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Case Report

Hereditary angio-oedema with normal C1-INH, developing recurrent acute abdomen after taking low-dose oestrogen–progestin: A case report

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ABSTRACT

Hereditary angio-oedema (HAE) is a rare genetic disease characterised by repeated episodes of temporary organ swelling. Three types of HAE are known, of which HAE with normal C1 inactivator is difficult to be diagnosed due to its lack of laboratory abnormalities. Here, we describe a case of HAE with normal C1 inactivator and recurrent acute abdomen following low-dose oestrogen–progestin therapy. Notably, genetic analysis by Sanger sequencing led to the identification of a recurrent heterozygous missense mutation c.988A > G (p.K330E) in the plasminogen (*PLG*) gene of the patient. Prophylactic tranexamic acid and on-demand selective bradykinin B2 receptor blockers are used to treat her symptoms.

KEYWORDS: Hereditary angio-oedema; C1 inactivator; HAE with normal C1 inactivator; plasminogen; *PLG*

Introduction

Hereditary angio-oedema (HAE) is a rare autosomal dominantly inherited disorder. Because the bradykinin regulation mechanism is not working properly, patients develop severe oedema in the deep dermis and subcutaneous tissue [1]. Multiple organs are affected, but some patients develop an acute abdomen as angio-oedema develops in the gastrointestinal tract [2]. The first step in diagnosing HAE is suspicion based on the episodes, followed by tests for C4 and C1 inactivator (C1 inhibitor: C1-INH). Of the three types of diseases, Type I and Type II HAE can be diagnosed based on a low level of C4, as well as reduced activity of C1-INH. It is challenging, however, to diagnose HAE with normal C1-INH (HAEnCI) because there are no aberrant laboratory findings [3]. In addition to physical stress, endogenous or prescription oestrogen can also cause HAE attacks [3].

In this report, we present a patient with HAEnCI who experienced repeated acute abdomens after using low-dose oestrogen–progestin (LEP) and carried a heterozygous mutation in the plasminogen (*PLG*) gene.

Case report

A 26-year-old Japanese woman started taking a LEP due to erratic menstruation 2 years ago. She visited our emergency outpatient department with abdominal pain 3 months later. Computed tomography (CT) scans revealed significant intestinal oedema and potential intestinal ischaemia (Figure 1(a,b)). Despite the concern of superior mesenteric artery thrombosis, an angiography revealed neither thrombosis nor ischaemia, and her symptoms subsided on their own in about a day. Mild stomach pains then continued and spontaneously disappeared after that. She returned to our emergency department with a recurrent acute abdomen.

There were no other symptoms, such as a fever, joint pain, or skin rash, other than abdominal pain. Physical examination revealed a muscular defence around her epigastrium. She did not seem to have any swelling in her lips or arms.

A haematological examination revealed high leucocyte (17,800/μl; neutrophil 81.9%, lymphocyte 13.8%, eosinophil 1.2%, basophil 0.3%, monocyte 2.8%) and D-dimer (9.0 μg/ml) levels, but other coagulation tests were normal. C-reactive protein, renal function, and liver function were all within normal limits. A CT scan revealed severe intestinal oedema resembling that from the previous event (Figure 1(c,d)). HAE was suspected at this point; however, both the serum C4 level and C1-INH activity were normal (C4 18 mg/dl and C1-INH 83%), and she denied experiencing episodes of her lip or hand swelling. The results of additional coagulation tests for lupus anticoagulant, anticardiolipin antibody Immnoglobulin G (IgG), anti-beta2-Glycoprotein I antibody IgG, Protein C, and Protein S were all normal. Antinuclear antibodies, anti-dsDNA IgG antibodies, and anti-Smith antibodies suggesting lupus enteritis were also negative. Although thrombosis was also suspected, her

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Figure 1. Contrast-enhanced CT. (A, B) First visit, axial and coronal. (C, D) Second visit, axial and coronal. Massive oedema from the small intestine to the colon with ascites is demonstrated.

symptoms spontaneously disappeared in approximately a day, and she was discharged.

Although the symptoms subsided when she stopped using LEP, she still experienced abdominal discomfort around twice a month. A genetic test was then performed to make her diagnosis. After obtaining written informed consent, we extracted genomic DNA from her peripheral blood sample and subsequently searched for mutations in *F12, PLG, ANGPT1, KNG1*, and *HS3ST6* genes by Sanger sequencing. As a result, we successfully identified a heterozygous missense mutation c.988A > G (p.Lys330Glu; p.K330E) in Exon 9 of the *PLG* gene (Figure 2). Finally, she was diagnosed as having HAEnCI (HAE-PLG).

