Genetic Characteristics of Chinese Patients With Hemorrhagic Cerebrovascular Disease

hui zhu
Jilin University First Hospital
yongliang teng
Jilin University First Hospital
Jingyao Liu (l_jy@jlu.edu.cn)
Jilin University First Hospital

Case report

Keywords: brain hemorrhage, hereditary, gene mutation, familial cavernous hemangioma, hereditary cerebral hemorrhage with amyloidosis

Posted Date: May 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-497520/v1

Abstract

Background

We investigate the clinical and genetic characteristics of hemorrhagic cerebrovascular disease in order to provide a new theoretical basis for the prevention and treatment of hereditary cerebrovascular disease.

Case presentation

Three hereditary cerebral hemorrhage cases were analyzed retrospectively. The patients' families were surveyed, the clinical characteristics summarized, and gene polymorphisms investigated. Among the three cases, two patients had familial cerebral cavernous hemangiomas, and genetic testing revealed a heterozygous mutation in the CCM1 gene, with a deletion of base (T) in exon 15 (c.1542delT). This mutation was also found in three family members of one proband who all had a history of cerebrovascular disease, while genetic testing was normal for the proband's unaffected family member. The last patient had hereditary cerebral hemorrhage with amyloidosis, Finnish type, and the proband, his mother, and his daughter were found to have a heterozygous G duplicate mutation at position 100 in exon 1 of the GSN gene (c.100dupG).

Conclusions

Future screening for genetic mutations associated with a high-risk of hereditary cerebral hemorrhage can help identify individuals at risk for this condition and thereby reduce the occurrence and progression of the disease. Such screening will further enhance the precision in preventing and treating cerebrovascular diseases.

1. Introduction

In recent years, research has determined that a combination of genetic and environmental factors can lead to the onset of cerebrovascular diseases. Most cerebrovascular diseases are multifactorial, while some are clinical syndromes manifested by certain neurogenetic disorders (1, 2). Currently, the majority of evidence related to the etiology of cerebrovascular disease has come from studies in western developed countries (3). Compared with the populations of western countries, the Chinese population has major differences in genetic background, lifestyle, habits and environment. So far, the research evidence linking genetics and environmental factors to the etiology of cerebrovascular disease in Chinese patients is inadequate. Although single gene mutations in cases of familial cerebrovascular amyloidosis, hereditary hemorrhagic telangiectasia, etc (4, 5). have been reported, genetic risk factors for hemorrhagic cerebrovascular disease remain to be identified in the Chinese population. In the present study, we investigated the genetic characteristics of three cases of hemorrhagic cerebrovascular disease with the goal of providing a new theoretical basis for the prevention and treatment of hereditary cerebrovascular disease.

2. Case Descriptions

2.1. Familial cavernous hemangioma

2.1.1. Case 1

A 42-year-old male patient presented with main clinical manifestations of limb paralysis, aphasia, and intermittent convulsions, and he had a history of multiple cerebral hemorrhage and hemangioma of the skin. The patient's mother, son and elder brother had a history of cerebral hemorrhage. Neurological examination showed consciousness, dysarthria, left limb muscle strength of grade 3, right limb muscle strength of grade 4, and bilateral Babinski response. Head computed tomography (CT) scanning of the proband showed multiple visible hemorrhagic foci in the bilateral basal ganglia with partial calcification of the cerebral hemisphere. Magnetic resonance imaging (MRI) of the head suggested multiple cavernous hemangiomas in the cerebral hemisphere, cerebellum, and brain stem, and typical mixed signal shadows could be seen especially on the T2-weighted sequence (Fig. 1). No abnormality was observed on MRI of the spine. Genetic testing revealed a heterozygous mutation in the CCM1 gene, with a deletion of base (T) in exon 15 (c.1542delT). This mutation of the CCM1 gene was found in three other patients (the patient's mother, son and elder brother) in the family, whereas the genetic test results were normal for the unaffected family member (Fig. 2). The patient's clinical diagnosis was familial cerebral cavernous hemangioma.

