

Acquired Angioedema – Occurrence, Clinical Features and Associated Disorders in a Danish Nationwide Patient Cohort

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Key Words

Angioedema · C1 inhibitor deficiency · Monoclonal B-cell lymphocytosis · Rituximab

Abstract

Background: The prevalence of acquired angioedema (AAE) is hitherto unknown and, to date, less than 200 patients have been reported worldwide. AAE is associated with lymphoproliferative conditions and autoantibodies against C1 inhibitor (C1INH). Rituximab (RTX) is increasingly used in the treatment of AAE patients. **Methods:** A nationwide study of AAE patients was performed in Denmark. Clinical features, associated disorders, treatments and outcomes were registered. **Results:** Eight AAE patients were identified. The diagnostic delay was on average 1 year and 8 months. Patients were treated with C1INH concentrate or icatibant on demand. Six patients were diagnosed with a clonal B-cell disorder during follow-up, on average 2.5 years after the first swelling. Two patients had monoclonal B-cell lymphocytosis (MBL). Two patients received RTX. **Conclusions:** AAE is a rare condition occurring in less than 10% of patients with C1INH deficiency in Denmark. AAE is highly associated with haematologic disorders, and we recommend yearly follow-up visits with clinical examination and blood tests including flow cytometry to diagnose B-cell conditions at an early stage. We report 2 patients with AAE and associated MBL, which is a

benign expansion of clonal B lymphocytes. MBL can be the precursor of chronic lymphocytic leukaemia or is associated with non-Hodgkin's lymphoma. If angioedema is poorly controlled with standard treatment regimens, we suggest treatment of the associated haematologic disorder. Based on a review of the literature and our own data, we recommend therapy with RTX, especially in patients with anti-C1INH autoantibodies.

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Introduction

Acquired angioedema (AAE) due to acquired C1 inhibitor (C1INH) deficiency is an extremely rare but potentially life-threatening condition with bradykinin-mediated angioedema [1, 2]. AAE generally manifests in adulthood and is characterized by recurrent swellings of skin and mucosa, which may be indistinguishable from hereditary angioedema (HAE) [3]. Historically, AAE has been divided into paraneoplastic type I associated with lymphoproliferative diseases and autoimmune type II defined by the presence of inactivating autoantibodies to C1INH [4–6]. Today, we know that this distinction is artificial, as many patients have lymphoproliferative diseases together with autoantibodies to C1INH [2, 7].

The frequency of AAE is not known, but there is an estimate of 1 patient with AAE for every 10 patients with HAE [8]. In a published abstract, 18 cases of AAE were identified among 380 patients with C1INH deficiency corresponding to 1 patient with AAE for every 20 HAE patients [9]. To date, less than 200 patients with AAE have been reported in the world literature. Most of these patients have been published as single case reports, but 9 papers and 1 abstract presented case series with at least 5 patients [6, 9–17]. There may be some overlap of published patients [6, 10, 13]. A thorough review of the condition and a summary of 136 published cases were given by Zingale et al. [2] in 2006. Since then, knowledge has expanded with regard to associated B-cell clonal disorders and therapeutic experiences with rituximab (RTX), which will be summarized in this paper together with original clinical and epidemiological data from the Danish cohort of 8 patients with AAE.

Material and Methods

Data from all Danish patients with AAE are included in this study. Patients were recruited from the National HAE Centre and a nationwide study of patients with C1INH deficiency in Denmark updated in January 2009 [3]. The patients registered with AAE by November 2012 are presented.

The diagnosis of AAE was based on angioedema symptoms developing in adulthood and blood tests showing C1INH function as well as C1INH antigen levels below 50%, low complement C4 (C4) and low complement C1q (C1q) [2, 7, 8]. None of our patients had a family history of angioedema. Clinical data were systematically collected from medical records, systematic interviews and clinical examinations.

All patients gave written informed consent. Permission was obtained from the Danish Data Protection Agency while approval from an ethics committee was not required.

Complement Testing

At the National Reference Laboratory (Unilabs), levels of C1INH and C4 were quantified using nephelometry, C1INH function was measured using a chromogenic assay and C1q was determined using radial immunodiffusion. Anti-C1INH autoantibodies were measured in Grenoble or Milan with the ELISA technique slightly modified after the method described by Alsenz et al. [4].