In family history, her mother was healthy, but her younger sister had similar abdominal discomfort episodes. Consistent with that, genetic testing revealed the identical *PLG* gene mutation in the younger sister, leading to determine the diagnosis of HAEnCI as well, whereas the mother was negative for the mutation (Figure 2). Prophylactic tranexamic acid and on-demand selective bradykinin B2 receptor blockers helped symptoms of both patients to be under control.

Discussion

HAE was initially noted in 1888, and it was determined in 1963 that C1-INH dysfunction was responsible [1, 4]. C1-INH is a complement regulatory molecule that inhibits the activation of complement C1. Mutations in *SERPING1*, the gene that codes for C1-INH, lead to C1-INH dysfunction, which results in angio-oedema [5]. There are three distinct types of HAE. *SERPING1* gene mutations are known to underlie Type I and Type II HAE. C1-INH deficit and dysfunction are the symptoms of Type I and Type II HAE, respectively. Type III HAE exhibits the same symptoms as normal C1-INH activity and is also called HAE-with-normal-C1-INH (HAEnCI) [6]. Although HAEnCI is rarer among the three types of HAE, several genes linked to the condition have recently been identified [7, 8]. Genetic abnormalities include clotting factor XII (*F12*), angiopoietin 1 (*ANGPT1*), *PLG*, and kininogen 1 (*KNG1*) [9–12]. Bradykinin hyperproduction or hyperfunction is caused by abnormalities in these four genes. There are cases of HAE without these mutations.

The first report of HAE with a *PLG* gene mutation (HAE-PLG) was published in 2018 [11]. The mutation reported was c.988A > G (p.K330E) in Exon 9 of the *PLG* gene [11], which was the same mutation identified in our affected siblings (Figure 2). The mutation caused a nonconservative amino acid substitution in the kringle 3 domain of the PLG protein. PLG activators change PLG into plasmin, which is the primary enzyme of fibrinolysis. Although the precise mechanism of PLG mutation in HAE is not fully understood, a recent study revealed that the mutant PLG induces bradykinin generation by cleavage of kininogen once the PLG is converted into plasmin [13]. The majority of HAE-PLG patients had episodes of angio-oedema of the tongue, but fewer had symptoms in their extremities or abdomen (Table 1). Some patients who suffer only intermittent abdominal pains may remain undiagnosed.

Her younger sister also took LEP for erratic menstruation and often complains of the same type of stomach ache. Before having been found to carry the PLG gene mutation, she mistook her menstruation pains for severe ones.

HAEnCI is also inherited in an autosomal dominant manner, but with less penetration. The majority of patients who develop HAEnCI are female after the age of 20 years, like this patient. Pregnancy and the use of oestrogen prescriptions are related to this disease [3, 6]. The association between HAE-PLG and oestrogen is unclear, and prior reports have varied between 14% and 83% [11, 14]. The impact of oestrogen in HAE-PLG was less than that in HAE-FXII [15]. A tissue PLG activator (t-PA) and PLG bind to fibrin to form trimers in the presence of clots and efficiently produce plasmin [16]. Known triggers like exogenous oestrogen, menstruation, and surgery may form small clots. Normally lysed spontaneously, but mutated plasmin can be generated by t-PA in patients with HAE-PLG and trigger an attack [13, 15]. D-Dimer levels are also high during HAE attacks [17].

When severe abdominal pain undertaking oral contraceptives or LEP appears together with elevated D-dimer levels, thrombosis is usually considered. Radiologically, intestinal oedema linked to HAE and acute enteritis seems indistinguishable. Because neither a decrease in C4/C1-INH nor common symptoms like hand or lip oedema were seen, a diagnosis was difficult to determine.

We are now able to treat patients with concentrated human C1 inactivator and selective bradykinin B2 receptor blockers [18, 19]. Additionally, for prophylaxis, we can administer tranexamic acid, human antihuman plasma kallikrein monoclonal antibodies, and regular C1 inhibitor supplementation [20, 21].

Patients who exhibit typical HAE symptoms are usually easily diagnosed, but those whose symptoms are limited to the abdomen, like hers, may not. Patients who develop stomach pain after using LEP or who have atypical menstrual cramps should be evaluated for HAE, and genetic tests should be considered if C4 and C1 inhibitors are normal.