2.1.2. Case 2

A 38-year-old female patient presented with main clinical manifestation of recurring headache. The patient had no convulsions or physical disabilities during the course of disease. She had been diagnosed with a cerebral cavernous hemangioma 1 year previously but did not receive treatment. The patient's mother and younger sister also suffered from cerebral cavernous hemangiomas. She patient had no history of hypertension or diabetes, and neurological examination showed no abnormal physical signs. Head CT scanning showed cerebral hemorrhage in the right basal ganglia and corona radiata. Head MRI revealed signal abnormalities in the left temporal lobe. Multiple patchy areas of abnormal signals were observed in the bilateral basal ganglia, corona radiata, and centrum semiovale. On susceptibility weighted-imaging (SWI), the left temporal lobe, bilateral frontal lobe, parietal lobe, occipital lobe, bilateral basal ganglia, corona radiata, centrum semiovale, and right corpus collosum showed abnormal signals, suggestive of cavernous hemangioma (Fig. 3). MRI of the cervical vertebra showed no abnormalities. Head magnetic resonance angiography (MRA) found no abnormalities. Upon hospitalization, the patient was diagnosed with cerebral hemorrhage and underwent neurosurgical treatment. On pathological examination, hematoxylin and eosin (HE) staining showed a left temporal hemangioma with hemorrhage, hemosiderin deposition, and inflammatory cell infiltration under high-power microscopy (Fig. 4). The patient's clinical diagnosis was cerebral cavernous hemangioma. Here clinical symptoms were alleviated after surgery, and she was discharged from the hospital after 15 days. She recovered after 3 months and

was able to perform daily self-care activities. Neither the patient nor her relatives underwent genetic testing.

2.2. Hereditary cerebral hemorrhage with amyloidosis

2.2.1. Case 3

A 39-year-old male patients had been hospitalized three times within a span of 3 days due to episodes of convulsions and unconsciousness. The patient had no physical disabilities or blurry vision; however, his mother had been previously diagnosed with cerebral hemorrhage. The patient also had no history of hypertension and diabetes, and neurological examination showed no abnormal physical signs. Head CT scanning showed hemorrhage in the bilateral basal ganglia. Head MRI suggested multiple vascular anomalies, and typical mixed signal shadows could be seen on the T2-weighted sequence. Low signal shadows were seen in the cerebral hemisphere. At the time, the patient's mother did not have any neurological deficits, but multiple vascular anomalies were observed on head MRI (Fig. 5). The patient's daughter and his younger brother had no clinical manifestations or abnormalities on neuroimaging. Genetic testing of the proband, his mother and his daughter revealed a heterozygous G duplicate mutation at position 100 in exon 1 of the GSN gene (c.100dupG). This mutation caused a reading frameshift during translation of the GSN transcript, which resulted in a change of the amino acid sequence of gelsolin protein (Ala34fs; frameshift mutation). No abnormalities were found in other family members (Fig. 6). The patient's clinical diagnosis was hereditary cerebral hemorrhage with amyloidosis, Finnish type.

3. Discussion

To date, research on hereditary cerebral hemorrhage in China and other countries has focused primarily on cerebral amyloidosis. In the present study, the genetic characteristics of two cases of familial cavernous hemangioma and one case of hereditary cerebral hemorrhage with amyloidosis were described in detail. The clinical features of these diseases were compared, and the finding differed from those of previous reports on monogenic hereditary cerebral hemorrhage.

Cerebral cavernous hemangioma occurs more commonly in young adults and rarely in the elderly (6). Most cases are sporadic, and single lesions are commonly seen in the brain. In addition, multiple lesions are common in patients with autosomal dominant familial cerebral cavernous malformation (CCMs). Anthropological analyses in recent decades reported higher incidence rates of CCMs in Hispanic and Chinese populations (7, 8).

Most hemorrhaging from CCMs occurs via an intracranial cavernous hemangioma. The risk of bleeding differs depending on the location of the cavernous hemangioma. The risk of bleeding recurrence is approximately 5–60% per year (9), and short-term recurrent bleeding is also often reported (10). Therefore, immediate treatment should be given upon the first bleeding event. Amongst the family

members of our three cases, four had a history of cerebral hemorrhage (3 male patients and 1 female patient), and none had a history of spinal cord hemorrhage. In fact, the coexistence of cerebral and spinal cord hemorrhage in patients with CCMs is extremely rare (11). Notably, Sirvente et al. reported that cutaneous vascular malformations appear only in patients with a CCM1 gene mutation and are not seen in patients with CCM2 and CCM3 gene mutations (12). In the study by Labauge et al, approximately 75% of patients with CCMs were found to have an isolated cerebral cavernous hemangioma on head MRI (13). Overall, about 60% of patients with CCMs who carry a gene mutation will have symptoms such as complex partial seizures, focal neurologic deficits, headaches and cerebral hemorrhage (9). Therefore, by investigating the gene mutations in the present cases, this study aimed to identify carriers of disease-causing genes within the patients' families for guidance of early treatment intervention or symptom relief.

