Journal of the Neurological Sciences 399 (2019) 3–5

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Cerebral hemorrhagic stroke associated with cerebral amyloid angiopathy in young adults about 3 decades after neurosurgeries in their infancy

ARTICLE INFO

Keywords:
Cerebral amyloid angiopathy
Amyloid β protein
Neurosurgery
Traumatic brain injury

Dear Editor,

Recently, there have been increasing numbers of evidence that cerebral β–amyloidosis could be transmitted between individuals [1–5]. Here, we describe 2 patients with cerebral amyloid angiopathy (CAA) associated with amyloid β protein (Aβ) (Aβ-CAA) about 3 decades after neurosurgeries, suggesting transmission of Aβ-CAA via the neurosurgeries contaminated with Aβ aggregates or induction of Aβ-CAA by the disturbance of Aβ clearance caused by neurosurgeries.

1. Case reports

1.1. Patient 1

A 30-year-old man, who had history of an evacuation surgery for left subdural hematoma and right subdural hygroma at 4-month-old and a subdural-peritoneal shunt surgery at 7-month-old in 1982, was admitted to a hospital with unprovoked seizure. Cadaveric dura mater grafting was not described in the records of the neurosurgeries. He had no history of hypertension or traumatic brain injury. Computed tomography (CT) scan showed convexity subarachnoid hemorrhage (SAH) in the bilateral frontal lobes. The patient started an anti-epileptic drug for epilepsy control, and discharged from the hospital without sequela a week after the admission.

Nine months after the first attack, he visited our hospital because of 6 months' history of cognitive impairment. Neurological examination revealed mild impairment of cognitive functions including recent memory, naming, and construction. The score of Mini Mental State Examination was 27/30. Magnetic resonance imaging (MRI) demonstrated linear and multiple hypointensity signals in cerebral cortices and subcortices on T2*-weighted gradient-recalled echo (Fig. 1A), and multiple subcortical hyperintensity signals on fluid-attenuated inversion recovery imaging (Fig. 1B). Positron emission tomography (PET) with ^{11}C-Pittsburgh compound B (PiB) revealed PiB uptake in the bilateral occipital, frontal, parietal and temporal lobes (Fig. 1C). Cerebrospinal fluid (CSF) examination showed mild elevation of protein concentration (44 mg/dL, normal 10–40 mg/dL) without pleocytosis, mild decrease of $A\beta_{1-42}$ (444 pg/mL, normal > 490 pg/mL) and $A\beta_{1-40}$ (7654 pg/mL, mean ± S.D. for 73 patients with Alzheimer's disease: 12,397 ± 4591 pg/mL), and normal value of phosphorylated tau (33 pg/mL, normal < 49 pg/mL). Genetic analyses revealed no mutation in the genes of amyloid precursor protein, presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*), and no duplication of *APP*. Genotype of apolipoprotein E (*ApoE*) is ε3/ε3. We diagnosed his illness as probable CAA-related hemorrhage according to the modified Boston criteria for CAA related hemorrhage [6] excluding the age criterion.

His cognitive impairment had not gotten worse without epileptic seizure for about 4 years. About 5 years after the first attack, he presented with aphasia and right hemiplegia, and CT scan revealed acute hemorrhage in the left frontal lobe.

1.2. Patient 2

A 30-year-old man complained of severe headache without head trauma, and brain CT revealed acute hemorrhage in the right parietal lobe and defect of the skull in the right parietal lobe which was apart from the hemorrhagic lesions (Fig. 1D and E). At 3-month-old, his mother fell down with holding him in her arms, and he hit his head on the floor and suffered from subdural hygroma. He underwent neurosurgery for growing skull fracture of right parietal region at 16-month-old in 1980. We could not obtain the information about the use of cadaveric dura mater at the neurosurgery. He had no history of hypertension. After lobar hemorrhage in the right parietal lobe at age 30, eight additional non-traumatic lobar hematomas occurred in a period of 6 months, and he fell to deep coma. Brain biopsy at the removal of hematoma at the eighth hemorrhage revealed Aβ deposition on vasculatures in the brain (Fig. 1F). Genetic analyses revealed no mutation at exon 16 or 17 in *APP* and ε3/ε3 genotype for *ApoE*, but neither *PSEN1* nor *PSEN2* were analyzed. We diagnosed his illness as probable CAA-related hemorrhage with supporting pathology according to the modified Boston criteria for CAA related hemorrhage [6] excluding the age criterion.

