SHORT REPORT

Familial leptomeningeal amyloidosis with a transthyretin variant Asp18Gly representing repeated subarachnoid haemorrhages with superficial siderosis

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Objectives: To report the clinical features of two Japanese brothers with familial leptomeningeal amyloidosis, showing a causative gene abnormality of a transthyretin (TTR) variant Asp18Gly, previously reported only in a Hungarian family.

Methods: The authors reported on a 42 year old man (patient 1) and his 45 year old brother (patient 2), both suffering from subarachnoid haemorrhage (SAH) without and with hydrocephalus, respectively. DNA sequences of the TTR gene were determined in both patients and the patients' clinical features described. A surgical biopsy of the leptomeninges was performed on patient 1.

Results: DNA sequence analyses demonstrated the glycine-for-aspartate substitution at position 18 of the TTR variant. Both patients revealed pyramidal tract signs and cerebellar ataxia. Audiometric studies showed bilateral, mild sensorineural hearing loss in the patients whose cerebrospinal fluid (CSF) protein levels increased. T1 weighted MRI after contrast administration showed diffuse leptomeningeal enhancement along the Sylvian fissures and over the surface of the brainstem, cerebellum, and spinal cord. Gradient echo T2* weighted MRI showed superficial siderosis mainly in the cerebellum. A biopsy of the leptomeninges was obtained from the spinal cord of patient 1. While performing the biopsy, the authors observed the varicose, elongating, and fragile veins on the dorsal surface of the spinal cord. Immunohistochemical study revealed marked deposits of TTR derived amyloid on his leptomeninges.

Conclusions: This is the second report of familial leptomeningeal amyloidosis with an Asp18Gly TTR gene mutation, clinically causing only CNS symptoms. Repeated SAH from fragile veins on the dorsal surface of the spinal cord seemed to induce superficial siderosis of the CNS. So far, there have been two reliable hallmarks leading to the diagnosis of leptomeningeal amyloidosis: diffuse leptomeningeal enhancement on contrast MRI and greatly increased CSF protein content. This study has contributed a third hallmark: the presence of superficial siderosis is useful in diagnosing leptomeningeal amyloidosis.

The most common form of familial amyloidosis is caused by mutations of the transthyretin (TTR) gene. More than 80 mutations of the TTR gene with single or double amino acid substitutions have been reported in the development of this disorder.¹ In familial TTR related amyloidosis, the presence of severe somatic and autonomic peripheral neuropathy is well known as the typical clinical feature. For this reason, this form of the disorder is referred to as a familial amyloid polyneuropathy (FAP).² However, some forms of familial TTR related amyloidosis preferentially

involve the leptomeninges and meningeovascular walls with a high association of amyloid derived vitreous opacity. These forms of the disorder are, therefore, referred to as familial leptomeningeal or oculoleptomeningeal amyloidosis.^{3–11} The Asp18Gly TTR gene mutation, which is representative of familial leptomeningeal amyloidosis, whose sole symptoms are caused by central nervous system (CNS) disorders, has so far been reported only in a Hungarian family.⁴

In this study, we present clinical pictures of two Japanese brothers with familial leptomeningeal amyloidosis with the same mutation. The disorder in both brothers was characterised by repeated subarachnoid haemorrhages (SAH) with superficial siderosis.

CASE REPORTS

Patient 1

Patient 1 was a 42 year old man who had been suffering from unsteady gait for two years. He recently experienced transient loss of consciousness and visited our department on 3 June 2002. At that time, he complained also of mild dysuria and erection disorder. He also disclosed an earlier diagnosis of optic neuropathy in both eyes.

His father and one of his older brothers were apparently healthy. Another brother suffered from unexplained SAH. His mother had died at about age 50, having lived in a bedridden state for a year after falling down some stairs. A cranial CT revealed brain atrophy.

At admission, patient 1 measured 173 cm in height and weighed 70.5 kg. His pulse rate was 72 and blood pressure was 103/70 mm Hg. Neurologically, he showed bilateral visual impairment, hyperreflexia in the four limbs, and ataxic gait. He showed no meningeal signs, sensory impairment, or orthostatic hypotension. His audiometric study showed bilateral, mild sensorineural hearing loss. Ophthalmological studies revealed vitreous opacity and glaucoma associated with optic atrophy in both eyes. Cerebrospinal fluid (CSF) presented clear but lemon yellow in colour and showed an increased protein level (115 mg/dl, normal: 10–40 mg/dl) without pleocytosis. On 8 June, patient 1 developed a dull headache with nausea and his gait disturbance became worse. A CSF examination on 11 June revealed xanthochromia and showed that the protein level had increased to 145 mg/dl with mild lymphocytic pleocytosis (27/mm³).