Case 2

was diagnosed with cerebral cavernous hemangioma, and the patient's clinical symptoms as well as imaging results fulfilled the diagnostic criteria for CCM. The patient's condition was further confirmed via pathologic examination. The patient's mother and younger sister were also diagnosed with CCM based on pathological examination. Unfortunately, no genetic testing was performed for the patient or her family members. However, through a survey of her family, it was concluded that the patient had familial cerebral cavernous hemangioma.

Hereditary cerebral hemorrhage with amyloidosis is an autosomal dominant genetic disease. Its pathological changes are similar to those of cerebral amyloid angiopathy (CAA) and include deposition of amyloid beta in cerebral blood vessels. Therefore, hereditary cerebral hemorrhage with amyloidosis is classified as familial CAA, and the three main types for which mutations have been identified are known as the Dutch, Italian and Icelandic types. The first two types (Dutch and Italian) are caused by mutations in the amyloid precursor protein (APP), with mutation sites for the Dutch-type and Italian-type at E693Q and E693K, respectively. The Icelandic-type is caused by mutant cystatin C (CST3). Hereditary cerebral hemorrhage with amyloidosis is clinically characterized by recurrent cerebral hemorrhage, dementia, etc., and the symptoms of cerebral hemorrhage usually appear around 50 years of age, with lobar hemorrhage being most common. As the disease progresses, brain imaging shows more changes related to leukoaraiosis, cerebral microbleed, and infarction (14).

Case 3

of this study was diagnosed with hereditary cerebral hemorrhage with amyloidosis, Finnish type (Finnish gelsolin amyloidosis, FGA), which an autosomal dominant genetic disorder, caused by a frameshift mutation in the GSN gene. This is different from the more common pathogenic genes of hereditary cerebral hemorrhage with amyloidosis. The classic clinical manifestations of FGA are convulsions, multiple cerebrovascular malformations, and multiple hemorrhagic foci (15), which were seen in the proband. Genetic testing confirmed a heterozygous G duplicate mutation in exon 1 of the GSN gene, which was the cause of the disease. The proband's mother and daughter also were carriers of the genetic mutation, but they had no history of related clinical manifestations. It is possible that the gene mutation

varies among different patients, resulting in variation in the pathogenesis and clinical manifestations (16). Notably, the proband was male, whereas his non-symptomatic, mutation-carrying family members were female, suggesting the possibility that the clinical manifestations of FGA are associated with gender.

A previous study of mutations of the GSN gene reported a single nucleotide substitution of G for A or T at position 654 (17), and the pathogenic locus of the mutation in Case 3 was not reported. No genetic mutation was observed in the younger brother of the proband, indicating that the mother was a heterozygous carrier of GSN gene mutation, as was confirmed by gene sequencing.

4. Conclusion

In conclusion, the genetic and molecular mechanisms of cerebral hemorrhage remain incompletely understood. Moving forward, screening for high-risk genes for hereditary cerebral hemorrhage can be applied to identify individuals with a high risk of cerebral hemorrhage, which will effectively reduce the occurrence and progression of the disease. Moreover, genetic testing for known mutations can assist in the diagnosis of cerebrovascular diseases, which will further improve the precision of treatment.

Declarations

Acknowledgments

Not applicable

Authors' contributions

JYL designed/performed most of the investigation, data analysis and wrote the manuscript; HZ and YLT provided Genetic testing and pathological assistance. All of the authors have read and approved the manuscript.

Funding

Not applicable

Availability of data and materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the ethics committee of The First Hospital, Jilin University (Ethical Approval Number: 2019270). All procedures performed in studies involving human participants were in accordance

with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from the patient and the donor.

Consent for publication

Consent for publication was obtained from all participants to the study. Data were published anornymously.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Neurology, The First Hospital, Jilin University, Jilin Road, No. 3302, Changchun 130031, China. [2]Department of Pathology, The First Hospital, Jilin University, Xinmin Street, No. 71, Changchun 130021, China.