2. Discussion

Both of 2 patients in the present study developed CAA-related hemorrhages, although they were still 30 years old. For Patient 1, PiB-PET study and CSF study supported our diagnosis [7]; seizure at the onset

https://doi.org/10.1016/j.jns.2019.01.051
Received 22 November 2018; Received in revised form 14 January 2019; Accepted 31 January 2019
Available online 01 February 2019

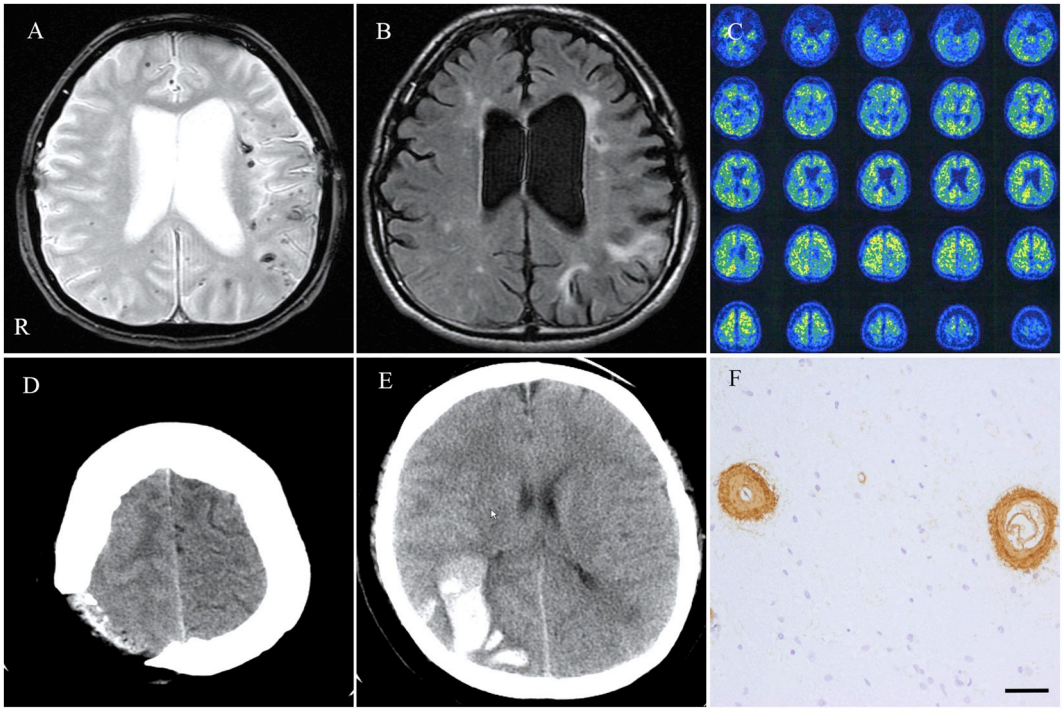

Fig. 1. Imaging and pathological studies of Patients 1 (A–C) and 2 (D–F). Brain magnetic resonance imaging on T2*-weighted gradient-recalled echo showed linear and multiple hypointensity signals in cerebral cortices and subcortices, which represented cortical superficial siderosis and multiple lobar microbleeds (A). Fluid-attenuated inversion recovery imaging revealed multiple hyperintensity signals in subcortices and deep white matter (B). Positron emission tomography with ^{11}C-Pittsburgh compound B showed amyloid deposition in the bilateral occipital, frontal, parietal and temporal lobes (C). Computed tomography scan of the head showed defect of the skull in the right parietal lobe (D), and acute hemorrhage in the right parietal lobe (E). Immunohistochemical study of the biopsied brain tissue using antibody against amyloid β protein (Aβ) showed Aβ deposition on vasculatures with thickening of vascular intima and concentric splitting of the wall of a vessel in the brain (F). Scale bar is 50 μm.

could be transient focal neurological episodes associated with CAA [8]. Although the onset of hereditary Aβ-CAA-related hemorrhages were early, they were sporadic cases, and had no genetic risk factors of Aβ-CAA. Importantly, they had the histories of neurosurgery during their infancy, although it remains unclear whether they received cadaveric dura mater graft or not at the neurosurgeries.

In our patients, we considered 2 possible reasons why they suffered from Aβ-CAA without genetic risk factors in spite of their younger age; one is transmission of Aβ-CAA via dura mater graft or neurosurgical instruments contaminated with Aβ aggregates, and the other is induction of Aβ-CAA by the disturbance of Aβ clearance caused by traumatic brain injuries or neurosurgeries.

A retrospective study and review of literatures showed that 10 patients with histories of neurosurgery at their childhood developed Aβ-CAA associated cerebral hemorrhage several decades after the neurosurgery, suggesting transmission of Aβ pathology and CAA [4]. Furthermore, a 46-year-old woman, who had history of cadaveric dura mater graft at 2-year-old, developed symptomatic Aβ-CAA [5]. These patients showed the possibility that Aβ-CAA might be transmitted through neurosurgeries or dura mater grafting. Both patients in the present study were the youngest (30 years old at the onset) among the patients with symptomatic Aβ-CAA reported so far.

Recently, clearance systems of cerebral Aβ, such as glymphatic system or intramural peri-arterial drainage (IPAD) pathways, have been proposed [9,10]. Because the neurosurgeries or the head traumas at their infancy could induce dysfunction of these clearance systems, Aβ might deposit in the cerebral vessels decades after the neurosurgeries or the head traumas.

