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Letter to the Editor

High prevalence of epilepsy in HAE with normal C1−INH

Dear Editor,

Hereditary angioedema (HAE) is characterized by recurrent episodes of subcutaneous or submucosal edema, gastrointestinal attacks, and upper airway edema including laryngeal obstruction.

Three types of HAE are currently recognized and genetically identifiable: HAE due to C1 inhibitor (C1−INH) deficiency (C1−INH-HAE-1), characterized by low level of functional C1−INH; HAE due to C1−INH dysfunction (C1−INH-HAE-2), characterized by normal amount but low functional C1−INH levels and caused by *SERPING1* mutations, leading to C1−INH deficiency.[1] HAE with normal C1−INH levels (HAE nC1-INH) encompasses diverse diseases and is an uncommon HAE type. HAE nC1-INH has been associated with mutations in several genes, including those for Factor XII (*FXII*), angiopoietin-1 gene (*ANGPT1*), plasminogen (*PLG*) and kininogen-1 (*KNG-1*).[2,3] However, in most cases, the underlying genetic mutation is unknown (HAE nC1-INH-unknown). Different types of HAE share common clinical features; however, few reports have shown that HAE attacks are accompanied by neurological symptoms. Headache was reported as an accompanying symptom of C1−INH-HAE in some reports.[4,5] In this report, we investigated neurological complications, including epilepsy, in patients with C1−INH-HAE and HAE nC1-INH.

We conducted a retrospective review of medical records for patients diagnosed with HAE the at Kobe University Hospital from 2003 to 2019. The following inclusion criteria were used to diagnose HAE nC1-INH: no response to antihistamines, steroids, or epinephrine; normal level of C4 or C1 inhibitor and normal function of C1−INH; no urticaria or pruritus; occurrence without offending drugs; and a positive family history.[6] Thirteen patients with C1−INH-HAE and five patients with HAE nC1-INH were consecutively enrolled in this retrospective study (Table 1). The study protocol was approved by the Ethics Committee of the Kobe University Graduate School of Medicine. The medical histories of three HAE patients with epilepsy are presented below.

Case 1 (HAE nC1-INH; J-1 in Table 1): A 32-year-old woman was referred to us in 2017 with a possible diagnosis of HAE. She had two generalized convulsive seizures at 9-years-old, was diagnosed with epilepsy, and had started phenobarbital therapy. However, focal impaired awareness seizures (FIAS) with loss of consciousness and oral automatism continued monthly. She discontinued phenobarbital at 14 years old. At 17-years-old, she developed different symptoms, including breathing difficulty, anxiety, palpitation, and vomiting. Her neurologist had adjusted her medication for the epilepsy symptoms, including focal aware seizures (FAS), FIAS, and focal to bilateral tonic-clonic seizures. The epilepsy medication could not suppress all the symptoms. At 31-years-old, she developed tongue edema, abdominal pain, laryngeal discomfort, and breathing difficulty. She was often admitted to the emergency room with those symptoms indicative of HAE. She experienced various angioedema symptoms including tongue edema, limb edema, abdominal pain, diarrhea, cough, urinary retention and vomiting immediately after the epileptic seizures. Her grandmother had facial and limb edema, and her mother had facial edema. Her blood tests revealed normal C4 and functional C1−INH levels. Based on the above-described criteria, we diagnosed her with HAE nC1-INH. Examinations to identify the underlying genetic mutations are underway. The results of brain magnetic resonance imaging (MRI) were normal. ^{123}I−N-isopropyl-p-iodoamphetamine single-photon emission computed tomography (SPECT) showed cerebral blood flow reduction of the right parietal lobe, and ^{123}I-iomazenil-SPECT showed benzodiazepine receptor reduction in the left temporal lobe. These brain scanning modalities were performed in interictal period. We repeatedly observed that blood pressure during epileptic seizures was within normal limit. Administration of plasma derived C1−INH during epileptic seizures and angioedema suppressed epileptic seizures in 8−16 min. We have never administered icatibant during epileptic seizures.

Case 2 (HAE nC1-INH; I-3 in Table 1): A 45-year-old woman consulted us with suspected HAE. She had migraine since childhood and developed epileptic seizures accompanied by impaired consciousness including seizures and depression at 20-years-old that deteriorated several times per month. She was diagnosed with epilepsy, including FAS and FIAS at 40-years-old and developed lip, tongue, and facial edema, vomiting, diarrhea, breathing difficulty, and lightheadedness twice monthly. She experienced facial edema, abdominal pain and migraine attack simultaneously without blood pressure elevation. Her grandmother had angioedema, and her mother had lip edema. Her sister and niece were diagnosed with HAE nC1-INH. Her blood tests showed normal C4 and functional C1−INH levels. We diagnosed her with HAE nC1-INH because of the lack of response to antihistamines, steroids, and epinephrine. Identification of the underlying genetic mutations is underway. Brain MRI showed punctate white matter lesions without edema both in the asymptomatic state and immediately after administration of plasma derived C1−INH following migraine attack. Both of plasma derived C1−INH and icatibant were effective for impaired consciousness including epileptic seizures.

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Table 1
Laboratory and disease activity characteristics of patients with C1−INH-HAE and HAE nC1-INH.

