A Japanese case of successful surgical resection of cerebral cavernous malformations with a *CCM2* mutation

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Abstract

Cerebral cavernous malformations (CCMs) are congenital abnormalities of cerebral vessels. Surgical resection is rarely considered for the control of epilepsy in a first seizure patient with vascular malformation. In contrast, lesions that produce repetitive or progressive symptoms should be considered for surgical resection as treatment. Herein, we report a Japanese patient with a *CCM2* mutation, c.609G>A (p.K203K) substitution, who showed drug-resistant epilepsy and dramatic improvement after surgical resection.

Key words: Cerebral cavernous malformation (CCM), *CCM2*, drug-resistant epilepsy

Introduction

Cerebral cavernous malformations (CCMs) are congenital abnormalities of cerebral vessels that affect 0.1 to 0.5 % of the population.[1] *CCM2* is one of the causative genes of familial CCM that regulates endothelial junctional stability and vascular barrier function by suppressing the activation of RhoA activity.[2] Several silent mutations in *CCM2* were reported as clinically pathogenic.[3] Here, we report the first Japanese patient with a *CCM2* mutation, c.609G>A (p.K203K) substitution, who showed dramatic improvement following surgical resection.[3]

Case Report

A 19-year-old woman had a family history of CCMs, in which her maternal uncle, maternal cousin, mother and brother also have CCM (Fig. 1a). She suddenly developed generalized seizures, and was taken to a hospital by ambulance (Fig.1b). Magnetic resonance imaging (MRI) of her brain showed multiple CCMs (Fig. 1c (i) - (vi), arrows). She was diagnosed with focal epilepsy with focal impaired awareness seizure (FIAS) due to these CCMs. At the time of onset, the frequency of seizure was once every 2-3 months. Seizures began with chest pain and palpitation, followed by limb stiffness and the loss of consciousness, events that lasted for a few minutes. Although she was treated with various anti-epileptic drugs, the frequency of seizures increased to 2-3 times a month when she was 32 years old (Fig. 1b). To manage epilepsy, she visited our hospital. She showed no neurological abnormalities. Based on long-term electroencephalography video monitoring, the origin of epilepsy was considered to be the right temporal lobe (Fig. 1d). Fluorodeoxyglucose-positron emission tomography showed decreased glucose metabolism in the area of a CCM located in the right

temporal lobe (Fig. 1c (ix), an arrow). Consequently, the cause of the seizure was diagnosed to the right temporal lobe CCM, and the temporal lobe was resected. Histology of the resected CCM showed clusters of dilated sinusoidal channels with thin walls filled with blood and hematoma-like lesions (Fig. 1e (i), (ii)). The margin of the CCM showed spindle-shaped cell hyperplasia (Fig. 1e (iii), (iv)). After surgery, the frequency of focal seizures dropped sharply and the use of anti-epileptic drugs gradually decreased (Fig. 1b).

Genetic studies of *CCM1*, *CCM2*, and *CCM3* were carried out with written informed consent from her and her parents. DNA analysis of her and her mother's *CCM2* gene revealed a c.609G>A (p.K203K) substitution (Fig. 1f (i)). QIAxcel semi-quantitative RT-PCR of their *CCM2* gene revealed that this mutation may lead to an abnormal splicing of exon 5 (Fig. 1f (ii)), as was previously reported.[3, 4] This mutation is located at the invariant G residue at the splice acceptor site adjacent to exon 6 and led to a premature termination codon. These may be involved in promoting exon 5 skipping.[3, 4] In addition, some of the mutations, including the c.609G>A (p.K203K) substitution, strongly suggest that *CCM2* lesions are haploinsufficient.[3]

Discussion

The risk of recurrent seizures after the first seizure is relatively high in CCM patients, compared with the general population because of recurrent microhemorrhages in CCM.[5] A 'two-hit' mechanism, requiring biallelic germline and somatic mutations in one of the three known *CCM* genes.[6] Somatic mutations in *CCM* genes were identified in the endothelial cells of CCM lesion tissue, highlighting the importance of endothelial cells as the primary site of CCM lesion pathogenesis.[6] Furthermore, *CCM2* regulates

endothelial junctional stability and vascular barrier function by suppressing the activation of RhoA activity.[2] The loss of *CCM2* function results in increased RhoA activity in the endothelium.[2] Inhibitors of HMG-CoA reductase have various effects, including the inhibition of RhoA activity in *CCM2* deficiency.[2, 7] It was suggested that inhibitors of HMG-CoA reductase such as statins may be a therapeutic candidate for familial CCM, as in this case.[2]

