The relationship between complement levels and disease activity in Japanese family cases of hereditary angioedema with C1-INH deficiency

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Letter to the Editor

The relationship between complement levels and disease activity in Japanese family cases of hereditary angioedema with C1-INH deficiency

Dear Editor,

Hereditary angioedema (HAE) with C1 inhibitor deficiency/defect (C1-INH-HAE) is a rare autosomal dominant disorder caused by deficiency (type 1) or dysfunction (type 2) of the C1 inhibitor (C1-INH) with the defective *C1INH* (*SERPING1*) gene.[1–3] Clinical manifestations of HAE include recurrent attacks of subcutaneous or submucosal edema, gastrointestinal attacks, and upper airway edema including laryngeal obstruction.[4] Although high levels of prothrombin fragment F1+2 and D-dimer and neutrophilia may occur during an HAE attack, there are few reports on the relationship between disease severity and/or activity of C1-INH-HAE and predictive parameters.[5,6] There are no reports examining such correlations in Japanese C1-INH-HAE cases. We focused on the relationship between complement parameters and disease activity in three Japanese family of type 1 HAE whose diagnoses were confirmed with *C1INH* genetic analysis.

Eight type 1 HAE patients from three Japanese families were consecutively enrolled in this retrospective study (Table 1). Diagnosis of C1-INH-HAE was made from decreased both functional and antigenic levels of C1-INH and positive family history, demonstrating that all patients were type 1 HAE (Table 1). It is strongly recommended that family members of individuals with HAE should be screened for the condition based on decreased quality of life due to delayed diagnosis and risk of the first attack without appropriate therapy.[7] Therefore, we screened family members positively. It is noteworthy that some patients without any past attacks are included in this study. Genetic mutations were found within exons 3 (family A), 7 (family C), and 8 (family B) of *SERPING1*, which was helpful in this diagnostic workup.[2] All patients provided informed consent. The study protocol was approved by the Institutional Review Board (Kyushu University; No 586-00).

Serum samples during symptom-free periods without any medication were used for the measurement of C3, C4, C1q, total hemolytic complement activity (CH50), C1-INH functional levels, and C1-INH antigenic levels. We retrospectively recorded attack severity and number over the past 5 years from medical records and by self-assessment of patients or family members. WHO guidelines for the management of HAE recommend that all attacks involving the face, neck, or abdomen should be considered for on-demand therapy, and treatment for attacks affecting the upper airways is mandatory.[7] Attacks that involved the face, neck, abdomen, or upper airways were defined as severe attacks and other subcutaneous attacks were defined as mild attacks in this study to differentiate attack severity.

Patient laboratory and disease activity characteristics are shown in Table 1. Serum C3 levels were within the normal range in all patients. In five of eight patients with HAE (62.5%), serum C4 levels were below the lower limit of the normal range. Three patients within the normal range for serum C4 were asymptomatic during their life. In four of eight patients with HAE (50.0%), serum CH50 levels were below the lower limit of the normal range. Serum CH50 levels were below the lower limit of the normal range in all patients with past attacks. Serum C1q levels were below the lower limit of the normal range in two of eight patients with HAE, aligning with past reports,[2] suggesting that a low-serum C1q level does not necessarily indicate acquired angioedema.

We examined the relationship between disease severity and/or activity of C1-INH-HAE and predictive parameters of serum complement in this case series. Functional C1-INH, C-INH antigen, C4, and CH50 levels were decreased in symptomatic patients than asymptomatic patients (Fig. 1). C3 level did not have the difference between symptomatic patients and asymptomatic patients (Fig. 1). Comparing functional C1-INH, C-INH antigen, C4, and CH50 levels with number of HAE severe attacks except for peripheral cutaneous angioedema revealed a significant negative correlation (Supplementary Fig. 1a). A significant negative correlation was found between serum levels of functional C1-INH, C-INH antigen, C4, and CH50 and number of peripheral cutaneous angioedema (mild attacks) (Supplementary Fig. 1b). No correlation was found between the number of each attack and C3 levels (Supplementary Fig. 1a, b).

To the best of our knowledge, this is the first report to examine the correlation between complement levels and disease activity in type 1 HAE Japanese cases confirmed by *SERPING1* genetic analysis. We observed that functional C1-INH, C-INH antigen, C4, and CH50 levels but not C3 were reduced in symptomatic patients than asymptomatic patients. Patients (A-2, B-3, C-3) whose functional C1-INH levels were upper than 30% were asymptomatic and within normal C4 levels, implying that less consumption of complement such as relatively high functional C1-INH and normal C4 levels could predict asymptomatic tendency. We found a significant negative correlation between serum levels of functional C1-INH, C-INH antigen, C4, and CH50, but not C3, and number of past HAE attacks. This tendency was also observed in each patient among their respective families who had the same genetic background.

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Table 1
Laboratory and disease activity characteristics of Japanese patients with type 1 HAE confirmed by genetic analysis.

