Hereditary and Acquired Angioedema: Experience with Patients in Puerto Rico

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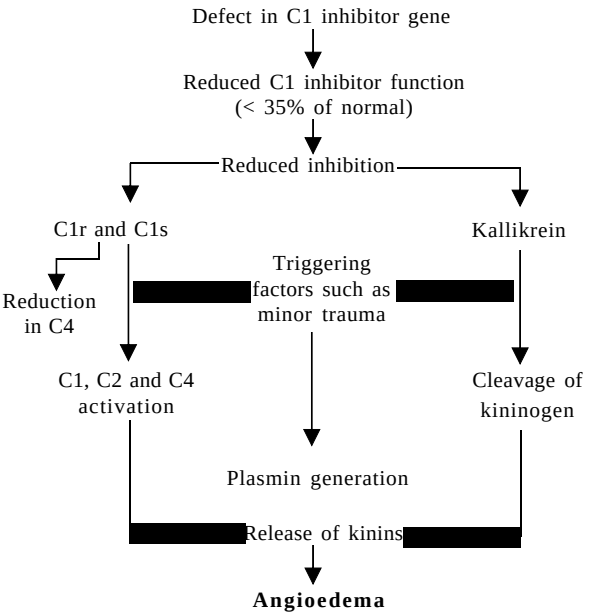
Hereditary (HAE) and acquired (AAE) angioedema are vascular reactions involving the sub mucosal tissues, representing localized edema caused by dilatation and increased permeability of the capillaries. HAE and AAE are clinical disorders characterized by angioedema that require prompt differentiation from other causes of angioedema in order to receive the most pertinent and effective therapeutic interventions. The aim of this report is to describe the clinical characteristics of patients with both HAE and AAE identified and followed at the Immunology Clinic of the University Hospital at the Puerto Rico Medical Center, their response and side effects to danazol therapy and their comparison with other series of similar patients reported in the literature. Overall, the patients in this sample presented a similar clinical profile compared to other reported series in the literature.

Key words: Hereditary angioedema, Acquired angioedema, Danazol.

Complement deficiencies account for approximately 2% of all primary immunodeficiencies. Hereditary angioedema has been etiologically related to a deficiency of the inhibitor of the first component of the classic complement cascade (C1 INH) (4-8). This condition is transmitted as an autosomal dominant trait that afflicts 1 in 10,000 to 1 in 150,000 individuals (1-3,6,7), with no gender predominance and has been reported in all ethnic groups (2,9). Traditionally, two types of HAE have been described: type 1 HAE, which has been associated to low antigenic and functional C1 INH levels and type 2 HAE, with normal or even increased antigenic levels of C1 INH but decreased functional activity (2). Recently, type 3 HAE has been described but it has not been related to abnormal concentration or functional abnormalities of C1 INH (1,2,10). Up to this time the pathophysiological or hereditary mechanisms of this disorder have not been elucidated (2).

Persons with HAE have one normal and one abnormal C1 inhibitor gene. The C1 inhibitor belongs to a family of serine protease inhibitors that constitute 20% of all inhibitors of the classical pathway. The pathogenesis of type 1 and type 2 HAE has been explained through indications that the low antigenic levels and or decreased functional activity of C1 INH permit the autoactivation of C1 and of the coagulation factors XIIa, XIIf and XIa and the uninhibition of activated kallikrein. It has been postulated that all these changes lead to an increased release of chemical mediators such as bradykinin and to the development of the clinical syndrome of angioedema (2) (Figure 1).