A fluid attenuated inversion recovery image (FLAIR) of magnetic resonance imaging (MRI) on 11 June showed high signal intensity in the cerebellar fissures, basal cisterns, and Sylvian fissures, which indicated the presence of SAH. In T1

Abbreviations: CSF, cerebrospinal fluid; FAP, familial amyloid polyneuropathy; FLAIR, fluid attenuated inversion recovery image; MRI, magnetic resonance imaging; SAH, subarachnoid haemorrhage; TTR, transthyretin.

Figure 1 Magnetic resonance imaging of patient 1. MRI studies were performed on patient 1 using 1.5-T MR units (Signa Horizon LX; GE Medical Systems, Milwaukee, WI, USA) equipped with a conventional spinal and head coil. In a T1 weighted image after contrast administration of spinal and cranial MRI, leptomeningeal enhancement was seen diffusely over the surface of the spinal cord, brainstem, and cerebellum (A and B). T2* weighted images showed symmetric rims of low signal intensity in the upper folia of the cerebellar hemispheres (C and D) and in the cortex diffusely of the longitudinal cerebral (E, arrowheads), the Sylvian (E, arrows), and other fissures.

weighted MRI after contrast administration, leptomeningeal enhancement was seen diffusely along the Sylvian fissures and over the surface of the brainstem, cerebellum, and spinal cord (fig 1A and B). The intensity of headache had decreased after several days and a FLAIR of MRI on 24 June showed no abnormalities.

A surgical biopsy of the leptomeninges, performed through Th1 hemilaminectomy on 18 July, revealed cotton like, white materials in the subarachnoid space (fig 2A) and elongating, varicose veins covering the dorsal surface of the spinal cord (fig 2B). These vascular walls seemed to be fragile, and repeated small blood leaks were easily induced by conventional operative procedures. On histological examination the biopsied leptomeninges, which included the surface white material, were thickened by heavy deposits of amyloid, and the subarachnoidal vascular walls were also involved with the amyloid deposits (fig 2C and D). All of the amyloid deposits were immunocytochemically labelled with an anti-TTR antibody (fig 2E). In the following search for systemic amyloidosis, amyloid deposits were observed in the biopsied specimens from the abdominal fat pad and gastroduodenal mucosa. Echocardiography disclosed a thickened interventricular septum and a left ventricular wall with a granular, sparkling appearance, indicating the presence of amyloid heart disease.

On August 27, patient 1 developed dull headache. FLAIR of MRI on 29 August again showed high signal intensity in the cerebellar fissures, basal cisterns, and Sylvian fissures, indicating the repeated SAH. After the patient rested, his headache disappeared and FLAIR of MRI on 4 September showed no abnormalities. The patient was released from the hospital on 6 September 2002.

Eight months after leaving the hospital, patient 1 exhibited unsteady gait during several episodes of dull headache. His neurological findings did not get worse. T2* weighted MRI on 13 June 2003 showed symmetric rims of low signal intensity in the upper folia of the cerebellar hemispheres (fig 1C and D) and in the cortex diffusely of the longitudinal cerebral, the Sylvian and other fissures (fig 1E). These findings on T2* weighted MRI indicated hemosiderin deposits.¹²

Patient 2

Patient 2 was an older brother of patient 1. When patient 2 was 40 years old (in 1997), he experienced transient dizziness

with vomiting and dull headache. Because of recurrent dizziness and unsteady gait, he was admitted to the hospital on 24 November 1999. He also complained of diplopia and numbness in his left foot. His CSF protein level was slightly high (53 mg/dl) without pleocytosis. Cranial CT and MRI showed no abnormalities. After the diplopia disappeared, he was discharged from the hospital on 3 January 2000. After suffering from headache and vomiting for a week, he returned to the hospital on 26 September 2000. Cranial CT revealed SAH with hydrocephalus but neither cerebral arterial aneurysm nor arteriovenous malformation was detected by repeated cerebral angiographies. Cerebral ventricular drainage was performed, which improved his hydrocephalus. However, because of recurrence of hydrocephalus, two more additional drainages were required. Finally, a ventriculoperitoneal shunt was inserted on 23 October, and he was released from the hospital on 15 November. He felt mild dysuria and erection disorder from November 2001 and left hearing impairment from January 2002.

