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, Keiko Shimizu, Masaru Asari, Chikatoshi Maseda, Kumiko Oka, Hiromi Yamada, Chisato Hoshina, Hiroki Doi, Daisuke Yajima, Hiroshi Shiono, Katsuhiro Ogawa

Department of Legal Medicine, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan
Department of Oral and Maxillofacial Surgery, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan
Department of Legal Medicine, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8570, Japan
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).

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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 (178/132 mmHg), visceral fat type obesity (abdomen 92 cm, body mass index 26.3) and high values of serum acylglycerol
(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 lIU/mL (normal 0.50–5.00 lIU/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 lIU/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.
Atherosclerotic changes were minimal, while few microaneurysms were seen in the cerebral arteries.

The number of SPs, which is a focal spheroidal collection of dilated, tortuous, and neuritic processes associated with microglial cells and reactive astrocytes at their periphery, was increased in various parts of the cerebral cortex (Fig. 3a–d). Some SPs contained a central amyloid core, whereas others did not. Immunohistochemically, SPs stained positively for Aβ (Fig. 3b), tau (Fig. 3c) and ApoE4 (Fig. 3d). NFTs, which are bundles of filaments in the cytoplasm of the neurons, were detected (Fig. 3e and f), and were positively stained for tau (Fig. 3f).

The numbers of SPs and NFTs were 20 per 200× microscopic field in the hippocampus, 18 in the temporal lobe, 13 in the frontal lobe, 10 in the parietal lobe, and 5 in the occipital lobe. These numbers were clearly elevated in comparison with those of non-AD individuals in the same age group (2–5/200× microscopic field) [11].

5. Discussion

The cause of death in the present case was probably attributable ICH damaging a large part of the brain stem, left cerebellum and left thalamus. The severe pulmonary congestion observed at the time of autopsy might have resulted from sudden cardiac insufficiency from damage of the vasomotor center in the brain stem. An acute gastric hemorrhage might have occurred from the acute stress caused by the ICH, leading vomiting blood as observed in the mouth and nose of the patient. The extensive hemorrhagic necrosis in a large part of the brain stem and cerebellum suggests that the course from the ICH onset to the loss of consciousness might have occurred rapidly, preventing the subject from informing anyone of his condition.

It is likely that CAA and hypertension occurred simultaneously to cause ICH. Hypertension is a major cause of ICH in 50–60% of elderly cases, whereas CAA which accounts for 10–20% of ICH cases...
is the most frequent cause in non-hypertensive cases [3]. However, hypertension might couple with CAA to induce ICH, because treatment via lowering the blood pressure has been reported to provide protection from CAA-related ICH [8]. In the present case, although hypertension was detected when the subject was alive, he was not prescribed with the proper medication. Hyperthyroidism might have been at least partially responsible for the hypertension, because examination of serum taken at the autopsy revealed increased anti-TSH receptor autoantibody and thyroid hormone levels, and decreased TSH levels. Thyroid hormones elevate blood pressure by increasing cardiac output due to increased heart contractility and enhanced peripheral oxygen demand. As the severity of atherosclerosis observed was mild, it is thus less likely to have contributed to the cause of hypertension.

CAA, SPs, and NFTs are not necessarily the hallmarks of AD, since they are also observed in the non-AD elderly [8–12]; however, SPs and NFTs are usually small in number (<2–5/200× microscopic field) in persons under the age of 50 [11]. In the present case, the SP and NFTs counts were 5–20/200× microscopic field, indicating that the counts were clearly increased. Although AD had not manifested clinically, it is possible that latent AD might underlie the development of CAA, SPs and NFTs in this case.

Although the subject did not exhibit any cognitive impairment or other psychiatric signs indicative of AD, the disease has been known to progress over a period of 2–3 decades. It has been reported that long preclinical stages, termed the pre-mild cognition impairment (pre-MCI) and mild cognition impairment (MCI) stages, precede a symptomatic diagnosis of AD [8,13]. Histopathological changes may occur in patients with pre-MCI and MCI criteria before satisfying the AD criteria. In this case, it is speculated that the cerebral changes that would have progressed to AD with time were inadvertently discovered upon autopsy.

Epidemiological and genetic studies have revealed that there are two types of AD: early- and late-onset [6,13]. The age-range distribution of early-onset AD patients is 25–65 years, with the majority of cases being observed at age 40–50 years, whereas the number of late-onset AD patients exponentially increases after age 60. Most early-onset AD is caused by mutations in the APP gene on chromosome-21, presenilin-1 gene on chromosome-14 and presenilin-2 gene on chromosome-1, being inherited in the autosomal-dominant manner [14,15]. Late-onset AD is not associated with a determinant gene mutation; however, the most established genetic risk factor by far is allelic variation of the ApoE gene (ε2, ε3 and ε4) on chromosome-19 [16,17]. In most populations, possessing one ε4 allele increases the likelihood of an AD-inducing carrier, and carrying two copies will increase the likelihood even more. Furthermore, the ε4 gene contributes to an earlier start of syndromes typical of late-onset AD [18]. Information from genetic analysis and family history is helpful in clarifying the pathological basis underlying the neuronal changes observed in this autopsy case.

In summary, the present autopsy of a case with ICH in his 40s revealed that his death was associated with CAA, SPs, and NFTs, which are histopathological changes accompanying AD. This suggests that, because CAA derived from AD might underlie cause of death from ICH, search for amyloid deposition in the cerebral blood vessels as well as SPs and NFTs is important in the field of forensic medicine.

References