Figure 1. Proposed Pathogenetic Mechanisms of Angioedema



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Both HAE and AAE usually occur in the first or second decades of life and are characterized by episodic swelling of the extremities, the face, the bowel wall (manifested by recurrent abdominal pain) and the upper airways. The latter is a potential lethal complication that may lead to asphyxiation (4,5,7,8). Several precipitating factors have been identified including trauma, stress, dental manipulation, menstruation and surgical procedures (2,4,7,11). However, the attacks of angioedema may also occur spontaneously (2). The diagnosis of type 1 HAE should be strongly considered when a patient with the above attacks presents laboratory evidence of decreased C4 (the substrate of activated C1) levels, normal C3 levels and C1q levels and a decrease in the antigenic levels of C1 INH. That of type 2 HAE is usually made when symptoms and signs of angioedema occur in association to decreased functional levels of C1 INH but normal antigenic levels of that protein. Approximately 25% of patients with HAE do not have a family history of that condition (2,3,9). These cases have been associated to spontaneous mutations in the gene encoding for C1 INH, which is located in chromosome 11 (2,3,6,11). So far, over 100 mutations of that gene have been described leading to both type 1 and 2 HAE (1,2,9,12).

Acquired angioedema (AAE) can present with signs and symptoms identical to those of HAE, but its onset usually occurs after the fourth decade of life (2,7,11). Two types of AAE have been also described, type 1 AAE, which is associated to lymphoproliferative disorders and type 2 AAE associated with autoantibodies directed against C1 INH (6,7,13). It has been reported that in type 1 AAE, the associated lymphoproliferative malignancy induces the production of antiidiotypic antibodies against the monoclonal immunoglobulins present on the surface of the malignant cells. That results in an excess production of immune complexes that activate C1 and increase the consumption of C1 INH (6,7,11,13,14) with ensuing low levels of C1 INH leading from then on to the same pathogenetic pathway described for HAE (2). In contrast in type 2 AAE, the autoantibody against C1 INH inactivates C1 INH rendering it nonfunctional (6,11). The excess of immune complexes (autoantibody-C1 INH complex) that ensue consumes C1 INH as occurs in type 1 AAE (7,13). The diagnosis of AAE is established when a patient presents with the same signs and symptoms of HAE after the fourth decade of life along with decreased C4 levels, a normal level of C3, a low C1q level and decreased functional levels of C1 INH (6,13). The presence of autoantibodies against C1 INH distinguishes type 2 from type 1 AAE (6).

The aim of this report is to describe the clinical characteristics and the response and side effects of therapy with danazol in a series of patients with both HAE and AAE evaluated and followed at the Immunology Clinic of the University Hospital at the Puerto Rico Medical Center.

Methods

Study Patients. The study group comprised patients referred to the Immunology Clinic of the University Hospital by their primary physicians for evaluation and management of recurrent angioedema. A total of 32 patients were studied over a period of twenty years. Initially, every patient underwent a complete history, physical examination and baseline laboratory tests through a uniform protocol. Baseline C4 and C1 inhibitor levels were measured using radial immunodiffusion. Whenever a normal C1 inhibitor level was confirmed in duplicate samples, then a functional hemolytic assay was performed. C1q levels were also measured by radial immunodiffusion and C1 inhibitor antibodies were assayed by the ELISA method. Complement assays were performed in duplicate at two separate laboratories, as determined by the patients' convenience.

Once the diagnosis of either condition was established treatment with danazol, an attenuated androgen, was offered if the patient had one or more attacks of angioedema per month or in the presence of one life-threathening attack such as laryngeal angioedema, regardless of frequency. All patients that accepted treatment after an explanation of the possible side effects of therapy were started on danazol 600mg/d and after 4 weeks the dose was lowered to 400mg/d. Thereafter, the medication was given as tolerated by the patient on an individual basis, with a goal of achieving a maintenance dose that kept under control the frequency and severity of the attacks to an acceptable level to the patient. No patient with an episode of laryngeal angioedema was given or maintained in a dose lower than 200mg/d of danazol. The dose of the medication was decreased to 100mg/d, if the patient had less or just one attack in 6 months. Patients who attained a maintenance dose were instructed to increase it to 600mg/d at least one week prior to any dental or surgical procedure. Patients younger than 20 years of age were not considered candidates for danazol, as well as women in the child-bearing period, if they were not utilizing a secure contraceptive method. All patients on danazol underwent yearly or as often as needed a laboratory evaluation through complete blood counts, a comprehensive metabolic panel, and a urinalysis. CPK and aldolase levels were assessed whenever myalgias or cramps were reported.