On 29 July 2003, patient 2's neurological findings showed hyperreflexia in the four limbs, ataxic gait, and hypesthesia in the left foot. Patient 2 did not exhibit meningeal sign, visual impairment, or orthostatic hypotension. His audiometric study revealed bilateral, mild sensorineural hearing loss. MRI findings, which consisted of diffuse leptomeningeal enhancement after contrast administration in T1 weighted image and symmetric rims of low signal intensity in the upper folia of the cerebellar hemispheres in T2* weighted image, were very similar to those seen in patient 1.

Gene analysis

Genetic testing was performed after informed consent. Genomic DNA was extracted from the leukocytes of both patients and their family members. The DNA sequence analysis of both patients showed the glycine-for-aspartate substitution at position 18 of TTR. The DNA sequence analyses performed on the father and the older brother were normal.

DISCUSSION

This is the second report describing familial leptomeningeal amyloidosis with an Asp18Gly TTR gene mutation. Several different TTR gene mutations (Val30Met, Val30Gly, Leu12Pro, Phe64Ser, Ala36Pro, Gly53Glu, Tyr69His,

Figure 2 Surgical biopsy of the leptomeninges of patient 1. The biopsy was performed through Th1 hemilaminectomy: on inspection, cotton like, white, and soft materials were seen in the subarachnoid space after dural incision (A) and varicose and elongating veins covered the dorsal surface of the spinal cord after arachnoid incision (B). On histological examination the biopsied leptomeninges, which included the surface white material, were thickened by heavy deposits of amyloid, and the subarachnoidal vascular walls were also involved with the amyloid deposits (C and D: Congo red stain). All of the amyloid deposits were immunocytochemically labelled with an anti-TTR antibody (E: immunohistochemical stain for TTR).

Ala25Thr, Tyr114Cys) have been shown to cause this form of amyloidosis.^{3–11} Some of the TTR gene mutations have been associated with both central and peripheral nervous system disorders, whereas others have been characterised mainly by CNS symptoms, including dementia, seizures, ataxia, and stroke like episodes. The two brothers in our study experienced only CNS symptoms, although amyloid deposits were shown in the gastrointestinal tract and abdominal wall fat tissues of patient 1. For this reason, Asp18Gly TTR induced amyloidosis is considered to be a peculiar form of hereditary systemic amyloidosis predominantly involving the CNS.

The two brothers (patients 1 and 2) in our study had unique clinical manifestations of recurrent SAH and superficial siderosis, which were shown in their MRI images. Neither of these manifestations was experienced by the Hungarian family mentioned earlier, but some of the family members presented with migraine like headache and vomiting, high levels of CSF protein, and high density areas along the Sylvian fissures (as shown on CT scans), all suggesting the occurrence of SAH in these members.⁴ Although SAH occasionally develops in patients with familial leptomeningeal amyloidosis,^{6–10} the pathogenetic mechanisms of this complication have never been clarified. During patient 1's surgical biopsy, we observed varicose, fragile veins on the spinal cord. In leptomeningeal amyloidosis, heavy amyloid deposits are commonly spread into subarachnoidal vessels, which seem to weaken the affected vascular walls. It is possible that these amyloid laden vessels are associated with repeated manifestations of SAH in patients with this disease.

Regarding superficial siderosis of the CNS, ataxia, sensorineural hearing loss, and pyramidal tract signs are known as the triad ascribed to this pathological condition.¹² Although development of these symptoms is not rare in patients with familial oculoleptomeningeal amyloidosis,^{4–10} the presence of superficial siderosis was described only in a family with Ala36Pro TTR.⁸ Recurrent SAH from subarachnoidal vessels with amyloid deposits seems to be responsible for the superficial siderosis of the CNS. Two reliable hallmarks that have led to the diagnosis of leptomeningeal amyloidosis have

been diffuse leptomeningeal enhancement on contrast MRI¹³ and greatly increased CSF protein content. In this study, we have added a third hallmark: the presence of superficial siderosis on T2* weighted MRI is also useful for diagnosing leptomeningeal amyloidosis.

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