Results

The study population consisted of 8 patients (2 women and 6 men) with an age range from 46 to 86 years at their first swelling attack. Clinical and biochemical data are shown in table 1. Two patients died (No. 3 and 8) of lymphoma and old age, respectively.

The frequency of attacks varied from at least 1 attack every month to less than 1 attack per year. All patients had swelling attacks involving the upper airways. In 5 patients, upper airway swellings were the initial symptom, and 1 patient (No. 4) needed an emergency tracheotomy. Six patients experienced facial swellings, 5 patients had abdominal pain attacks and 4 patients had peripheral swellings of extremities. Three males had relapsing genital swellings. Six patients reported that trauma or psychological stress provoked some of their angioedema attacks.

The mean duration from the onset of symptoms to the diagnosis of AAE was 1 year and 8 months (0 months to 5 years). In 6 patients, allergy was the initial tentative diagnosis and treatment with anti-allergic medications (antihistamines, corticosteroids and in 4 cases adrenaline) had been used without effect. In patient No. 3 (genital swelling), infection was initially suspected, and in patient No. 7 (peripheral swelling), trauma-induced swelling was the first presumptive diagnosis.

Seven patients received long-term prophylaxis (LTP) with tranexamic acid seemingly effective in 5 patients whose attack frequency went down. Patient No. 7 stopped treatment with danazol due to lack of efficacy. Seven patients received acute on-demand therapy (ODT) with plasma-derived C1INH concentrate (pdC1INH), and patient No. 3 was provided with icatibant. Patient No. 2 had very frequent swellings of his face and upper airways, and he was trained in self-injection of intravenous pdC1INH and later subcutaneous icatibant. Since 2009 he has used 93 vials (46,500 units) of pdC1INH and 71 syringes of icatibant.

Underlying Diseases in the Danish Cohort of AAE Patients

At the time of the first swelling attack, 1 patient was known with a former non-haematological malignancy and 2 patients subsequently developed a non-haematological cancer. Patient No. 6 had a highly differentiated prostate cancer diagnosed 4 years earlier. Patient No. 2 was diagnosed with a malignant melanoma (Clark level II) 2 years after his first swelling attack, and patient No. 7 was diagnosed with a carcinoid tumour after 5 years. All 3 patients were treated with surgery, and patient No. 7 received additional chemotherapy. However, the treatments did not affect the frequency or severity of angioedema attacks. None of the 8 patients had an established haematologic disorder at the onset of AAE, but during follow-up, clonal B-cell disorders were diagnosed in 6 patients: splenic marginal zone lymphoma, monoclonal B-cell lymphocytosis (MBL) in 2 patients, small lympho-

Table 1. Clinical and biochemical data in 8 Danish patients with AAE

Patient No.	1	2	3	4	5	6	7	8
Gender/age at first swelling, years	F/58	M/57	M/46	F/67	M/69	M/82	M/60	M/86
Diagnostic delay of AAE	6 months	4 years	6 months	0 months	2 months	16 months	5 years	2 years
C1INH antigen, g/l (normal range 0.21–0.39)	0.10	0.05	0.03	<0.03	<0.03	<0.03	0.06	0.06
C1INH activity, % (normal range 70–130)	46	<20	20	29	43	20	<20	<20
C4, g/l (normal range 0.10–0.40)	<0.04	0.08	0.32	0.04	<0.04	<0.04	0.05	<0.04
C1q, µmol/l (normal range 0.29–0.60)	0.185	<0.01	0.14	<0.01	0.04	0.11	0.01	<0.01
Anti-C1INH autoantibodies	ND	pos. IgM ¹ pos. IgG ¹	neg. ²	neg. ¹	pos. IgM ²	neg. ¹	ND	ND
Concomitant diseases		melanoma				prostate cancer	carcinoid tumour	
Treatment		surgery				surgery	surgery, chemo	
Associated haematologic disorders	SMZL	MBL	SLL	SLL	MBL			WM
Treatment of haematologic disorders	none	none	multi-chemo RTX	prednisolone RTX				none
Period from first angiooedema attack until diagnosis of haematologic disorder	2 months	7 years	1 month	8 months	2 years			5 years
Total number of attacks in follow-up period	4	136	6	3	16	6	>250	5
Peripheral	X	X	X				X	
Abdominal	X	X	X		X		X	
Upper airways	X	X	X	X	X	X	X	X
Facial		X	X		X	X	X	X
Genital swelling		X	X				X	
Erythema marginatum	no	yes	no	no	no	no	no	no
Trigger factors	no	trauma, stress	trauma	no	stress	trauma	infection	infection
Therapy acute attacks	pdC1INH	pdC1INH icatibant	icatibant	pdC1INH	pdC1INH	pdC1INH	fresh frozen plasma pdC1INH	pdC1INH
Long-term prophylaxis	TX	TX	TX	TX		TX	danazol, TX	TX
Follow-up after diagnosis of AAE, years	5	3	1 ³	5	2	4	11	7 ³