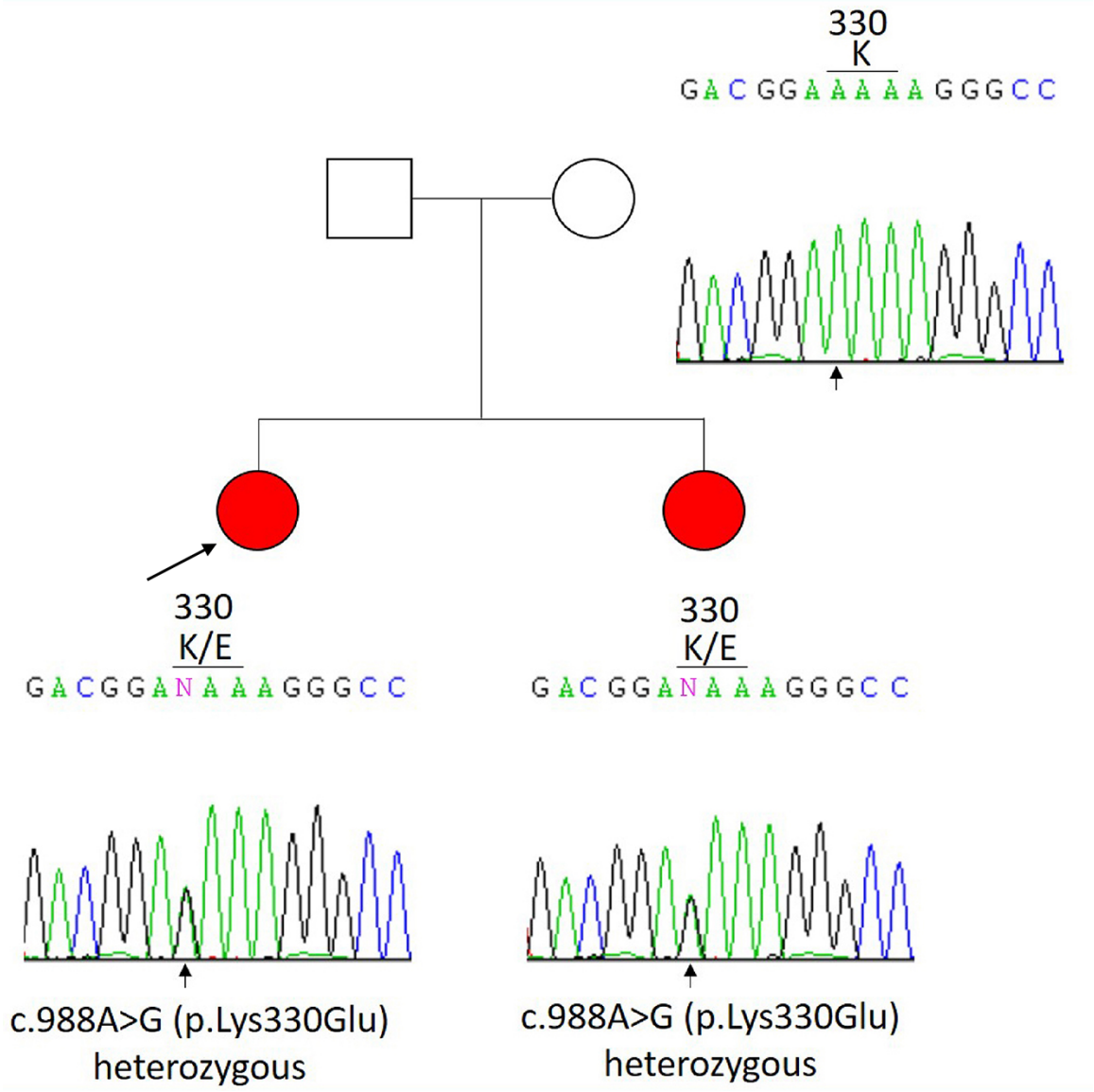

Figure 2. Family tree. Genetic testing for the *F12, PLG, ANGPT1, KNG1*, and *HS3ST6* genes was performed on the patient, her mother, and her sister. She and her sister were heterozygous for the missense mutation c.988A > G (p.K330E) in Exon 9 of the *PLG* gene, while her mother was negative for the mutation.

Table 1. Clinical characteristics of HAE-PLG.

					Symptom (%)						Triggers (%)
Author	Mutation	No. of patients	Gender, M/F	Age of onset (range)	Face	Lips	Tongue	Extremities	Abdomen	Larynx	Oestrogen
Bork *et al.* [11]	K330E	60	13/47	30 (5–72)	77	NA	78	10	30	10	14
Belbezier *et al.* [22]	K330E	8	2/6	23 (6–64)	62	62	87	0	50	NA	33
Yakushiji *et al.* [23]	K330E	4	1/3	47 (26–94)	25	50	50	0	25	25	NA
Bork *et al.* [14]	K330E	10	4/6	27 (16–56)	10	80	50	0	10	30	83
Present cases	K330E	2	0/2	19, 24	0	0	0	0	100	0	100

M/F, Male/female; NA, information not available.

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T. Nakayama certify that no other persons have made substantial contributions to the work.

Conflict of interest

None declared.

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Patient consent

We obtained written informed consent for the publication of this report from the patient. The signed consent form is retained by the corresponding author.

Ethical approval

Not applicable.

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