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Cerebral amyloid angiopathy as a cause of an extensive brain hemorrhage in adult patient with Down's syndrome – a case report

Tadeusz Mendel[1], Ewa Bertrand[2], Grażyna M. Szpak[2], Tomasz Stępień[2], Teresa Wierzba-Bobrowicz[2]

[1]Second Department of Neurology, [2]Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland

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Abstract

A case of 54-year old woman who deceased due to consequence of extensive brain hemorrhage is presented. The patient was admitted to our Department of Neurology due to progressive quadriparesis as a complication of the cervical spinal cord compressive myelopathy. On the third day after neurosurgical decompression of the spinal cord sudden worsening of neurological and general condition was observed, finally caused death. An autopsy study revealed an extensive brain lobar hemorrhage and a dorsal-ventral compression of the cervical spinal cord. Alzheimer's disease-type degenerative changes with concomitant CAA were seen in light microscope examination. Extensive foci of demyelination were found especially in dorsal funiculi of the cervical spinal cord. Smaller foci of demyelination were present in anterior funiculi due to the stenosis of vertebral canal.

Key words: cerebral amyloid angiopathy, Down's syndrome, brain hemorrhage, spinal cord compression.

Introduction

Cerebral amyloid angiopathy (CAA) is a progressive degenerative process of leptomeningeal and brain parenchymal vessels caused by accumulation of amyloid deposits in their walls [2,11,16,25,28].

Amyloid deposition is a prominent feature of a number brain disorders, in which amyloid fibrils are found within blood vessel walls, the neuropil (neuritic plaques) and neurons (neurofibrillary tangles) [14,25,30]. These include Alzheimer's disease (AD), AD changes associated with Down's syndrome (DS), neurologically asymptomatic amyloidosis, Parkinson dementia of Guam, dementia with Lewy bodies (DLB), hereditary cerebral hemorrhage with amyloidosis of Icelandic origin (HCHWA-I), hereditary cerebral hemorrhage with amyloidosis of Dutch origin (HCHWA-D), and sporadic cerebral amyloid angiopathy (SCAA) [1,4,8,9,13,25].

There are pathological associations between β-amyloid protein, apolipoprotein alleles, CAA, Alzheimer's

Communicating author:
Tadeusz Mendel, MD, PhD, 2nd Department of Neurology, Institute of Psychiatry and Neurology, Sobieskiego Str. 9, 02-957 Warsaw, Poland, phone +48 22 458 28 27, e-mail: mendel@ipin.edu.pl

disease and Down's syndrome [3,16-18,27]. CAA is frequently associated with Alzheimer's disease; however the relationship between CAA and Down's syndrome is poorly known [20]. Middle-age Down's syndrome patients develop dementia with pathological hallmarks that are characteristic for Alzheimer's disease [30]. Autosomal dominant Aβ-related CAA had been mainly associated with rare missense mutation of the APP gene located within the Aβ coding sequence [5].

Down syndrome is common genetic disorder affecting around 1 in 800 live birds in the human population [17,19]. It is caused by a complete, or occasionally partial, triplication of chromosome 21 resulting in a complex and variable phenotype [10,16]. The mechanism by which trisomy 21 leads to the characteristic Down's syndrome phenotype are unclear.

The disorder is primarily characterized by cognitive and language dysfunction coupled with sensory and neuromotor deficits and a neuropathology primary characterized by decreased brain size and weight plus abnormal gyrification and neurogenesis. DS are also individuals who are likely to suffer from a board range of symptoms outside of the nervous system, including abnormal craniofacial development, congenital heart problems, and immune defects [15,19,29].

We present a case of a middle-aged woman with Down's syndrome who apart from the expected lesions of Alzheimer's disease had widespread CAA with subsequent intracerebral hemorrhage which was the immediate cause of death.

Case presentation

A 54-year-old female with Down syndrome was admitted to our Department of Neurology due to progressive quadriparesis as a complication of the cervical spinal cord compressive myelopathy lasting for a few hours. Cervical spinal cord compression localized in C4-C6 was confirmed by MRI (Fig. 1).

