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Case Report

Brain stem hemorrhage due to cerebral amyloid angiopathy: The autopsy of a patient with Alzheimer's disease at a young age

Seiji Ohtani [a], Keiko Shimizu [a], Masaru Asari [a], Chikatoshi Maseda [a], Kumiko Oka [a,b], Hiromi Yamada [a], Chisato Hoshina [a], Hiroki Doi [a], Daisuke Yajima [c], Hiroshi Shiono [a], Katsuhiro Ogawa [d,*]

[a] Department of Legal Medicine, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan
[b] Department of Oral and Maxillofacial Surgery, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan
[c] Department of Legal Medicine, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
[d] Department of Pathology, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan

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ABSTRACT

We report findings from an autopsy of a male in his 40s who died of a brain stem hemorrhage associated with cerebral amyloid angiopathy (CAA), senile plaques (SPs) and neurofibrillary tangles (NFTs), which are histopathological changes associated with Alzheimer's disease (AD). Our immunohistochemical study demonstrated amyloid β (Aβ) deposition in the small cerebral arteries and SPs. Although hypertension (178/132 mmHg) was detected, the subject was not treated accordingly. CAA coupled with hypertension might have caused the intracerebral hemorrhage (ICH).

1. Introduction

Spontaneous intracerebral hemorrhages (ICHs) due to abrupt rupture of arteries in the cerebral parenchyma occur preferentially at the basal ganglion–thalamus (65%), pons (15%), or cerebellum (8%). Severe hemorrhages may result in not only irreversible brain damage but also acute death within hours or days. ICH commonly occurs in late adult life with a peak incidence at approximately 60 years of age and much less frequently in younger persons [1]. Sustained hypertension is the most common cause of ICH, accounting for more than 50–60% of ICH cases. Hypertension causes a number of abnormalities in the arteries that are vulnerable to ruptures, including atherosclerosis, hyaline degeneration, and microaneurysms [2]. In addition to hypertension, other local and systemic factors, such as coagulation disorders, drug abuse, neoplasms, amyloid angiopathy, infectious and noninfectious vasculitis and vascular malformations, may cause or contribute to ICHs.

Cerebral amyloid angiopathy (CAA) is caused by deposition of amyloid β (Aβ) in blood vessels. Aβ is a proteolytic cleavage product of amyloid β precursor protein (APP) [3–5]. Histopathologically, CAA is characterized by thickening of the walls and narrowing of the vascular spaces in small cerebral arteries. CAA accompanies >90% cases of Alzheimer's disease (AD), although it can also be found in 20–40% of non-AD patients over 60 years of age [3,6]. However, sporadic CAA cases rarely appear before 60 years of age [3]. CAA is not only susceptible to ICH by itself but also contributes to ICH in conjunction with hypertension [3–5,7].

We hereby report on an autopsy of a previously healthy man who died of sudden ICH in his late 40s. Histopathological analysis revealed CAA, increased senile plaques (SPs) and neurofibrillary tangles (NFTs), which are cerebral changes that usually accompany AD [8–12]. Additionally, Aβ deposition was located in the small cerebral arteries and SPs.

2. Case report

An unmarried man in his late 40s, 170 cm tall and weighing 73 kg, was found dead in his apartment by policemen early on an April morning. They visited the deceased's house having received notification of his absence from his office. The deceased was wearing indoor clothing and lying supine on his bed on discovery. A brownish bloody fluid had oozed from his nose and mouth and had stained the pillow and sheet. It was confirmed that he had been alive two evenings before he was found dead. Although there was no history of physical or psychiatric disease, data of hypertension (172/132 mmHg), visceral fat type obesity (abdomen 92 cm, body mass index 26.3) and high values of serum acylglycerol

* Corresponding author. Tel.: +81 166 68 2433; fax: +81 166 68 2439.
E-mail address: ogawak@asahikwa-med.ac.jp (K. Ogawa).

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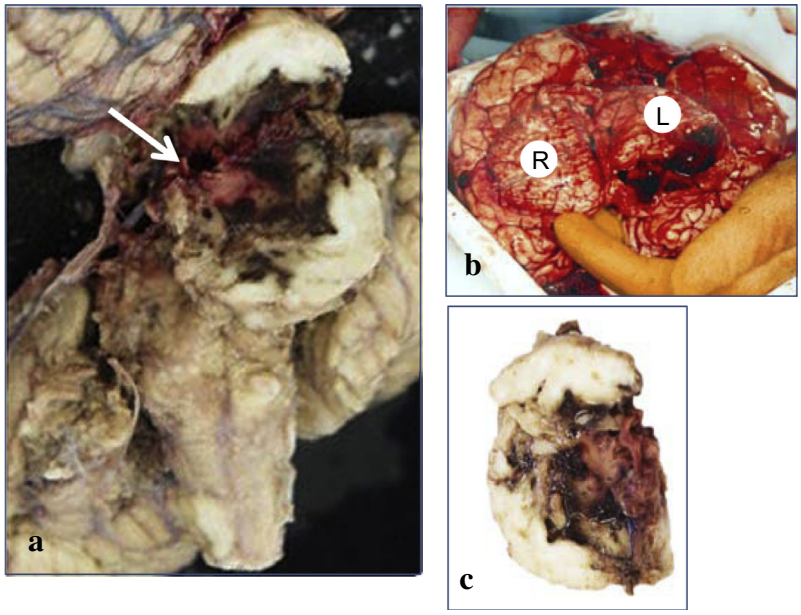