F = Female; M = male; ND = not determined; pos. = positive; neg. = negative; chemo = chemotherapy; SMZL = splenic marginal zone lymphoma; WM = Waldenström macroglobulinaemia; multi-chemo = multi-chemotherapy; TX = tranexamic acid.

¹ Anti-C1INH autoantibodies were measured by ELISA assay at the University of Grenoble, France.

² Anti-C1INH autoantibodies were measured by ELISA assay at the University of Milan, Italy.

³ Patient has died.

cytic lymphoma (SLL) in 2 patients and Waldenström macroglobulinaemia. The haematologic conditions were diagnosed on average 2.5 years (1 month to 7 years) after the first angioedema attack. Patient No. 3 was diagnosed with SLL transforming into a diffuse large cell B-cell lymphoma (Richter transformation). Despite multi-chemotherapy and RTX treatment, he died at the age of 47. Patient No. 4 had SLL and was treated with low-dose prednisolone for an associated immune haemolytic anaemia. Patient No. 5 was diagnosed with MBL and started RTX 3 months ago. He has had 1 single attack 3 weeks after starting this treatment regimen consisting of 4 infusions administered at 1-week intervals. In patients No. 1, 2 and 8, the haematologic conditions were biologically benign and remained untreated.

Discussion

This is the first nationwide survey of AAE making it possible to calculate a minimal prevalence of AAE in Denmark corresponding to 1:930,000 people. This number is 1/13 of the HAE prevalence in Denmark [3]. As we are a National HAE Centre and recruit patients from the whole country as well as from the National Reference Laboratory and the Patient Organization for C1INH deficiency, we believe that we have included all AAE patients diagnosed in Denmark. There is a diagnostic delay, since the condition is often misdiagnosed as allergy at the beginning, and furthermore, some patients with AAE may remain undiagnosed, suggesting that the real prevalence is likely to be higher.

All our patients were older than 40 years of age at their first angioedema attack, in accordance with the literature showing that age at onset was more than 40 years in 94% of patients [8]. Patients had low values of complement C1INH antigen, C1INH function, C4 and C1q at least once. Two out of 5 patients tested in this study had anti-C1INH autoantibodies, described in the literature in 71 out of 136 patients [2]. However, not all 136 patients had been screened for anti-C1INH autoantibodies. C1INH deficiency in AAE is caused by increased C1INH catabolism secondary to hyperactivation of the classical complement pathway and/or inactivating autoantibodies to C1INH and elevated plasma levels of cleaved C1INH [4–8, 18]. The common final pathogenetic event is an activation of the contact-kinin system leading to rises in bradykinin, which binds to B2 receptors and increases endothelial permeability resulting in oedema [19]. Both our patients with anti-C1INH autoantibodies had MBL

in accordance with the fact that clonal B-cell disorders are often associated with autoimmune manifestations [20].

The mean duration from the onset of symptoms to the diagnosis of AAE was 1 year and 8 months, which is much less than the average diagnostic delay of HAE, being 16.3 years [3], and comparable to the diagnostic delay in the largest reported study of 23 patients with AAE showing a diagnostic delay of 2 years and 5 months [6]. It is important to establish a diagnosis of AAE as early as possible, as attacks can be life threatening and require special treatment. Patient No. 4 was severely affected by an upper airway oedema presenting with stridor, cyanosis and bradycardia. She had an emergency tracheotomy and developed minor neurologic sequelae. After this episode, AAE was diagnosed and she was treated with pdC1INH for subsequent attacks.

