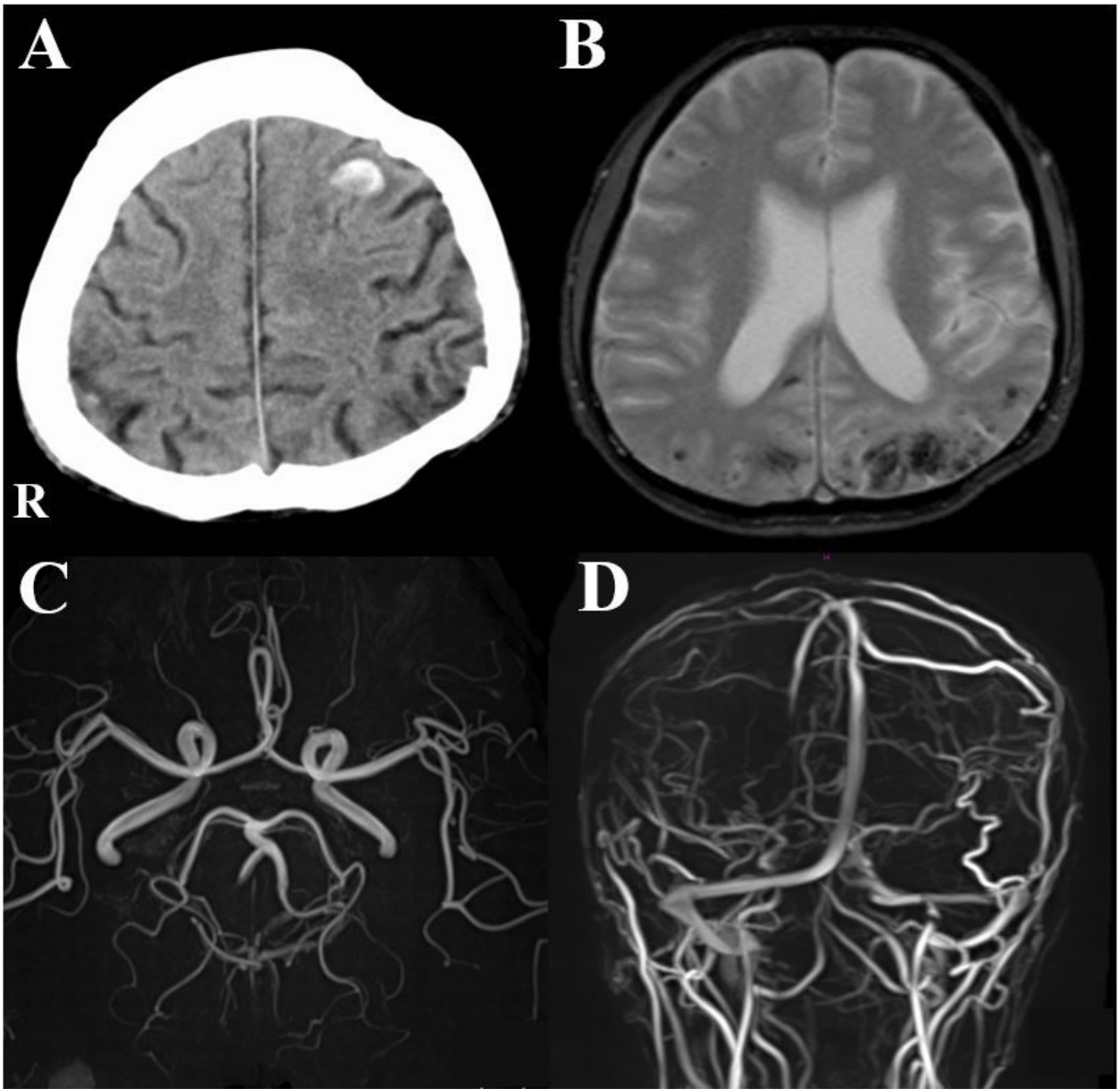

Figure 1

(A) shows head CT. It shows a left frontal lobar hemorrhage. (B) shows T2* susceptibility-weighted image. There are spot-like low intensity signals diffusely especially in the left occipital lobe and some of which are old subcortical hemorrhage. (C) shows magnetic resonance angiography (MRA). (D) shows magnetic resonance venography (MRV). There are no vessel abnormalities.

Supplementary Files

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