Surgery is rarely considered for first seizure patients with vascular malformation.[8] However, lesions that produce repetitive or progressive symptoms such as progressive seizures, multiple hemorrhages, and neurological deficits should be considered for surgical resection.[9] In the present case, the proband showed multiple CCMs and long-term drug-resistant epilepsy (Fig. 1b). Prompt control of epilepsy was achieved by surgical resection.

We report a Japanese patient with a *CCM2* mutation who showed dramatic improvement in drug-resistant epilepsy after surgical operation. We propose that surgical resection of the origin of epilepsy should be considered as a treatment for symptomatic epilepsy of multiple CCMs.

Conflicts of interest

The authors disclose no potential conflicts of interest.

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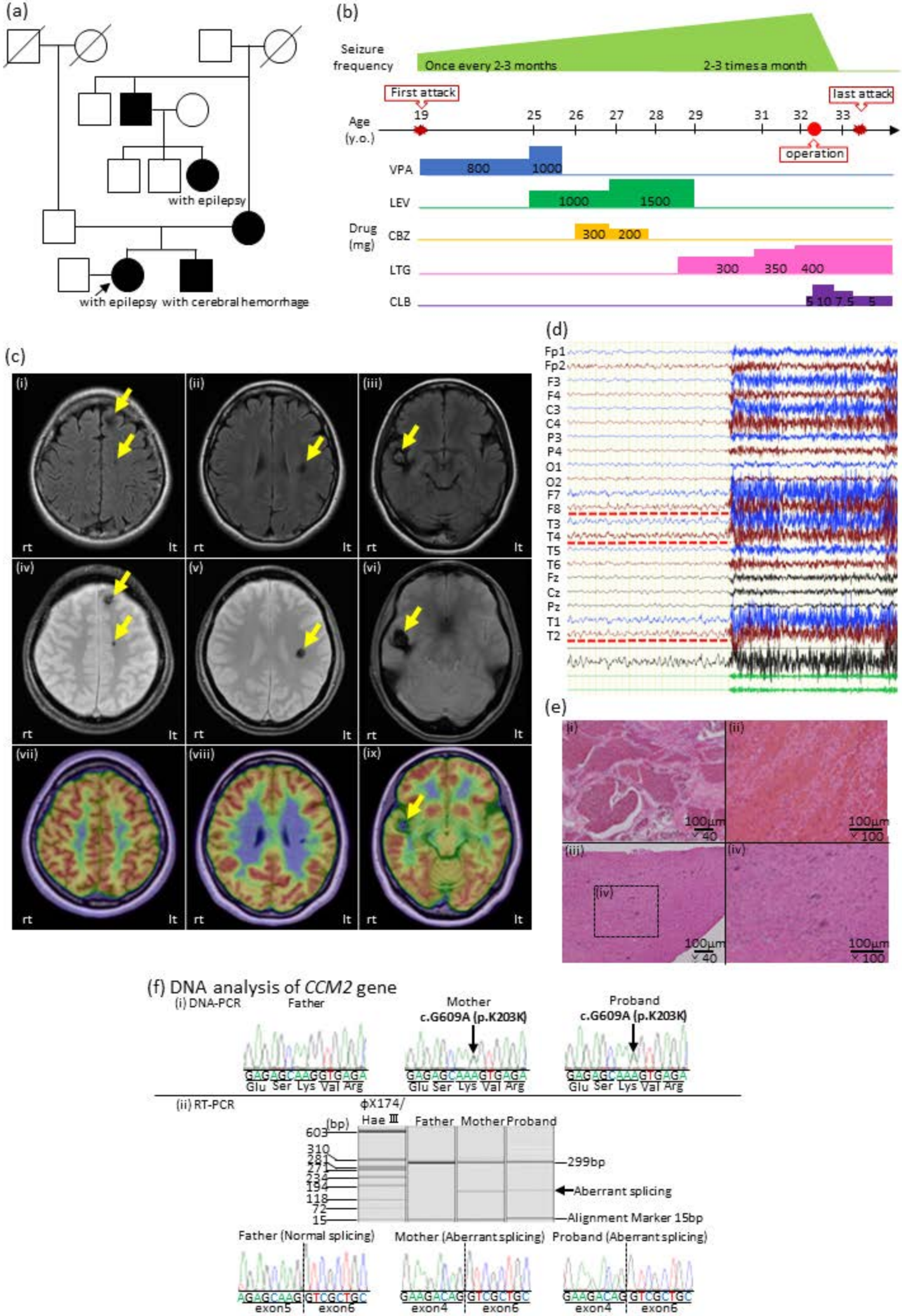
Figure Legend

