



Case report

“A case report: Co-occurrence of cerebral amyloid angiopathy and multiple sclerosis”



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ABSTRACT

Cerebral amyloid angiopathy (CAA) is a chronic pathological condition characterized by progressive accumulation of amyloid protein in the wall of cerebral blood vessels, both leptomeningeal and cortical.

That may result in the development of such conditions as microaneurysms, hemorrhagic, ischaemic brain injury and contribute to cognitive impairment.

We herein report a case of Iowa-type hereditary cerebral amyloid angiopathy (CAA) mutation diagnosed with MS. The family of the reported patient had performed genetic testing due to the history of intracerebral hemorrhage. Sequence analysis of exon 17 of the APP gene showed the presence of the D694N g.275272 G > A (c.2080 G > A) mutation, which caused the substitution of aspartate for asparagine at position 694 of APP. Alike the discussed patient, this mutation has been found in other family members in an autosomal dominant pattern of inheritance. Contrary to the rest of the family, the reported patient has been diagnosed with multiple sclerosis based on McDonald criteria.

Recent studies shed light on the possible link between the APP accumulation and MS progression. It has been indicated that amyloid can prove a vital role in neuroimmunology, whereas the accumulation of APP in the CNS has been suggested to be a potential biomarker for the progression of MS. Moreover, the amyloid positron-emission tomography (amyloid-PET) has been demonstrated to serve as a diagnostic tool for establishing the degree of demyelination and remyelination in MS.

Even though, one swallow does not make a summer, this finding would be another step forward in the understanding of pathological processes underlying the pathogenesis of MS.

1. Introduction

Cerebral amyloid angiopathy (CAA) is a chronic pathological condition characterized by the progressive accumulation of amyloid protein in the wall of cerebral blood vessels, both within the leptomeningeal and cortical regions of the brain. This condition can present with different clinical manifestations, such as microaneurysms, and hemorrhagic and ischemic brain injuries (Vinters, 1987; Revesz et al., 2003). Among the CAA cases, the hereditary forms of CAA are fairly rare and the pathophysiology of many forms is still under debate (Mok et al., 2014). Nonetheless, the majority of these forms of CAA are related to mutations of the genes encoding the amyloid- β precursor protein (APP) (familial form of amyloid angiopathy Dutch type), cystatin (Icelandic type), gelsolin (Finnish type), and others (Greenberg, 2002).

Multiple sclerosis (MS) is a chronic autoimmune disorder resulting

in recurrent attacks on the myelinated axons in the central nervous system (CNS), leading to the gradual accumulation of multifocal demyelinated lesions (Calabresi, 2004; Hauser and Goodwin, 2008; Weinschenker, 1996; Olek, 2011). Interestingly, recent reports suggest that the decisive event in MS pathogenesis is the focal extravascular leakage of blood components as a consequence of blood-brain barrier integrity failure (Frohman et al., 2006). Recent research has detected APP expression in axons surrounding the plaques in MS and the correlation of amyloid- β with the different stages of MS has been proven. These findings add to the hypothesis that amyloid may be a key player in the development of MS.

For the first time, we present a clinical case of a patient with the Iowa-type hereditary CAA mutation who was diagnosed with MS. To this date, the patient has not developed the typical clinical manifestations of the mutation such as leukoencephalopathy, calcifications in the occipital lobes of the brain, or progressive cognitive impairment.

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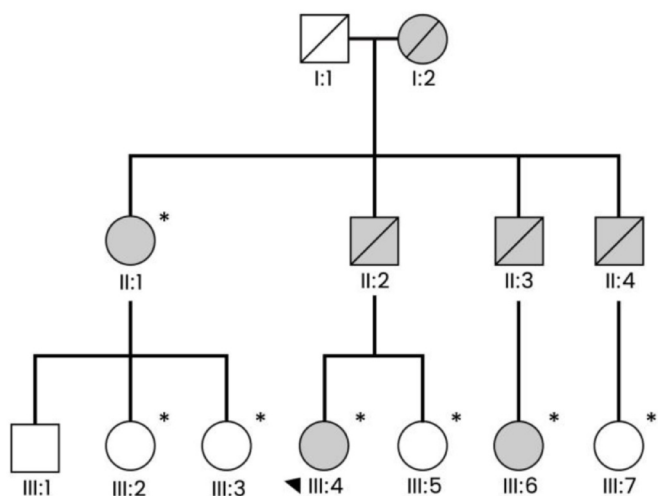


Fig. 1. Family tree of the patient with MS and the Iowa-type hereditary CAA mutation. Illustration by Paulina Szuba.

2. Case report

A female patient III:4 (Fig. 1) aged 33 has been diagnosed with MS. Unlike the rest of her family affected by the previously mentioned mutation, the patient smoked an average of 50 cigarettes per week and has done so since adolescence. She was admitted to the Department of Neurology for the first time in 2010 at the age of 24 years. At the time of admission, she presented with weakness of the right upper limb, which lasted for one week. At that time, an MRI was performed revealing a disseminated demyelinating process occurring within the brain and the medulla.