References

1. Pezzini A, Busto G, Zedde M, Gamba M, Zini A, Poli L, et al. Vulnerability to Infarction During Cerebral Ischemia in Migraine Sufferers. Stroke. 2018;49(3):573-578.
2. Wassertheil-Smoller S, Qi Q, Dave T, Mitchell BD, Jackson RD, Liu S, et al. Polygenic Risk for Depression Increases Risk of Ischemic Stroke: From the Stroke Genetics Network Study. Stroke. 2018;49(3):543-548.
3. Choi JC. Genetics of cerebral small vessel disease. Journal of stroke. 2015;17(1):7-16.
4. Karschnia P, Nishimura S, Louvi A. Cerebrovascular disorders associated with genetic lesions. Cellular and molecular life sciences : CMLS. 2019;76(2):283-300.
5. Rattani A, Dewan MC, Hannig V, Naftel RP, Wellons JC, 3rd, Jordan LC. Cerebral hemorrhage in monozygotic twins with hereditary hemorrhagic telangiectasia: case report and hemorrhagic risk evaluation. Journal of neurosurgery Pediatrics. 2017;20(2):164-169.
6. Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, et al. The natural history of familial cavernous malformations: results of an ongoing study. Journal of neurosurgery. 1994;80(3):422-432.
7. Mao Y, Zhao Y, Zhou LF, Huang CX, Shou XF, Gong JL, et al. A novel gene mutation (1292 deletion) in a Chinese family with cerebral cavernous malformations. Neurosurgery. 2005;56(5):1149-1153.

8. Rigamonti D, Hadley MN, Drayer BP, Johnson PC, Hoenig-Rigamonti K, Knight JT, et al. Cerebral cavernous malformations. Incidence and familial occurrence. The New England journal of medicine. 1988;319(6):343-347.
9. Ferroli P, Casazza M, Marras C, Mendola C, Franzini A, Broggi G. Cerebral cavernomas and seizures: a retrospective study on 163 patients who underwent pure lesionectomy. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2006;26(6):390-394.
10. Barker FG, 2nd, Amin-Hanjani S, Butler WE, Lyons S, Ojemann RG, Chapman PH, et al. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. Neurosurgery. 2001;49(1):15-24.
11. Toldo I, Drigo P, Mammi I, Marini V, Carollo C. Vertebral and spinal cavernous angiomas associated with familial cerebral cavernous malformation. Surgical neurology. 2009;71(2):167-171.
12. Sirvente J, Enjolras O, Wassef M, Tournier-Lasserve E, Labauge P. Frequency and phenotypes of cutaneous vascular malformations in a consecutive series of 417 patients with familial cerebral cavernous malformations. Journal of the European Academy of Dermatology and Venereology : JEADV. 2009;23(9):1066-1072.
13. Labauge P, Laberge S, Brunereau L, Levy C, Tournier-Lasserve E. Hereditary cerebral cavernous angiomas: clinical and genetic features in 57 French families. Societe Francaise de Neurochirurgie. Lancet. 1998;352(9144):1892-1897.
14. Castano EM, Frangione B. Non-Alzheimer's disease amyloidoses of the nervous system. Current opinion in neurology. 1995;8(4):279-285.
15. Kiuru-Enari S, Somer H, Seppalainen AM, Notkola IL, Haltia M. Neuromuscular pathology in hereditary gelsolin amyloidosis. Journal of neuropathology and experimental neurology. 2002;61(6):565-571.
16. Atula S, Nikoskinen T, Saastamoinen A, Strbian D, Schmidt EK, Kiuru-Enari S. Gender differences in the clinical course of Finnish gelsolin amyloidosis. Amyloid : the international journal of experimental and clinical investigation : the official journal of the International Society of Amyloidosis. 2016;23(1):33-38.
17. Maury CP, Kere J, Tolvanen R, de la Chapelle A. Finnish hereditary amyloidosis is caused by a single nucleotide substitution in the gelsolin gene. FEBS letters. 1990;276(1-2):75-77.

