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Case report

Hemorrhagic stroke, cerebral amyloid angiopathy, Down syndrome and the Boston criteria☆

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ABSTRACT

A stroke, or a cerebrovascular accident (CVA) is a life-threatening condition which often results in permanent or significant disability in the adult population. Several classifications of CVAs exist, one of them being based on the mechanism of injury of brain tissue: ischemic (85–90%) and hemorrhagic (10–15%). In a hemorrhagic stroke an intercranial bleeding occurs, leading to the formation of a focal hematoma typically located in the basal ganglia of the brain (approx. 45% of cases). A common yet underestimated cause of intracerebral hemorrhage is cerebral small vessel disease with microhemorrhages, including the cerebral amyloid angiopathy (CAA). This condition is associated with the deposition of amyloid-beta in arterial walls (in soft meninges, subcortical areas and the cerebral cortex). Research has shown that causes of hemorrhagic changes in the brain include genetic disorders, such as Down syndrome. The association is caused by the so-called 'gene dosage effect', as the gene for the precursor protein for amyloid-beta is located in chromosome 21. We wish to present the case of a 60 year old patient with Down syndrome who suffered a hemorrhagic stroke without antecedent hypertension. Based on the history taken, diagnostic imaging and the source literature, a diagnosis of cerebral amyloid angiopathy as the source of the bleeding was made (however it must be noted that without a full post-mortem examination, the Boston criteria allow only for a 'probable cerebral amyloid angiopathy' diagnosis to be made). The authors hereby also report the need to modify the Boston criteria for cerebral amyloid angiopathy.

1. Introduction

According to the World Health Organisation report, cerebrovascular diseases including strokes are the second leading cause of death in high and middle-income countries, surpassed only by the ischemic heart disease [1]. Projections of global mortality and disease burden until the year 2030 predict an increase in the number of deaths caused by strokes, which is attributed to an aging population [2]. Poland is one of

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the few Eastern European countries with rising mortality rates due to strokes [3]. The poorest outcomes were associated with hemorrhagic strokes: the intracerebral hemorrhage and the subarachnoid hemorrhage [4,5]. Classic risk factors for intracerebral hemorrhage are hypertension, aneurysms, vascular malformations, bleeding diatheses, the use of psychoactive substances, brain tumors and cerebral amyloid angiopathy, among others [6]. According to the source literature, the cerebral amyloid angiopathy was found in approximately one third of patients with lobar intracerebral hemorrhages [7]. Pathological changes associated with CAA may be found in patients with Alzheimer's disease as well as Down syndrome, although their importance in the latter case is not fully understood. There are reported cases from various countries, including Poland, of histologically confirmed intracerebral hemorrhages in patients with Down syndrome with coexisting cerebral amyloid angiopathy [8–10]. In Down syndrome there is an overexpression of genes located in the triplicated chromosome 21. In case of *APP* (amyloid precursor protein APP) the expression is increased four to five times in individuals with DS (Ann N Y Acad Sci. 1993 Sep 24;695:91–102. Regulation and expression of the Alzheimer's beta/A4 amyloid protein precursor in health, disease, and Down's syndrome. Beyreuther K, Pollwein P, Multhaup G, Mönning U, König G, Dyrks T, Schubert W, Masters CL). This overexpression of APP is thought to be responsible for Alzheimer's-like dementia in patients with DS (Neurology 2004; 62:1996–1998, M. Margallo-Lana, C.M. Morris, A.M. Gibson, et al.). The AD-like dementia start at the median age of 50 years, which strongly suggests that beta-amyloid exists not only in the brain but also in small vessels. However, only 22% of patients suffering from AD have cerebral microbleeds. (Cerebral microbleeds and Alzheimer's disease, Charlotte Cordonnier and Wiesje M. van der Flier, in Cerebral Microbleeds edited by David J. Werring, Cambridge University Press, London, 2011). The post-mortem examination of 117 brains of patients with AD revealed signs of CAA in 97 brains (83%), out of which 30 (25,6%) showed moderate to severe CAA. Brains in the latter group revealed more ischemic and hemorrhagic changes compared to the group with little to no amyloid angiopathy (Neurology. 1996 Jun;46(6):1592–6. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. Ellis RJ, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, Heyman A). The available body of research indicates that there is a connection between the *APP* gene expression, CAA and hemorrhagic strokes.