She lived at home with parents and functioned independently. Past medical history was entirely noncontributory with no evidence of diabetes or atherosclerosis. She had no family history of dementia or intracerebral hemorrhage.

She had neurosurgical decompression of the spinal cord. On the third day after operation sudden worsening of neurological and general condition was observed, finally caused death.

Material and methods

The brain autopsy material was fixed in 4% paraformaldehyde in 0.1 M phosphorane-buffer saline and embedded in paraffin. The specimens were stained with H&E, PAS, Congo Red, Klüver-Barrera methods and immunohistochemically with the following antibodies; neurofilaments (NFTs, Novocastra, 1 : 50), anti tau (DAKO, 1 : 200), anti Aβ 1-40 (Serotec, 1 : 250), anti Aβ 1-42 (Serotec, 1 : 250) and anti ubiqutin (DAKO, 1 : 150).

Results

An autopsy study revealed an extensive brain lobar hemorrhage (Fig. 2) and a dorsal-ventral compression of the cervical spinal cord on the level C4-C6 (Figs. 3 and 4). Alzheimer's disease-type degenerative changes presenting as a many amyloid plaques and neurofibrillary tangles with concomitant cerebral amyloid angiopathy were seen in light microscope examination using immunohistochemical methods (Aβ and tau) (Figs. 5 and 6). Tau staining neurofibrillary tangles and neuropil threads were observed mainly in the frontal cortex (Fig. 6). Alzheimer's like changes in CA1 region of the amonal cortex were presented using ubiquityn (Fig. 7). Cerebral amyloid angiopathy (CAA) was diagnosed showing severe Aβ deposits in the wall of the meningeal vessels (Fig. 8)

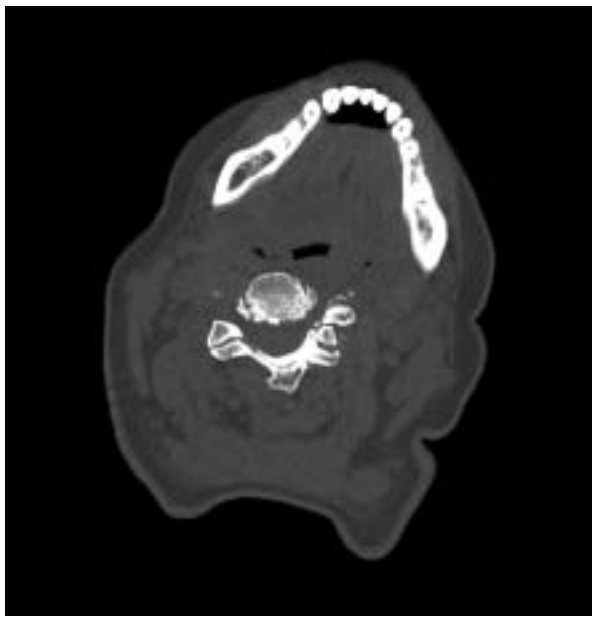

Fig. 1. A magnetic resonance imaging scan of the cervical spinal cord. Cervical spinal cord compression at the C4-C6 level.

Fig. 2. Haemorrhagic infarct in the patient with cerebral amyloid angiopathy and Down's syndrome.