Figures

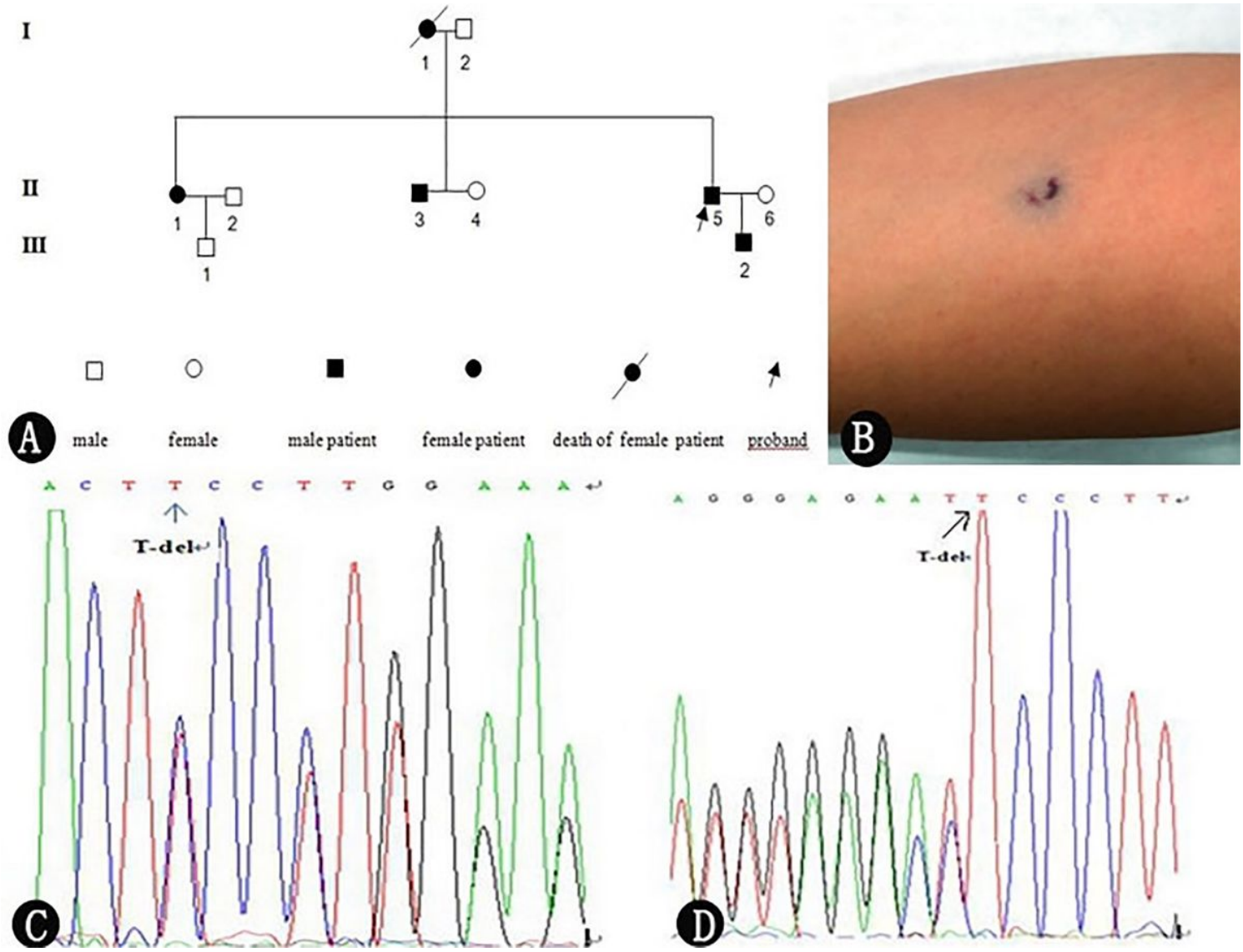

Figure 1

Case 2. A: Pedigree of the family with familial cerebral cavernous malformations (CCMs). B: Skin cavernous hemangioma of the proband's sister. C and D: Representative sequencing results from a patient in the family, with notation of a "T" deletion mutation in c.1542 of exon15 in CCM1 (C, forward sequencing and D, reverse sequencing).