Statistical Analysis. The statistical analysis was done with Fisher's exact test to compare the C1 INH level before

treatment and after treatment with danazol. The same test was used to compare C4 levels pre-treatment and post that treatment. Signed Rank test was used to compare the frequency of the attacks of angioedema before and after treatment with danazol. A p value <0.05 was considered to represent a significant difference.

Results

Table 1 contains a summary of the baseline clinical characteristics of the sample of patients studied. Thirty-two patients were identified with HAE. Twenty four (75%) patients were classified as type 1 HAE and eight (25%) as type 2 HAE. An overall female preponderance was observed, as 16 women (67%) were in the type 1 HAE group and 7 (87.5%) on the type 2 HAE group. It was found that all patients with type 2 HAE had a positive family history of angioedema; this however occurred in 20 (83.3%) of type 1 HAE.

Table1. Profile of Patients with Hereditary Angioedema

	Type I	Type II
Number of patients	24 (75%)	8 (25%)
Men	8 (33%)	1 (12.5%)
Women	16 (66%)	7 (87.5%)
Family history	20 (83.3%)	8 (100%)
Age range	6 to 62	13 to 73

As shown in Table 2, all 32 patients showed peripheral angioedema as their presenting symptom. Twenty seven (84.3%) presented with abdominal pain, twenty two (64.7%) had facial angioedema and eight (25%) had pharyngeal angioedema as their presenting symptom, respectively.

Table 2. Presenting Symptoms

Symptoms	Number of Patients (%)
Peripheral angioedema	32 (100%)
Abdominal pain	27 (84.3%)
Facial angioedema	22 (64.7%)
Pharyngeal angioedema	8 (25%)

The number of attacks of angioedema during the time of maximal symptoms ranged from 1 per month to 4 per week, the time to symptoms suggestive of a diagnosis of HAE ranged from 2 months to 38 years, with a mean of 13.1 years and the most frequent precipitating factors identified were trauma, stress, dental manipulation, appendectomy and menses. (Tables 3 to 5).

Of the group studied, seventeen patients were treated with danazol. Of those, sixty-four percent achieved a maintenance dose of 200 mg/d, 18 percent a dose of both 100 mg/d and 300 mg. The period of time that patients were on observation while taking danazol ranged from 3 months to 10 years. The decrease in frequency of angioedema attacks after treatment was impressive in that the number of attacks after treatment ranged from 1 every 2 months to 1 per year (Figure 2).

Table 3. Number of Attacks of Angioedema During Time of Maximal Symptoms

Frequency	Number of Patients
1 per month	10 (31.25%)
2 per month	3 (9.375%)
3 per month	3 (9.375%)
1 per week	3 (9.375%)
2 per week	6 (18.75%)
3 per week	6 (18.75%)
4 per week	1 (3.125%)

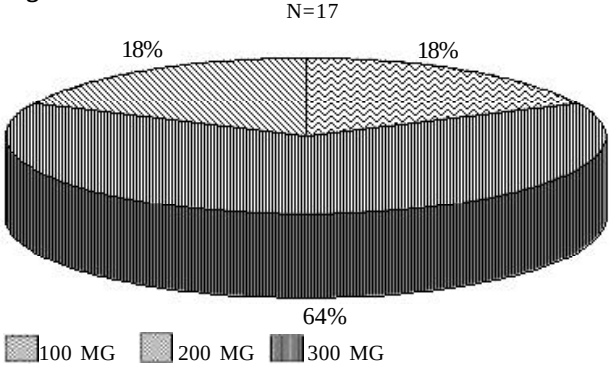
Table 4. Time to Diagnosis

Years	Number of Patients (%)
0 to 5	6 (18.75%)
6 to 10	9 (28.13%)
11 to 15	5 (15.625%)
16 to 20	6 (18.75%)
21 to 25	3 (9.36%)
26 to 30	2 (6.25%)
> 31	1 (3.13%)

Table 5. Triggering Factors

Factor	Number of Patients
Trauma	20
Stress	15
Dental manipulation	3
Appendectomy	2
Tonsillectomy	1
Menses	5

Figure 2. Maintainance Dose with Danazol



A moderate increase in C1 INH antigen levels was observed in the treated patients and a more marked increase in C4 levels occurred, as shown in Tables 6 and 7.