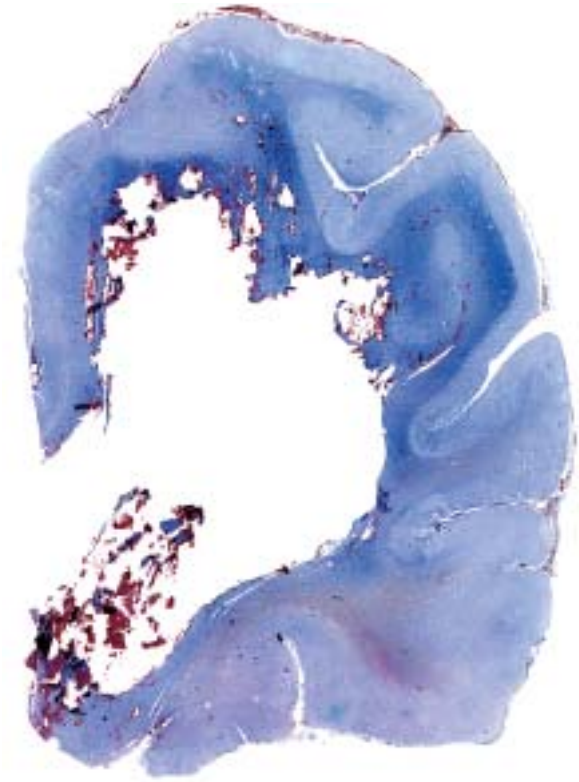

Fig. 3. Haemorrhagic focus in the substantia alba in the frontal lobe. Klüver-Barrera.

Fig. 4. Maculated demyelinization area in the substantia alba of the cervical spinal cord. Klüver-Barrera.

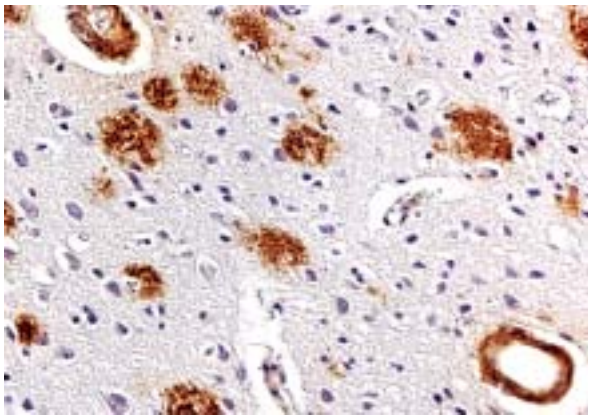

Fig. 5. Amyloid plaques and Aβ deposits in the wall of cortical vessels. Anti-Aβ. × 200.

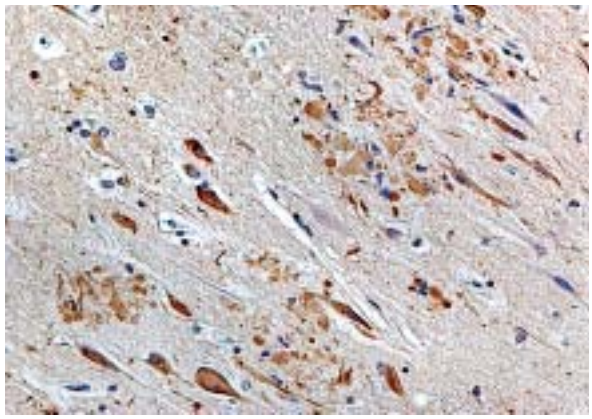

Fig. 6. Neurofibrillary tangles (NFTs) and neuropil threads in the frontal cortex. Anti-tau. × 200.

and cortical vessels (Fig. 9) mostly localized in frontal and occipital lobes.

In dorsal-ventral compression of the cervical spinal cord on the level C4-C6 demyelination as result of spinal cord compression was diagnosed. Extensive foci of demyelination were found especially in dorsal funiculi (Fig. 10) and in anterior funiculi due to the stenosis of vertebral canal (Fig. 11).

The general autopsy performed on this patient was otherwise unremarkable.

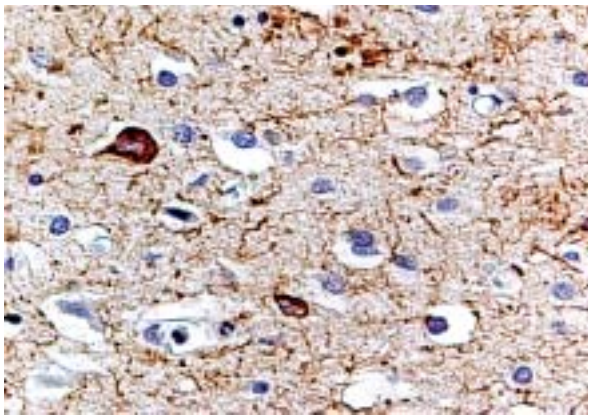

Fig. 7. Alzheimer's-like changes in the CA1 region of the amonal cortex. Anti-ubiquitin × 200.