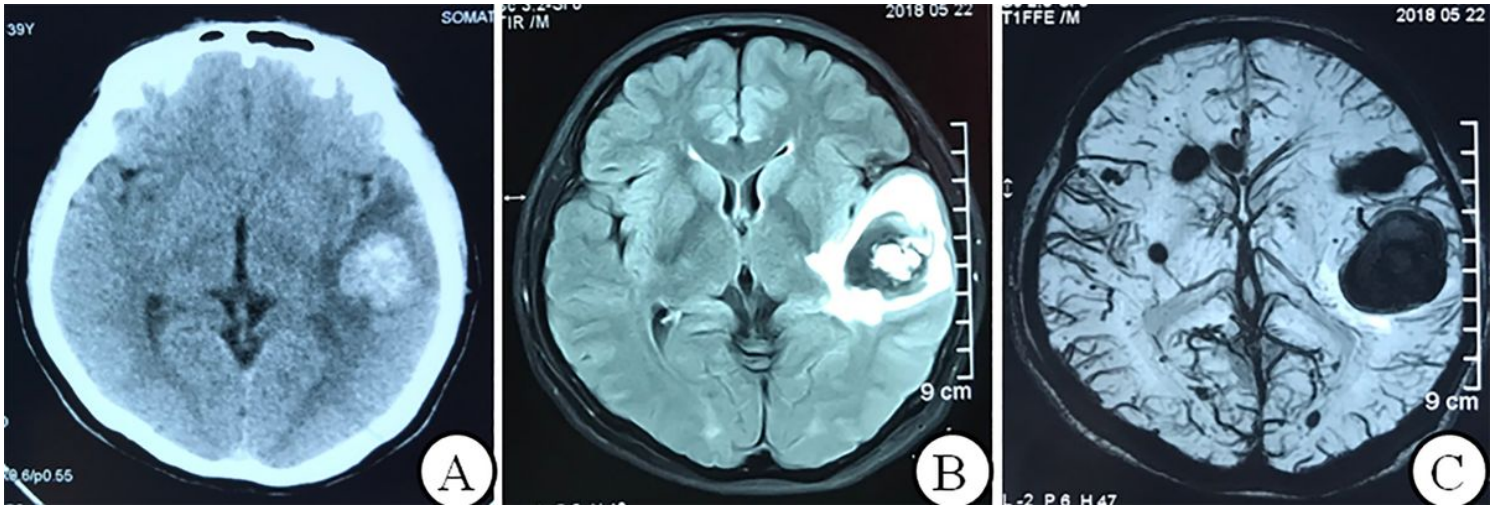

Figure 2

A: Head CT scan showing hemorrhage in the right basal ganglia and corona radiata. B: Head MR image (FLAIR) showing abnormal signals in the left temporal lobe. C: Head SW image showing abnormal signals in the bilateral frontal lobe, temporal lobe, parietal lobe, occipital lobe, bilateral basal ganglia, and right corpus collosum, suggesting cavernous hemangioma.