In conclusion, we described 2 patients who developed Aβ-CAA related hemorrhage at 30-year-old about 3 decades after neurosurgeries. These patients indicated the possibilities of human-to-human transmission of Aβ-CAA via dura mater grafting or neurosurgeries, or of Aβ-CAA induced by the disturbance of Aβ clearance due to neurosurgeries or traumatic brain injuries. We emphasize that Aβ-CAA should be considered in the differential diagnosis even for young patients with intracerebral hemorrhage and the history of neurosurgery should be confirmed as a potential risk factor.

Funding

This work was supported by a grant-in-aid from the Research Committee of Prion Disease and Slow Virus Infection, the Ministry of Health, Labour and Welfare of Japan (TH and MY), Amyloidosis Research Committee, the Ministry of Health, Labour and Welfare of Japan (MY) and Japan Agency for Medical Research and Development18kk0205009 (TI).

Competing interests

None declared.

Ethics approval

This study was conducted with the approval of the institutional ethics committee at Kanazawa University (2842-1).

References

[1] M. Meyer-Luehmann, J. Coomaraswamy, T. Bolmont, S. Kaeser, C. Schaefer, E. Kilger, A. Neuenschwander, D. Abramowski, P. Frey, A.L. Jaton, J.M. Vigouret, P. Paganetti, D.M. Walsh, P.M. Mathews, J. Ghiso, M. Staufenbiel, L.C. Walker, M. Jucker, Exogenous induction of cerebral β-amyloidogenesis is governed by agent and host, Science 313 (5794) (2006) 1781–1784.

[2] Z. Jaunmuktane, S. Mead, M. Ellis, J.D. Wadsworth, A.J. Nicoll, J. Kenny, F. Launchbury, J. Linehan, A. Richard-Loendt, A.S. Walker, P. Rudge, J. Collinge, S. Brandner, Evidence for human transmission of amyloid-β pathology and cerebral

amyloid angiopathy, Nature 525 (7568) (2015) 247–250.
[3] T. Hamaguchi, Y. Taniguchi, K. Sakai, T. Kitamoto, M. Takao, S. Murayama, Y. Iwasaki, M. Yoshida, H. Shimizu, A. Kakita, H. Takahashi, H. Suzuki, H. Naiki, N. Sanjo, H. Mizusawa, M. Yamada, Significant association of cadaveric dura mater grafting with subpial Aβ deposition and meningeal amyloid angiopathy, Acta Neuropathol. 132 (2) (2016) 313–315.
[4] Z. Jaunmuktane, A. Quaegebeur, R. Taipa, M. Viana-Baptista, R. Barbosa, C. Koriath, R. Sciot, S. Mead, S. Brandner, Evidence of amyloid-β cerebral amyloid angiopathy transmission through neurosurgery, Acta Neuropathol. 135 (5) (2018) 671–679.
[5] D. Herve, M. Porche, L. Cabrejo, C. Guidoux, E. Tournier-Lasserve, G. Nicolas, H. Adle-Biassette, I. Plu, H. Chabriat, C. Duyckaerts, Fatal Aβ cerebral amyloid angiopathy 4 decades after a dural graft at the age of 2 years, Acta Neuropathol. 135 (5) (2018) 801–803.
[6] J. Linn, A. Halpin, P. Demaerel, J. Ruhland, A.D. Giese, M. Dichgans, M.A. van Buchem, H. Bruckmann, S.M. Greenberg, Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy, Neurology 74 (17) (2010) 1346–1350.
[7] A. Charidimou, J.O. Friedrich, S.M. Greenberg, A. Viswanathan, Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy: a meta-analysis, Neurology 90 (9) (2018) e754–e762.
[8] A. Charidimou, A. Peeters, Z. Fox, S.M. Gregoire, Y. Vandermeeren, P. Laloux, H.R. Jager, J.C. Baron, D.J. Werring, Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis, Stroke 43 (9) (2012) 2324–2330.
[9] N.J. Albargothy, D.A. Johnston, M. MacGregor-Sharp, R.O. Weller, A. Verma, C.A. Hawkes, R.O. Carare, Convective influx/glymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways, Acta Neuropathol. 136 (1) (2018) 139–152.
[10] A. Louveau, B.A. Plog, S. Antila, K. Alitalo, M. Nedergaard, J. Kipnis, Understanding the functions and relationships of the glymphatic system and meningeal lymphatics, J. Clin. Invest. 127 (9) (2017) 3210–3219.

Tsuyoshi Hamaguchi[a], Junji Komatsu[a], Kenji Sakai[a], Moeko Noguchi-Shinohara[a], Satoshi Aoki[b], Takeshi Ikeuchi[c], Masahito Yamada[a,*]

[a] *Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan*
[b] *Department of Neurosurgery, Toyama Prefectural Central Hospital, Toyama, Japan*
[c] *Department of Molecular Genetics, Brain Research Institute, Niigata University, Niigata, Japan*
E-mail address: m-yamada@med.kanazawa-u.ac.jp (M. Yamada).

[*] Corresponding author at: Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa 920-8640, Japan.