Table 6. C4 Values Pre and Post Treatment

	Post Treatment Number of Patients*	Post Treatment Number of Patients
Parameter	(n=16)	(n=16)
Low C4	16 (100%)	3 (18.75%
Normal C4	0	12 (75%)
High C4	0	1 (6.25%)

* Data not available in one patient

Table 7. C1 Inhibitor Antigen Pre and Post Treatment (n = 15)

Parameter	Pre Treatment Number of Patients*	Pre Treatment Number of Patients
Low C1 INH Antigen	12 (80%)	8 (53.3%)
Normal C1 INH Antigen	3 (20%)	7 (46.7%)

* Data not available in two patients

As listed in Table 8 the more frequent side effects reported with danazol after at least 6 months of treatment were: headaches (7 patients, 43.8%), weight gain (5 patients, 31.3%), amenorrhea (4 patients of a total of 12 females with menses, 33.3%), myalgias/cramps (3 patients, but all had normal CPK and aldolase, 18.%), microscopic hematuria (1 patient who resolved over time without discontinuation of danazol, 6.25%), and increased liver enzymes (2 patients, which normalized with a decreased in dose, 12.5%).

Table 8. Reported Side Effects in Patients after 6 Months of Therapy with Danazo (n = 16)

Side Effect	Symptom
Headaches	7
Weight gain	5
Amenorrhea	4*
Myalgias/Cramps	3[1]
Microscopic hematuria	1[2]
Liver enzymes	2[3]

[1] Normal CPK and aldolase
[2] Resolved with time
[3] Normalized with a decrease in dose

Other medical conditions present in the patients with HAE are described in Table 9.

Only two patients in this series were identified as having acquired angioedema. One was a 60-year-old woman with a 10-year history of angioedema. Subsequent follow up led to the identification of chronic lymphocytic leukemia, leading to a final diagnosis of AAE type 1. She received treatment for her leukemia with improvement of the angioedema. The other patient was a 47-year-old woman with a 5-year history of angioedema. No other medical condition was identified in her case but an antibody against C1 inhibitor was found. She received steroid therapy with improvement of angioedema.

Table 9. Other Medical Conditions Present

Condition	Number of Patients
Thyroiditis	1
Diabetes type 2	4
Seizures	1
Ig Deficiency	1
Crohn's disease	1
SLE	1
Rheumatoid arthritis	1
Alopecia universalis	1
Membranoproliferative Glomerulonephritis	1
HIV	1

Discussion

As reported in other series, danazol therapy was very effective in reducing the frequency of HAE attacks in the studied population (5,7,15). All patients treated with danazol in our study had a marked decrease in the frequency of the attacks of angioedema. This clinical response did not significantly correlate with an increase in the antigenic levels of C1 INH, thus establishing a difference between our patients and those in other reported series where the correlation was found to be more significant. (9,15). This difference could be partially explained by the fact that our analysis did not envision a comparison between absolute levels of C1 INH pre and post danazol treatment as in the other reported series. It is to be recognized that our patient population underwent laboratory assays in different reference laboratories and thus the results required comparison with different normal ranges and subsequently designated as high, normal or low as defined by the normal range of each reference laboratory. However, in contrast to our findings, in the series with statistically significant increases in C1 inhibitor levels, those levels failed to reach normal values as in the majority of our patients. As reported in other series, C4 levels increased significantly with danazol treatment in our patient population. It is important to stress that the response to treatment should be based on a decrease in the frequency and severity of angioedema attacks and not on laboratory parameters.