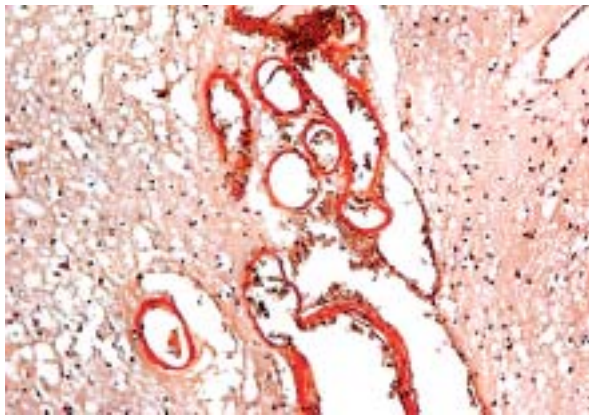

Fig. 8. Aβ deposits in the wall of meningeal vessels. Congo red. × 100.

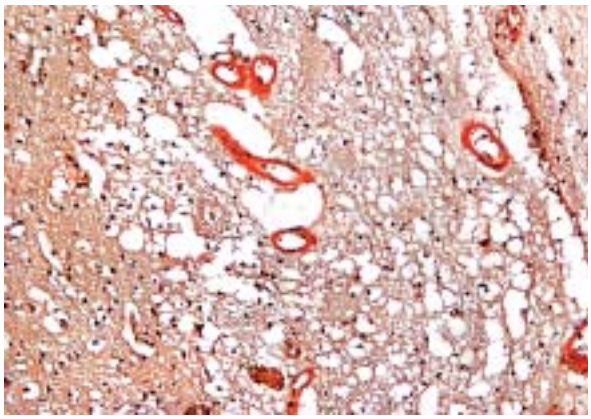

Fig. 9. Aβ deposits in cervical vessels. Congo red. × 200.

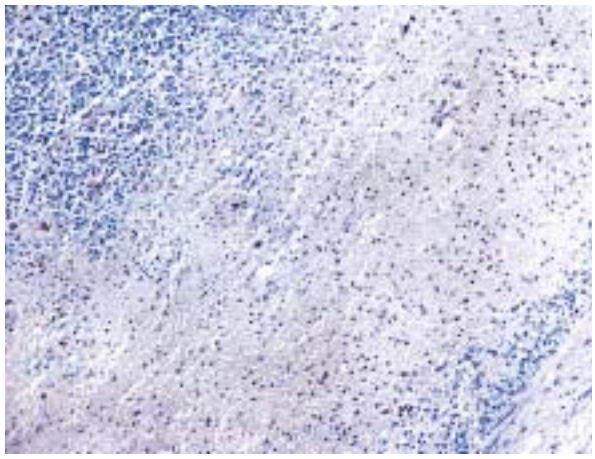

Fig. 10. Demyelinization of the substantia alba in the posterior funiculus directly to the end of the gray posterior commissure. Klüver-Barrera × 100.

Diagnosis

Cerebral amyloid angiopathy as a cause of an extensive brain hemorrhage in adult patient with Down's syndrome and the dorsal ventral compression of the cervical spinal cord on the level C4-C6.

Discussion

We present a case of middle-aged woman with Down's syndrome who apart from the expected lesions of Alzheimer's disease had widespread CAA with subsequent intracerebral hemorrhage which was the immediate cause of death.