Only one of our patients reported erythema marginatum. Although this symptom is a clinical clue to the diagnosis and well described in about half of patients with HAE [3], it is rarely reported within the AAE literature, and as far as we know only illustrated once [21]. We wonder if erythema marginatum is an overlooked symptom in AAE or if the prevalence is actually lower than in HAE. Within the HAE population, it is generally accepted that the symptom is most prevalent in children and young adults, and this could be one explanation for the lower frequency in AAE. Other prodromal symptoms in HAE and probably AAE are unusual fatigue, flu-like symptoms, nausea, abdominal cramps and tingling of the skin [22].

Frequency of symptoms varied between patients – from one attack every second year to monthly attacks in others. LTP with tranexamic acid works better than danazol in AAE [7, 8, 11, 23]. Acute attacks of AAE are treated with pdC1INH on demand. However, some patients with anti-C1INH autoantibodies become highly resistant [7, 13, 24]. In 3 of our patients, the dose of pdC1INH had to be increased from 1,000 units to 1,500 units to be effective, but we did not observe any genuine drug resistance. After dose escalation, patient No. 2 was switched to the bradykinin B2 receptor antagonist icatibant, which worked fast and efficiently. In the literature, a total of 11 patients have been treated successfully with icatibant [17, 21, 25–27]. Another ODT is ecallantide, a kallikrein inhibitor that prevents bradykinin release, which has been used effectively in 2 patients [8]. We could not find any publications of recombinant C1INH concentrate used in AAE, but suggest that this could work as well. These therapies are all evidence based and

Table 2. Published AAE cases treated with RTX

Publication	Patients	Gender/ age, years	Underlying disorders	Anti-C1INH autoantibodies	Treatment of haematologic disorders	Response
Ziakas et al. [31], 2004	1	M/67	MGUS (IgM)	pos.	Cycloph, RTX	partial
Levi et al. [32], 2006	3	F/45 F/70 M/68	follicular B-cell lymphoma none identified	pos. (IgG)	CS, Cycloph, RTX RTX CS, Cycloph, RTX	complete complete complete
Sánchez-Cano et al. [35], 2008	1	F/66	Sjögren's syndrome	pos. (IgM)	CS, RTX	complete
Hassan et al. [33], 2011	1	F/84	MGUS (IgM)	pos. (IgM)	RTX	complete
Lam et al. [34], 2012	1	F/80	SMZL		RTX	complete
Branellec et al. [12], 2012	7	F/54 M/79 M/61 F/51 F/82 F/80 F/75	none identified MZL MGUS (IgA) MGUS (IgG) none identified MGUS (IgG) MZL	pos. (IgM) pos. (IgM) pos. (IgA) pos. (IgG) pos. (IgM) pos. (IgM) neg.	CS, RTX Cycloph, RTX CS, RTX RTX RTX RTX RTX, CS	complete complete partial complete partial none none
This study	2	M/46 M/69	SLL MBL	neg. pos. (IgM)	multi-chemo, RTX RTX	partial partial

M = Male; MGUS = monoclonal gammopathy of undetermined significance; pos. = positive; Cycloph. = cyclophosphamide; F = female; CS = corticosteroids; SMZL = splenic marginal zone lymphoma; neg. = negative; multi-chemo = multi-chemotherapy.

licensed for HAE after double-blind, randomized placebo-controlled trials [28], thus being used off-label in AAE.

Six of our 8 patients were diagnosed with a haematologic condition during the follow-up period. The lymphoproliferative disorders were diagnosed on average 2.5 years after the first swelling attacks. In none of our patients, a lymphoproliferative disorder was known when angioedema started; however, in 2 patients (No. 1 and 3), abnormal blood counts and/or enlargement of lymph nodes were noticed at the initial hospital contact for AAE, and further examinations lead to diagnoses of splenic marginal zone lymphoma and SLL. Flow cytometric analyses of peripheral blood were performed in patients No. 2, 4 and 5 and lead to a presumptive diagnosis of a haematologic condition, which was confirmed by bone marrow biopsy. Patients No. 2 and 5 were diagnosed with MBL, and patient No. 4 was diagnosed with SLL. Patient No. 8 was diagnosed with Waldenström macroglobulinaemia.