Subsequently, an MRI in T2 and FLAIR sequences were performed. It showed numerous hyperintense scattered lesions of various sizes in the white matter of both hemispheres of the brain within the frontal and parietal lobes, in the periventricular and juxtacortical locations. The area of the larger foci measured up to 6 mm. Single foci were also presented in the temporal lobes (Fig 2-3).

In the sagittal plane, smaller foci up to 4 mm were present in the corpus callosum. An ischemic change of 12 × 2 mm was found in the anterior leg and knee of the right internal capsule. The proton density-weight images also revealed demyelinating lesions in the spinal cord at C1, C2, C3 level and the upper edge of the C4 vertebra.

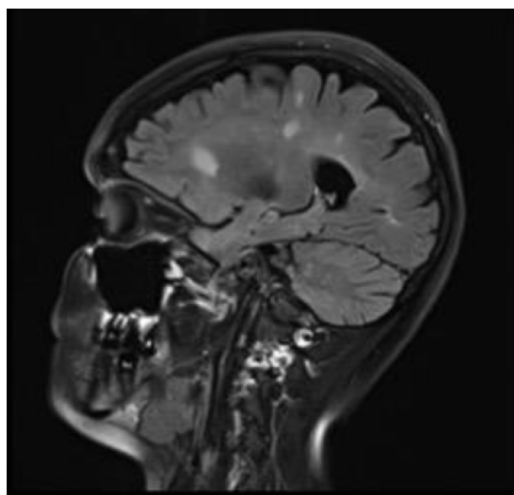


Fig. 2. Sagittal fluid-attenuated inversion recovery (FLAIR) image displaying multiple lesions within the frontal lobe and the temporal lobe of the brain corresponding to multiple sclerosis.

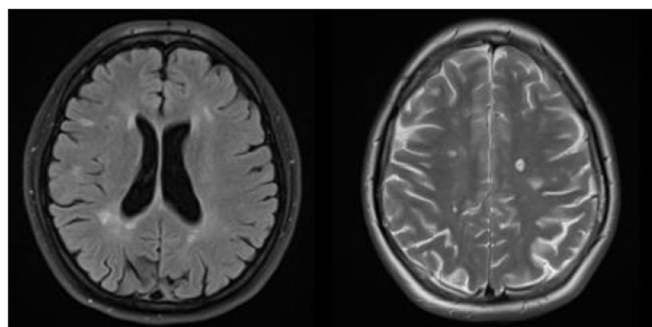


Fig. 3. Axial fluid-attenuated inversion recovery (FLAIR) on the left and an axial T2-weighted MRI on the right displaying multiple lesions consistent with multiple sclerosis.

The second relapse of MS occurred in 2018 when the patient was 32 years old. During her second admission, the patient presented with weakness of the left lower limb and paresthesia of the left half of the torso, resolving after one month. At that time, a brain MRI was performed, revealing new demyelinating lesions in both hemispheres. The area of the larger foci now measured up to 14 mm. In the medial parts of the cerebellum including the pedunculus and the pons, similar changes of up to about 7 mm were found. No focal changes enhanced (Fig. 4). Therefore, the diagnosis of MS was made based on McDonald criteria.

3. Genetic studies

Fig. 1 presents the family members who underwent genetic testing due to history of intracerebral hemorrhage. The patient's aunt II:1 was first found to have a mutation. Sequence analysis of exon 17 of the APP gene showed the presence of the D694N g.275272 G > A (c.2080 G > A) mutation, which caused the substitution of aspartate for asparagine at position 694 of APP. D694N corresponds to position 23 of amyloid-β. This mutation was then found in our patient and her cousin III:6 in an autosomal dominant pattern of inheritance.

The biological effect of this mutation has been shown to affect peptide structure in vitro, changing the structure of the protein by introducing a turn instead of a bend motif (Krone et al., 2008). Further in vitro experiments have proven that this mutation promotes fibrillogenesis of amyloid-β resulting in greater amyloid-induced toxicity (Van Nostrand et al., 2002 Nov; Van Nostrand et al., 2001), and suggests that patients with this mutation may have a higher predisposition for developing MS.

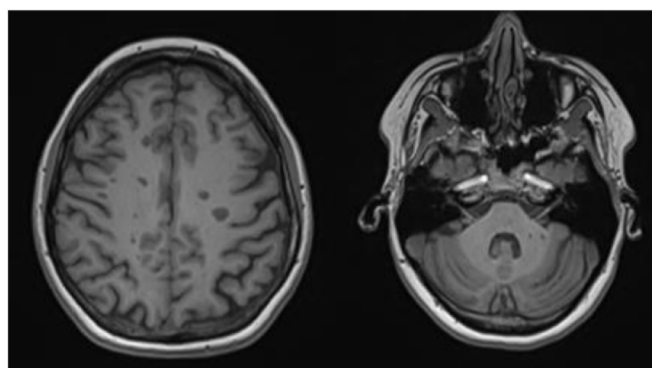


Fig. 4. Axial fluid-attenuated inversion recovery (FLAIR) images showing non-enhancing multiple lesions linked to the development of multiple sclerosis.