This study presents the case of a Down syndrome patient; after taking into consideration the patient's history, pathogenesis, and additional diagnostic studies, it was possible to establish an antemortem diagnosis of probable cerebral amyloid angiopathy based on the Boston criteria. However, the authors maintain that by applying the Occam's razor principle, the degree of probability is much higher than the criteria would lead one to believe.

2. Case report

A 60-year-old patient with Down syndrome (diagnosis based on patient's phenotype as well as available documentation) was admitted to the clinic with an acute onset of right-sided hemiparesis preceded by loss of consciousness. There were no signs of cranial trauma, nor any information indicative thereof from the paramedics. Neurological examination on admission revealed that the patient was conscious, somnolent, with incoherent speech, had eye deviation towards the left side, central facial palsy, paralysis of right upper limb and vestigial movement in right lower limb. Plantar reflex was present in the right lower limb. Deep tendon reflexes were diminished on the right side. The CBC, PT, PTT, LFTs, glucose and BUN values were within normal limits. A CT scan revealed a hemorrhagic focus in deep structures of the left hemisphere, which corresponded to the presented symptoms (Fig. 1) as well as bilateral lacunae of approx. 6 mm in diameter in basal ganglia.

In addition, calcifications in lenticular nuclei were noted. The patient was disqualified from surgical management. Due to the lack of history of hypertension, a contrast enhanced head MRI with a susceptibility weighted imaging (SWI) sequence was ordered to differentiate from other causes of bleeding, bearing in mind the association between Down

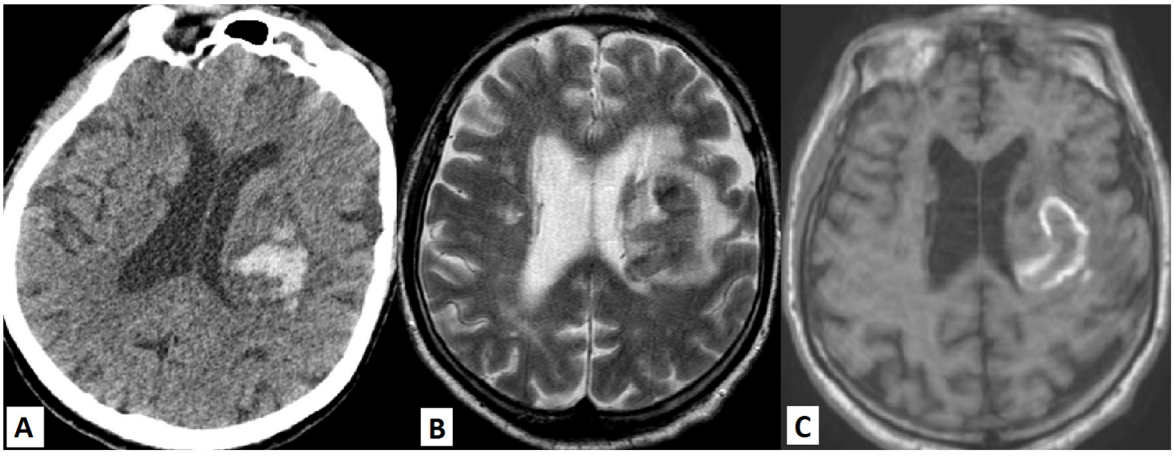

Fig. 1 – Hemorrhagic region in early subacute stage in deep structures of the left hemisphere with surrounding edema and modeling of the lateral ventricle. Also periventricular lacunar infarcts can be noticed on both sides. A – CT scan, B – T2-dependent axial image, C – T1-dependent axial image.