Patient No.	Age	Sex	C3 (mg/dl)	C4 (mg/dl)	CH50 (IU/ml)	Functional C1-INH activity (%)	C1-INH antigen (mg/dl)	C1q (mg/dl)	Severe attack	Mild attack
A-1	27	F	104	4.4	18.8	<25	4	9.3	5	15
A-2	69	F	83	15.7	35	37	10	9.2	0	0
B-1	29	F	105	1.3	<10	<25	7	3	39	140
B-2	8	F	123	6.9	20	27	8	9.4	0	0
B-3	27	F	99	15.7	36	33	8	8.6	0	0
C-1	36	F	86	4.4	10.3	<25	5	7	16	150
C-2	8	M	95	6.4	35	28	10	14	0	0
C-3	64	F	94	17.8	43.6	33	9	9	0	0
Normal range			65–135	13–35	25–51	>70%	11–26	8.8–15.3		

The British sign in patient No. means the same family and they have the same genetic mutations. All complement and C1-INH levels were measured during symptom-free periods. Severe attack: attacks involving the face, neck, abdomen, or upper airways over the past 5 years. Mild attack: peripheral subcutaneous attacks over the past 5 years.

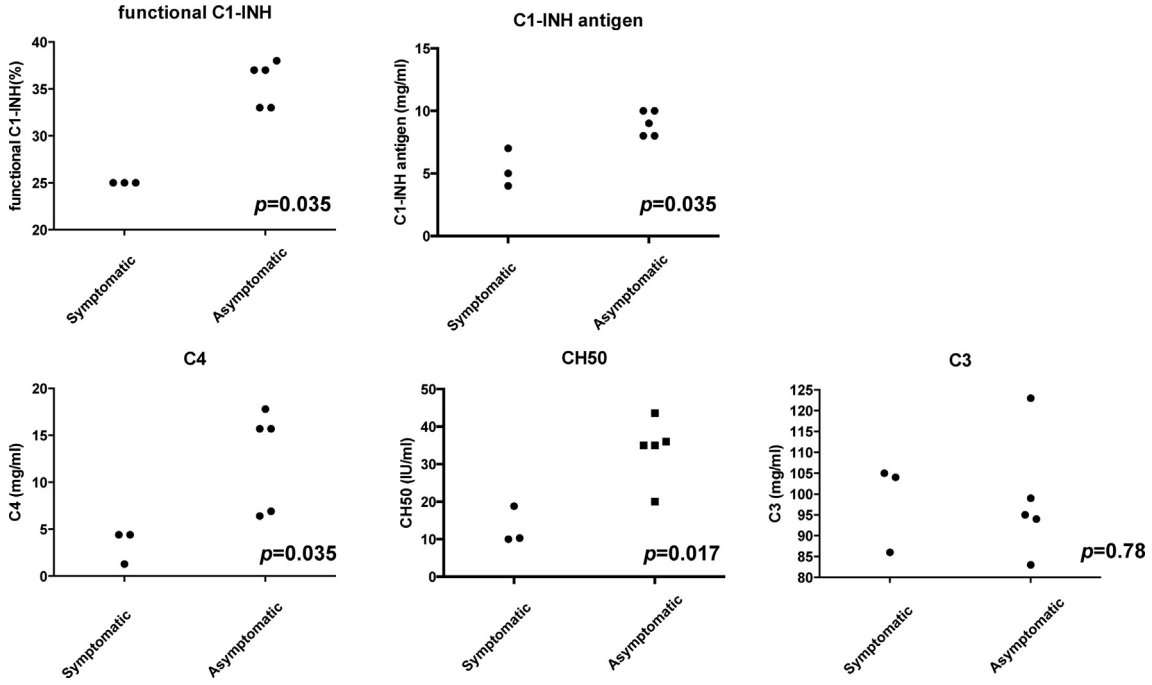

Fig. 1. The comparison of complement levels between symptomatic (frequent attacks) and asymptomatic (no attacks) patients. A p-value <0.05 was considered statistically significant; Mann–Whitney U test.

Kelemen *et al.* found a significant correlation between HAE disease severity score and baseline levels of functional C1-INH, and no correlation between HAE disease severity score and other complement parameters (C4 and CH50).[6] This difference may be a result of different inclusion criteria, as those researchers only included patients with repeatedly low functional or antigenic C1-INH levels and low C4 concentrations. Thus, the results of this study suggest that serum levels of functional C1-INH, C-INH antigen, C4, and CH50 during symptom-free periods might be useful as predictive parameters of type 1 HAE disease activity, although our results are limited by the small number of cases.

Ohsawa *et al.* reported that serum C4 levels were within the normal range in three of five Japanese asymptomatic HAE patients with low C1-INH functional levels.[8] Tarzi *et al.* reported that levels of C4 were within the normal range in five untreated HAE patients.[9] Our study included three patients with normal C4 levels. Previous reports emphasize that the diagnosis of HAE cannot be excluded by normal levels of complement C4.

In conclusion, serum levels of complement parameters such as functional or antigenic C1-INH, C4, and CH50 during symptom-free periods might be useful laboratory biomarkers of type 1 HAE disease activity.

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A.F. collected and analyzed the patient's data and wrote the manuscript. S. T., K. L. and K.W. collected the patient's data. C. H. analyzed the patient's data. T. H. analyzed the patient's data, wrote the manuscript and modified the manuscript. C.N. supervised the project and wrote the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.alit.2018.03.002.

Conflict of interest

TH and AF have financial relationships about consultant lecture fee with CSL Bering and Shire. The rest of the authors have no conflict of interest.

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