4. Family medical history

According to the family history, the patient's grandmother (I:2) presented with her first episode of stroke at the age of 40 and died of a hemorrhagic stroke 20 years later aged 60. The patient's grandfather (I:1) died at the age of 76 without any neurological disorders. The patient's cousin (III:6) was admitted to a neurological clinic at age 30 because of a menstrual migraine. A neurological examination found no symptoms in this patient and an MRI revealed no abnormalities. The patient's father and two uncles died in middle age due to hemorrhagic strokes.

The patient's eldest uncle (II:4) was brought to the clinic at age 47 with a severe headache. A 28 × 20 × 20 mm hematoma involving the right temporal lobe was found (without vascular defects in cerebral angiography). Six months later, a 65 × 28 mm midbrain hematoma of the left hemisphere was discovered when it resulted in aphasia and right-sided hemiparesis. He suffered from another hemorrhagic stroke, 6 × 4.5 × 4.5 cm in the left fronto-temporal region three years later, and he died at the age of 54, suffering from post-stroke epilepsy. There were no other risk factors for stroke in this patient.

The patient's second uncle (II:3) suffered from left-sided hemianopsia as a result of a hematoma, 2.3 cm, at the age of 38. He was diagnosed with seizures five years later, and was treated with carbamazepine. Another stroke, a 40 × 25 mm hemorrhage in the left temporal lobe occurred at the age of 44, and at the age of 46, he suffered another hemorrhagic stroke caused by an intracerebral hematoma, 50 × 40 × 60 mm, in the temporal and parietal lobes, with a rupture into the right lateral ventricle. This resulted in left-sided hemiparesis, and he died a month later.

The patient's aunt (II:1) suffered a cerebral hemorrhagic stroke in the left occipital lobe at the age of 43. She had been diagnosed with depression six years prior and presented with no risk factors for stroke. Her first symptoms were left-sided hemicrania, right homonymous superior quadrantanopia and dizziness, and CT revealed a 62 × 34 mm hematoma in the left occipital lobe and numerous small ischemic changes. An MRI showed scarring and softening areas in the left occipital lobe, a post-stroke cavity at the base of the left temporal lobe, and numerous scattered ischemic changes in the white matter. Two years later, she suffered a secondary generalized tonic-clonic seizure, and today is cognitively impaired with features of dementia.

The patient's father (II:2) suffered a hemorrhagic stroke at the age of 42. An intracerebral hematoma 5.5 × 3.5 cm in the right temporal region was surgically evacuated. After four months, a recurrent intracerebral hemorrhage in the same region was treated conservatively. At the age of 47, he suffered from more hemorrhages in the left hemisphere of the brain that eventually resulted in cortical blindness and aphasia. He died at the age of 48.

5. Discussion

We present an uncommon case of a patient with Iowa-type hereditary mutation diagnosed with MS. Recent studies shed light on the possible link between APP accumulation and MS progression. It has been indicated that amyloid may prove to play a vital role in neuroimmunology, and this remains a topic of active research. The accumulation of APP in the CNS has been suggested to be a potential biomarker for the progression of MS (Chandra, 2015). Amyloid positron-emission tomography (amyloid-PET) has been demonstrated in another study to be a viable diagnostic tool for establishing the degree of demyelination and remyelination in MS. Matías-Guiu et al. reported that in patients with MS, B-APP accumulates in damaged axons (Matías-Guiu et al., 2016), and pathology studies have supported their findings of an increased expression of amyloid-β expression in demyelinating plaques (Lassmann, 2011; Trapp et al., 1998; Ferguson et al., 1997).

This case report adds to the literature surrounding APP contribution in the development of MS. However, this is an unprecedented

hypothesis. To date, it is difficult to distinguish the role of AP accumulation in MS, as the literature thus far has not yet provided any solid evidence. Further studies are required before definitive conclusions can be made. Moreover, there have not been any reports as to how the Iowa-type hereditary mutation may be manifested in MS.

6. Conclusion

Whenever a patient presents with an intracerebral hemorrhage, many factors such as hypertension, cerebral aneurysms, vascular malformations, amyloid angiopathy, bleeding disorders, brain tumors, head trauma, drugs, and others should always be taken into consideration.

Until now, there have not been many reports on the Iowa-type hereditary cerebral amyloid angiopathy. Little is known about the link between MS and CAA. However, the increasing number of articles concerning the role of APP in MS indicates that there should be a higher index of suspicion in patients with the APP mutation. Hereditary forms of CAA, while rare, should be considered during differential diagnosis of MS. We believe that this case is another step towards understanding the pathological processes underlying the pathogenesis of MS. This presentation of a Polish family with an Iowa-type mutation suggests that a deeper analysis of the family history in every patient with hemorrhagic stroke may increase the opportunity for effective preventative treatment.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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