Figure 1) (a) Family tree of the present case. Her maternal grandfather, maternal cousin, mother and brother also have CCM. Her cousin also showed symptomatic epilepsy. Her brother underwent surgical operation for cerebral hemorrhage due to CCM. (b) The time course of symptoms and treatment of the present case. CBZ: Carbamazepine; CLB: Clobazam; LEV: Levetiracetam; LTG: Lamotrigine; mg: milligrams; VPA: Valproate; y.o.: years old. (c) (i-iii) FLAIR imaging of brain magnetic resonance imaging (MRI) showed multiple CCMs in the left subfrontal cortex, inside left parietal lobe, and right temporal lobe (arrows). (iv-vi) T2-star imaging of the brain MRI showed multiple microbleeds as a low signal lesion in the same position (arrows). (vii-ix) Fluorodeoxyglucose-position emission tomography showed decreased glucose metabolism in the area of the CCM located in the right temporal lobe (arrow). (d) Result of long-term electroencephalography video monitoring. The origin of epilepsy was considered to be the right temporal lobe (red dotted underlines). (e) (i, ii) Histological findings of the resected CCM showed clusters of dilated sinusoidal channels with thin walls filled with blood (i) and hematoma-like lesions (ii) (hematoxylin and eosin (HE) staining; scale bar = 100 μm). (iii, iv) The margin of the CCM showed spindle-shaped cell hyperplasia (HE staining; Scale bar = 100 μm). (f) (i) DNA-PCR of her and her mother's *CCM2* gene revealed a c.609G>A (p. K203K) substitution (arrows), while her father's *CCM2* gene was normal. (ii) QIAxcel semi-quantitative RT-PCR of her and her mother's *CCM2* gene. This mutation led to an abnormal splicing of exon 5 (arrow), while her father's *CCM2* gene was normal. bp: base pair.


(a)
with epilepsy
with epilepsy
with cerebral hemorrhage
(b)
Seizure frequency
Once every 2-3 months
2-3 times a month
First attack
last attack
Age (y.o.)
19
25
26
27
28
29
31
32
33
operation
VPA
800
1000
LEV
1000
1500
Drug (mg)
CBZ
300
200
LTG
300
350
400
CLB
5
10
7.5
5
(c)
(i)
(ii)
(iii)
(iv)
(v)
(vi)
(vii)
(viii)
(ix)
rt
lt
(d)
Fp1
Fp2
F3
F4
C3
C4
P3
P4
O1
O2
F7
F8
T3
T4
T5
T6
Fz
Cz
Pz
T1
T2
(e)
(i)
(ii)
(iii)
(iv)
100μm
×40
100μm
×100
(f) DNA analysis of CCM2 gene
(i) DNA-PCR
Father
Mother
c.G609A (p.K203K)
Proband
c.G609A (p.K203K)
GAGAGCAAAGGTGAGA
Glu Ser Lys Val Arg
(ii) RT-PCR
ϕX174/
Hae Ⅲ
(bp)
Father
Mother
Proband
603
310
281
271
234
194
118
72
15
299bp
Aberrant splicing
Alignment Marker 15bp
Father (Normal splicing)
Mother (Aberrant splicing)
Proband (Aberrant splicing)
AGAGCAAGGTCGCTGC
exon5
exon6
GAAGACAGGTCGCTGC
exon4
exon6
GAAGACAGGTCGCTGC
exon4
exon6