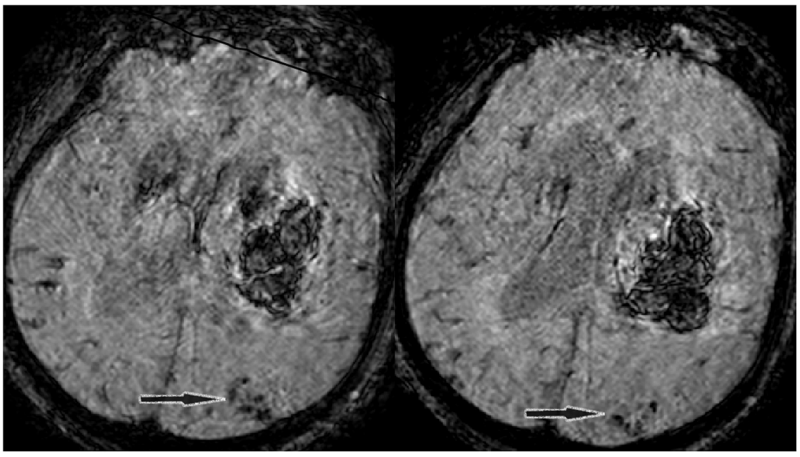

Fig. 2 – SWI axial images. The large hemorrhagic region in deep structures of the left hemisphere. The smaller areas of signal loss in the left occipital lobe indicating bleeding – arrows.

syndrome and CAA. The study revealed a subacute hemorrhagic focus (43 mm × 28 mm × 51 mm) in the left hemisphere. The SWI sequence showed small low-signal lesions scattered subcortically, with the highest concentration in the left occipital lobe. In addition, periventricular lesions congruent with vascular changes were noted. An ultrasound of carotid and vertebral arteries revealed no significant hemodynamic changes (Fig. 2).

The patient's condition fluctuated throughout the hospital stay. A severe case of pneumonia unresponsive to treatment developed, which subsequently led to the patient's death a month later. Due to a known cause of death as well as the wishes of the patient's family, an autopsy was not performed.

3. Discussion

The Boston criteria (proposed by neurologists studying strokes in the Boston region and published in 2001) allow only for the diagnosis of a 'probable amyloid angiopathy' to be made. However, an evaluation of the criteria showed a 100% correlation between radiologic changes seen in the CT scan and/or MRI characteristic for the cerebral amyloid angiopathy, and changes found in autopsy material [11]. A more recent study applied and evaluated the Boston criteria to a population suffering from a hereditary form of amyloidosis, the Dutch-type cerebral CAA, characterised by a mutation in codon 693 of the *APP* gene. Both in the symptomatic and asymptomatic groups of patients (an improvement on the original 2001 study) a T2* MRI sequence had a high sensitivity in detecting CAA lesions. The sensitivity of the Boston criteria improved when microbleeds were included, and it did not decrease with the exclusion of hemorrhages in the deep white matter, basal ganglia, thalamus, and brainstem. (Descriptive Analysis of the Boston Criteria Applied to a Dutch-Type Cerebral Amyloid Angiopathy Population van Rooden, MSc; Jeroen van der Grond, PhD; Rivka van den Boom, MD, PhD; Joost Haan, MD, PhD; Jennifer Linn, MD; Steven M. Greenberg, MD, PhD; Mark A. van Buchem, MD, PhD). However, other pathologies presenting with asymptomatic microbleeds such as Fabry disease, CADASIL, CARASIL, COL4A1 and COL4A2 mutations related microangiopathy, or Susac's syndrome [12,13]. The Boston criteria have not been updated in over a decade, and they do not take into account the genetic and pathologic link between Down syndrome and the cerebral amyloid angiopathy.

According to the authors of this study, a careful evaluation of the Boston criteria [11], case reports [8–10], imaging studies and exclusion of other causes of hemorrhage provide an antemortem diagnosis of cerebral amyloid angiopathy with a greater degree of probability that the Boston criteria in isolation. An analogy can be made to the evolution of diagnostic criteria of Alzheimer disease. It is now acceptable to make such a diagnosis based on the patient's history, imaging studies and genetic profiling to exclude the trisomy of the 21 chromosome, without a histopathological confirmation [14], which several decades ago would not have been possible [15].

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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