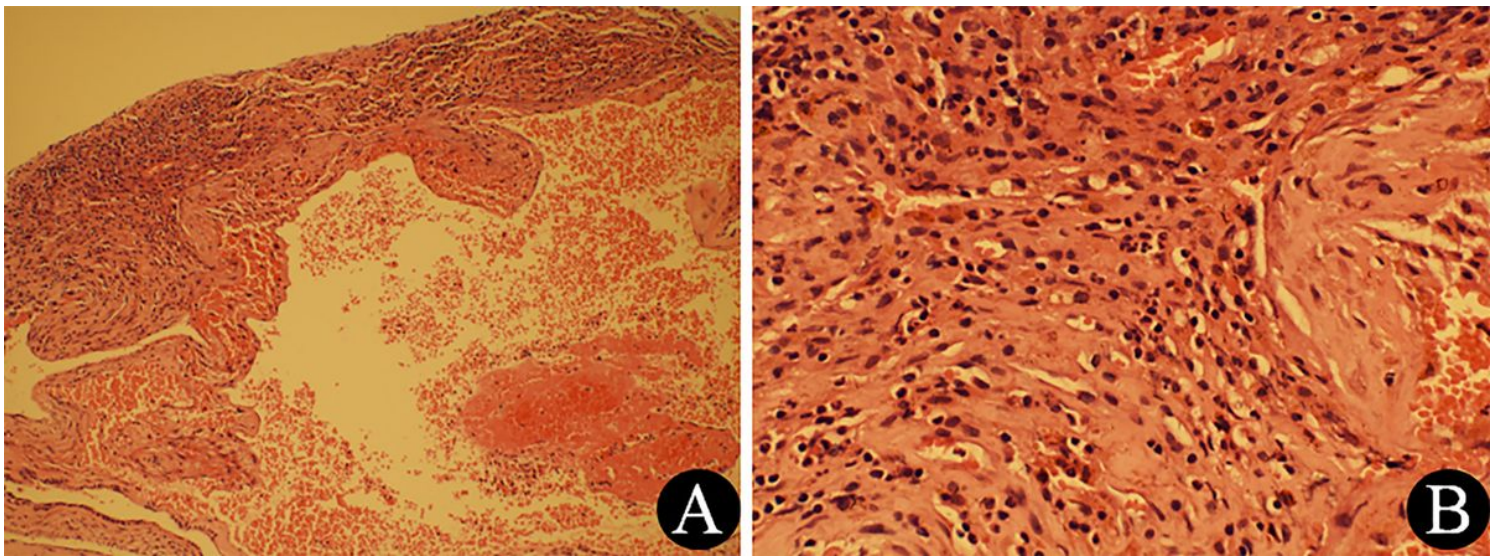

Figure 3

Pathological examination results. A: HE staining showing hemorrhage in the left temporal hemangioma (magnification, 100×). B: HE staining showing hemosiderin deposit and inflammatory cell infiltration in the left temporal hemangioma (magnification, 400×).

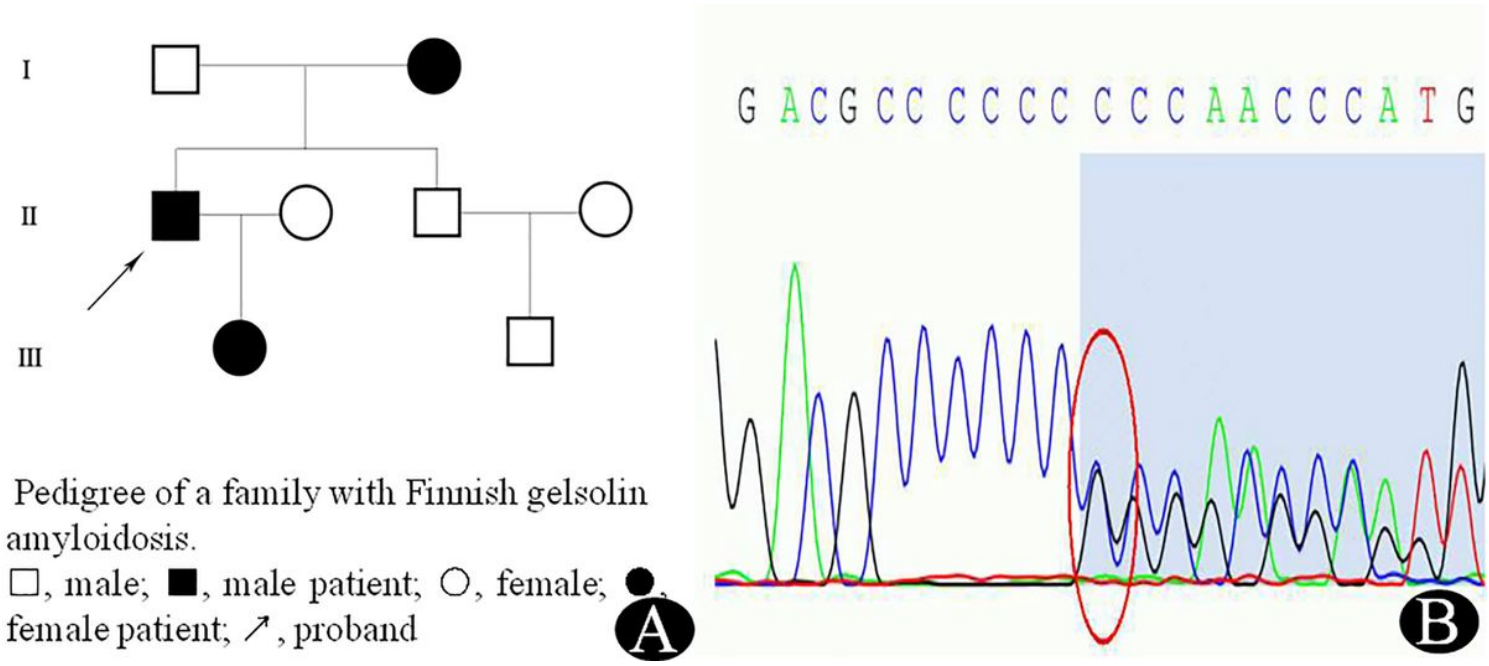

Figure 4

Case 3. A: Pedigree of the family with Finnish gelsolin amyloidosis. B: DNA sequencing of the GSN gene in the patient's family member, showing a heterozygous G duplicate in exon1 (c.100dupG) of the GSN gene.