Treatment with danazol is not innocuous as evidenced

by the frequency of side effects reported by our patients and other series (7,15), although one series (5) reports less frequency of side effects (except for menstrual irregularities) at lower maintenance doses. This fact highlights the importance of discussing the risks and benefits of treatment with patients prior to starting therapy and of weighing the possibility of decreasing the frequency of the attacks of angioedema versus side effects. The higher the dose of danazol the more effective it is in decreasing the frequency of attacks of angioedema but at the expense of a higher probability of side effects.

Our patient population was a severely affected one by the condition, as evidenced by the frequency of angioedema attacks experienced and the majority of our patients suffered from them for a considerable period of time before the correct diagnosis of HAE or AAE was made. The mean period before diagnosis for our patient population was 13.1 years, where that parameter was 21 years in other reported series. (16). That fact and the availability of effective therapy for HAE and AAE, emphasize the importance of considering them in the differential diagnosis whenever one is evaluating patients with angioedema, as patients with these two conditions will not respond to treatment with antihistamines used for allergy-mediated angioedema. Allergic angioedema was the most common suspected etiology in our patient population.

Several articles report an increased incidence of autoimmune diseases in patients with HAE (2,7,16-18). In our patient population we found some with autoimmune mediated diseases, but due to the small number of patients, we did not compare the incidence of these disorders in the general population versus our patient population. The mechanisms that could explain the association of HAE with autoimmune diseases is not yet clear. Of the group of patients studied only two turned out to have the acquired form of angioedema. The first patient presented angioedema prior to a diagnosis of chronic lymphocytic leukemia. This underscores the association of AAE type 1 with malignant diseases and the reason why some authors upon diagnosing AAE type 1 recommend an evaluation that includes immunophenotyping of peripheral blood lymphocytes for circulating malignant B cells, serum protein and immunoelectrophoresis for underlying dysproteinemias and computed tomography of the chest, abdomen and pelvis to identify a possible lymphoproliferative disorder or a solid tumor. It is to be stressed that an initial negative work up does not rule out the possibility of an underlying malignant disorder due to the observed prolonged lag time between the occurrence of the syndrome of AAE and a subsequent diagnosis of the malignant disease (13). Therefore, follow up visits must be planned so as to ensure early diagnosis of an underlying malignant condition. As in our case, it has been reported that AAE type 1 attacks decrease in frequency or can even resolve completely upon remission of the malignant disease (2). It has also been observed that in cases in which cure is not possible, the frequency of angioedema attacks can be decreased or attenuated with anabolic steroids as in HAE (6,7,11,13).

The second patient was diagnosed with AAE type 2 and had no other associated medical condition and showed a low antibody titer to C 1 inhibitor protein. It is of utmost importance to remember that in all cases in which a diagnosis of acquired angioedema is made, further differentiation into either Type 1 or Type 2 is mandatory since the latter will have no response to anabolic steroids and will only require the utilization of immunosuppressive therapy (6,7,11,19).

Resumen

Tanto el angioedema hereditario como el angioedema adquirido son dos condiciones médicas caracterizadas clínicamente por presentar un cuadro variable de angioedema, que por su potencial de gravedad y en ocasiones por su frecuencia y severidad requieren la más rápida identificación y diferenciación de otros desórdenes clínicos con una presentación similar, de forma que puedan ser tratados eficazmente.

El propósito de este informe es presentar las características clínicas y nuestra experiencia con un grupo de pacientes que fueron referidos para evaluación y a los cuales se les hizo el diagnóstico de angioedema hereditario y angioedema adquirido en nuestro servicio de Inmunología Clínica en el Hospital Universitario y el Centro Médico de Puerto Rico. También se presenta la respuesta clínica y los efectos secundarios de la terapia ofrecida a estos pacientes, haciéndose una comparación de nuestra serie con series similares de pacientes evaluados y tratados por otros autores en la literatura médica.

En general, los pacientes con el diagnóstico de angioedema hereditario en nuestra serie presentaron un perfil de características clínicas similares al compararse a pacientes informados en otras series. Sólo dos de nuestros pacientes fueron identificados con el diagnóstico de angioedema adquirido, los cuales se presentan en este escrito puntualizando su perfil clínico particular y las recomendaciones terapéuticas para esta condición.

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