The present case is unusual in that Down's syndrome, Alzheimer's disease, CAA and intracerebral

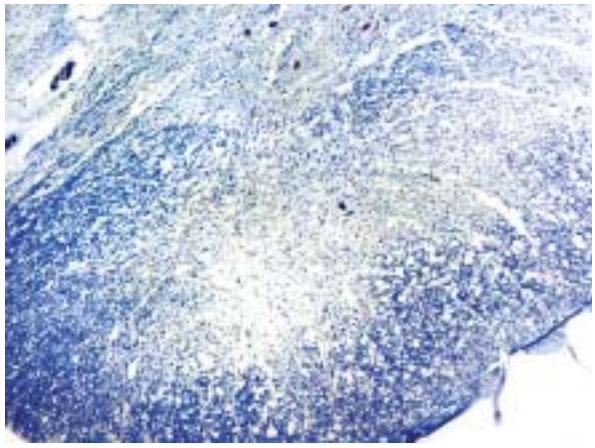

Fig. 11. Demyelinization area in the substantia alba in the anterior funiculus of the cervical spinal cord. Klüver-Barrera. × 50.

hemorrhage were found to coexist in a single patient. Intracerebral hemorrhage was arisen as a result of CAA.

Patients with Down's syndrome are described to have stroke [3,8,21]. In a 10-year follow-up of more than 10 000 individuals with Down's syndrome, prevalence of cerebrovascular diseases as a cause of mortality was found to be more frequent in this population than expected in the general population according to age and gender [7]. The association of Down's syndrome with the precious development of Alzheimer's disease was first reported by Jevis in 1948. He described the characteristic features of neurofibrillary tangles and senile plaques in three Down's patients [3]. Ellis generalized that "in Down's syndrome, the reward for survival beyond age forty is presenile dementia" [9]. Glenner and Wong in 1984 isolated from the cerebrovascular amyloid the protein β in Alzheimer's disease, which was homologous to a similar amyloid protein found in adult Down's syndrome [12]. Down's syndrome patients express abnormally high levels of APP, as a result of their having three copies of chromosome 21 (on which the gene encoding APP is located). These patients nearly always develop early-onset AD [5,19,22,23]. Very young DS brains contain high levels of diffuse Aβ1-42 amyloid, an apparently nonfibrillar form of Aβ aggregate that is not associated with surrounding neuronal death [16]. The documented association of Down's syndrome with CAA is not common. There are only a few reports of cerebral hemorrhage in patients with CAA and DS [3,8,10,20,21,24].

CAA is known as a cause in 5-10% of spontaneous intracerebral hemorrhage [8]. CAA has been found to be an important cause of massive, non-traumatic, non-hypertensive cerebral hemorrhage in the elderly [3,25]. In 1985, Cosgrove presented 7 of 24 patients of whom no other cause of hemorrhage could be demonstrated at autopsy [6].

Cerebral amyloid angiopathy and Alzheimer's disease may occur in Down's syndrome, presumably because of the increases expression of β-amyloid precursor protein (APP) associated with trisomy 21, the chromosomal location of the APP gene [5,19,22,23]. The overexpression of the amyloid precursor protein (APP) gene on chromosome 21 has been proposed as the central event leading to AD pathology in DS in keeping with the amyloid cascade hypothesis [19].

The co-existence of NFTs and Aβ plaques in Down's syndrome (trisomy 21) patients suggests that extra copies of genes on chromosome 21 are capable of inducing the pathologic lesions characteristic of AD [11]. In DS patients, three copies of APP gene, possession of the apoE4 allele, and age (46 years) predisposed to Alzheimer's disease and cerebral amyloid angiopathy whereas the apoE ε2 allele predisposed to haemorrhage from the amyloid laden blood vessels [21].

The clinical manifestations of DS are variable. Atlantoaxial dislocation or subluxation occurs in 10 to 20% of patients with DS [15]. DS patients develop dementia of Alzheimer type 20-30 years earlier than people in the general population and older DS patients are more frequently affected by this type of dementia [16,26].

Conclusions

It should be remembered that having a patient with Down's syndrome not only Alzheimer's disease type degenerative changes can occur, but also cerebral amyloid angiopathy. Intracerebral hemorrhages as a complication of CAA can cause a death in patients with Down's syndrome.

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