AAE is associated with B-cell lymphoproliferative disorders ranging from monoclonal gammopathy of un-

known significance to malignant lymphomas and leukaemias. To the best of our knowledge, we report the first 2 patients in the world literature with AAE and associated MBL. MBL is a benign expansion of clonal B lymphocytes [20] that can be seen as the B-lymphocyte analogue of monoclonal gammopathy of unknown significance described in 35% of patients with AAE [2]. MBL has a conversion rate to CLL of about 1–2% per year [20, 29, 30]. Patients with MBL should undergo an evaluation by a haematologist/oncologist that includes a complete physical examination with comprehensive lymph node examination. In the absence of constitutional symptoms (fever, night sweats, fatigue and weight loss), individuals with MBL can be distinguished from those with the closely related SLL, based on the absence of palpable lymphadenopathy or organomegaly.

According to the literature, few cases of AAE are associated with solid neoplasms, infections and autoimmune diseases, and a minority of patients may be otherwise healthy [2, 6, 7]. Three of our patients had malignant tumours, but association with their C1INH deficiency was doubtful.

If angioedema is poorly controlled with LTP and ODT, treatment of the underlying disease should be considered. Successful treatment of an underlying lymphoma can result in permanent or temporary reversal of the clinical and/or biochemical abnormalities of AAE [2, 9, 11, 16]. Patient No. 3 normalized his C1INH after therapy with RTX and chemotherapy. RTX is a chimeric, mouse-human monoclonal antibody directed against CD20 on B cells introduced in the treatment of AAE and associated diseases in 2004 [31]. RTX works through a targeted B-cell depletion that eradicates autoreactive clones as well as normal B cells. RTX has been used successfully in the treatment of various forms of B-cell neoplasms and autoimmune diseases and has a good safety profile. The treatment effect usually lasts 6–12 months. In general, more than half of patients will get a complete or partial response, though often temporary. A total of 14 patients with AAE treated with RTX, including 11 patients with associated lymphoproliferative conditions, have previously been published (table 2), with a follow-up period between 6 and 24 months. We add 2 more patients, although we only have short follow-up periods (3–7 months). The first report from Ziakas et al. [31] described 1 patient with less severe and less frequent symptoms after therapy with RTX. In a recent publication from the French National Reference Centre for Angioedema, 7 patients were described with a complete clinical efficacy in 3, partial in 2 and therapeutic failure in another 2 patients [12]. Levi et al. [32] published 3 AAE patients who went into complete clinical remission, and single case reports can be found too [33–35]. One may assume that the treatment efficacy is dependent on the existence of anti-C1INH autoantibodies as a basic pathogenic factor, because RTX may disrupt the anti-C1INH antibody formation. Indeed, Branellec et al. [12] suggested that efficacy was only observed in patients with type II AAE. In 3 of 14 published patients with AAE treated effectively with RTX, data on anti-C1INH autoantibodies were lacking (table 2). In many AAE patients, treatment of the associated lymphoproliferative disorder with RTX will be justified, and a therapeutic efficacy of the underlying disease could have a positive influence on AAE.

Conclusion

We have presented a cohort of 8 Danish patients with AAE, together with a review of the literature confirming a high association between AAE and B-cell disorders. Due to this strong correlation, we recommend at least one

yearly follow-up visit with a clinical examination and blood tests for haematologic conditions (complete blood count, SR and plasma/urine analysis for M component). Furthermore, we suggest flow cytometry analysis of peripheral blood to diagnose B-cell disorders at an early stage. Although not all B-cell disorders including MBL require treatment per se, we consider that our data support the idea of RTX treatment as a low-risk option for treatment of the aberrant immune response in AAE patients with highly unpredictable and potentially life-threatening swelling attacks that may profoundly affect the quality of life. Especially patients with anti-C1INH autoantibodies may respond to RTX treatment. The end-point criteria for RTX treatment is clinical resolution of angioedema attacks. Systematic reviews are needed to establish the cost-effectiveness and safety of RTX and to compare the prices and efficacy of drugs targeting the angioedema swellings. The rarity of AAE makes clinical trials almost impossible.

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