Patient No.	Age	Sex	C3 (mg/dl)	C4 (mg/dl)	CH50 (IU/ml)	Functional C1−INH activity (%)	C1−INH antigen (mg/dl)	Facial edema	Limb edema	Gastrointestinal Attacks	Epilepsy
A-1	29	F	105	1.3	<10	25	7	+	+	−	−
A-2	5	F	123	6.9	20	27	8	−	−	−	−
A-3	27	F	99	15.7	36.6	33	8	−	−	−	−
B-1	36	F	86	4.4	10.3	25	<5	+	+	+	−
B-2	8	M	95	6.4	35	28	10	−	+	−	−
B-3	64	F	94	17.8	43.6	33	9	−	−	−	−
C-1	27	F	104	4.4	18.8	25	4	−	+	+	−
C-2	69	F	83	15.7	32.8	37	12	−	−	−	−
D-1	24	F	94	3.8	21.3	<25	4	−	−	−	−
E−1	26	F	132	1.8	<18	<25	4	+	+	+	−
F-1	76	M	79	2.1	18	<25	6	+	−	−	−
G-1	61	F	120	8.3	32.1	<25	9	+	−	−	−
H-1	83	M	113	12.9	56.6	35	5	+	+	+	−
I-1	40	F	118	22.9	29.1	93	NT	+	−	+	−
I-2	7	F	87	9.8	27.7	101	NT	+	−	+	−
I-3	45	F	71	20.7	39.6	88	NT	+	−	+	+
J-1	32	F	90	14.2	20.6	109	NT	+	−	+	+
K-1	4	F	96	17.1	40.2	140	NT	+	−	−	+
Normal range			65−135	13−35	25−51	70−130	11−26				

The same uppercase letter before the patient No. indicates the same family. All complement and C1−INH levels were measured during symptom-free periods. We diagnosed 13 patients (A-1 to H-1) with C1−INH-HAE and 5 patients (I-1 to K-1) with HAE nC1-INH. F, female; M, male; NT, not tested.

Case 3 (HAE nC1-INH; K-1 in Table 1): A 4-year-old girl consulted us with suspected HAE. She had developed lower leg and facial edema, breathing difficulty, vomiting, and diarrhea from 2-years-old. She had suspected food allergy and croup syndrome. Antihistamines, epinephrine, and corticosteroids were resistant to recurrent edema. At 3-years-old, she had recurrent seizures and was diagnosed with epilepsy including FAS and FIAS. She experienced facial edema and epileptic seizures simultaneously. Her mother had abdominal pain and intestinal edema as indicated by echo ultrasonography. Her two sisters had facial and lip edema. Her blood tests showed normal C4 and functional C1−INH levels. We diagnosed her with HAE nC1-INH based on the above-described criteria. We have never administered plasma derived C1−INH or icatibant during her epileptic seizures.

We identified three cases of HAE nC1-INH complicated by epilepsy. By contrast, patients with C1−INH-HAE showed no neurological symptoms. The prevalence survey at our facility revealed that frequency in complication of epilepsy is significantly higher in HAE nC1-INH than that in C1−INH-HAE (Table 2).

To the best of our knowledge, HAE with epilepsy has not yet been reported, although some studies have reported cases of angioedema other than HAE with neurologic manifestations.

Sunder TR *et al.* reported two children with recurrent neurological symptoms associated with angioedema.[7] Ji *et al.* reported two cases of subacute marked tongue edema resulting in airway compromise in patients with refractory status epilepticus requiring prolonged pentobarbital coma.[8] By contrast, Göring *et al.* reported the misdiagnosis of epilepsy and migraine in a multicenter retrospective study of HAE.[9]

In Cases 1 and 2, epilepsy was induced by menstruation and physical and psychological stress. Because these are well-known exacerbating factors of HAE, epilepsy in these patients is likely associated with HAE attack. The point prevalence of active epilepsy is 6.38 per 1000 persons (95% confidence interval: 5.57−7.30).[10] The prevalence of epilepsy among all HAE patients at our facility was 16.7% (3/18), suggesting a high epilepsy prevalence in HAE patients. Moreover, we demonstrated that the prevalence of epilepsy in HAE nC1-INH was higher than that in C1−INH HAE.

Bradykinin plays a significant role in the pathogenesis of HAE.[11] A recent study using human cerebral microvascular endothelial cells demonstrated that activation of bradykinin 1 receptor induces pro-inflammatory cytokines including interleukin-6, intracellular molecule-1, and vascular cell adhesion molecule-1 and increases the vascular permeability.[12] Similar mechanism is proposed as the pathophysiology of transient cerebral edema in posterior reversible encephalopathy syndrome, which is closely associated with hypertension and epileptic seizures.[13–15] Both hyper- and hypo-perfusion have been associated with posterior reversible encephalopathy syndrome and focal epilepsy during transient manifestations.[13,14,16]

Table 2
Prevalence of epilepsy in patients with HAE nC1-INH and C1−INH-HAE.

	C1−INH-HAE (n)	HAE nC1-INH (n)	Total
Without epilepsy	13	2	15
With epilepsy	0	3	3
Total	13	5	18

Fisher's exact test; $p = 0.012$.

Since the pathophysiological mechanism underlying how HAE patients develop epilepsy is still unclear, this cross-sectional single center study warrants further investigation of the relationship between epilepsy and HAE.

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Conflict of interest

AF has received speaking honoraria from Shire (a Takeda Company) and CSL Behring. MK has received speaking honoraria from Daiichi Sankyo. The rest of the authors have no conflict of interest.

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