Fig. 1. Macroscopic view of the brain: (a) hemorrhagic necrosis of the pons (arrow) in the brain stem; (b) hemorrhagic necrosis of the left cerebellum (arrow); and (c) hemorrhagic necrosis inside the left cerebellum.

(350 mg/dl) and γ-GTP (76 U/L) were apparent in his routine annual work-place medical records. The deceased was not under any medical treatment nor was he a habitual smoker.

3. Materials and methods

3.1. Histological analysis

Isolated brain tissues were fixed with a phosphate-buffered 10% formalin solution for two weeks, dehydrated with a series of graded ethanol, and were xylene-treated before being embedded in paraffin for sectioning. Apart from staining with the hematoxylin and eosin reagent, the tissue sections were stained by the Elastic van Gieson and Bodian staining methods as well.

3.2. Immunohistochemistry

Antibodies against Aβ (Leica Microsystems, Tokyo, Japan), tau (Leica Microsystems), apoprotein E (ApoE; Millipore, Darmstadt, Germany), and CD34 (DAKO Japan) were used as the primary antibodies. The sections were sequentially treated with 3% hydrogen peroxide, 10% bovine serum and the aforesaid primary antibodies. Primary antibody binding was detected using a Histofine simple stain kit (Nichirei Biosciences, Tokyo, Japan), and the nuclei were stained with hematoxylin.

3.3. Quantification of histopathological changes

The numbers of SPs and NFTs were counted in the cortex and hippocampus in randomized 200× microscopic fields, and cerebral damage was evaluated according to Khachaturian's criteria for AD [11].

4. Results

4.1. Autopsy findings

The brain weight was 1511 g. Hemorrhagic necrosis involved mainly the brain stem (including the pons, diencephalon, and midbrain) and left cerebellum (Fig. 1a–c), and extensive necrosis was observed in the left thalamus. The ventricular and arachnoidal spaces were filled with blood. The primary site of ICH, however, could not be determined due to severe autolytic changes. Transtentorial herniation from the generalized brain edema was observed mainly at the lower interior portion of the left temporal lobe. The arteries, including the brain basilar arteries, showed weak atheromatous changes. The lungs showed severe congestion, and both pleural spaces contained a clear yellowish fluid (left, 150 ml; right, 70 ml). The gastric space was filled with blood, and multiple shallow ulcers ranging 1–3 mm in size were observed on the gastric mucosa. The liver (1463 g) and heart (405 g) showed fatty changes, while no abnormalities were detected in other organs, including the kidneys, pancreas, spleen and adrenal glands. Furthermore, there were no apparent signs of trauma or asphyxia.

4.2. Laboratory findings

Abnormal thyroid function (vs normal lower and upper range values) was detected by analysis of the autopsy blood sample: thyroid stimulating hormone (TSH) 0.491 μIU/mL (normal 0.500–5.00 μIU/mL), triiodothyronine 4.03 ng/mL (normal 0.08–1.60 ng/mL), free triiodothyronine 16.1 pg/mL (normal 2.30–4.30 pg/mL), total thyroxine 6.73 μg/dL (normal 6.10–12.4 μg/mL), free thyroxine 2.26 ng/dL (normal 0.90–1.70 ng/mL), and TSH receptor autoantibody 8.4 IU/L (normal <2.0 μIU/L). No drugs were detected by toxicological examination with LC/MS/MS analysis.

4.3. Histopathological and immunohistochemical findings

Thickening of walls in the small arteries and narrowing of vascular spaces in the cerebral parenchyma and arachnoid tissues were observed. Congo red staining revealed amyloid deposition in the arterial walls that showed brilliant green color under phase-contrast microscopy (Fig. 2a and b). Immunostaining of CD34, a marker for endothelial cells, was occasionally disrupted or negative in the affected arteries, while that of Aβ revealed deposition in the affected arteries (Fig. 2c). Either Congo red or Aβ staining was negative for the blood vessels in non-brain tissues.