Hereditary angioedema and thyroid autoimmunity

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SUMMARY Sera from 91 patients with hereditary angioedema were screened for thyroid antibodies. The results for the 77 patients more than 17 years old were compared with previously published data for the prevalence of thyroid disease in a large community (Whickham). Of the female patients with hereditary angioedema, the prevalence of thyroglobulin antibodies (TGA) was 14.0%, higher than the expected 3% ($p < 0.001$). The prevalence of thyroid microsomal antibodies (TMA) was 20%, also higher than the expected 7.6% ($p < 0.01$). The age distributions of the females in both groups differed: in the group with hereditary angioedema there was a greater proportion of younger patients which should have resulted in a lower prevalence of thyroid antibodies. Adjusting for related patients with hereditary angioedema, there was still an increased prevalence of TGA ($p < 0.01$) and TMA ($p < 0.01$).

Hereditary angioedema is a rare disease characterised by oedema of subcutaneous tissues, respiratory tract, and bowel. It is inherited as an autosomal dominant trait and is caused by a deficiency of serum C1 esterase inhibitor. Two types of deficiency have been described: type 1 with a low activity of C1 esterase inhibitor and the rarer type 2 with a normal or raised activity of a dysfunctional C1 esterase inhibitor. Patients with both types of deficiency are predisposed to syndromes similar to systemic lupus erythematosus and discoid lupus erythematosus.¹⁻⁶ Some 2% may develop such syndromes.³ Hereditary angioedema has also been described in association with glomerulonephritis.⁷⁻⁹ In addition, there is a report of one family in which members affected by hereditary angioedema had C3 nephritic factor.¹⁰

At least three different chromosomal regions have been shown to have a part in the complement system, and some are linked to HLA. At present the flows linkage for hereditary angioedema is unknown, but studies have confirmed that the locus for type 1 hereditary angioedema is well outside the HLA complex.¹¹

On finding three patients who had hereditary angioedema and autoimmune thyroid disease, we were prompted to enquire whether there was an association between hereditary angioedema and thyroid autoimmune disease.

Material and methods

Dermatologists and physicians in the United Kingdom who were known to be interested in hereditary angioedema and the directors of the supra-regional or regional centres which carry out C1 esterase inhibitor assays (Cardiff, Birmingham, Cambridge, Sheffield, Newcastle and Glasgow) were contacted. Frozen stored sera deficient in C1 esterase inhibitor and sera obtained from patients with hereditary angioedema especially for the study were screened for thyroid antibodies by each centre, all of which participated in the United Kingdom National External Quality Scheme. Additional tests—antinuclear factor, T4, and thyroid stimulating hormone—were carried out on all freshly obtained samples and, where sufficient serum was available, on stored samples. In all cases analytical results were assessed for normality in relation to the laboratory's own reference range.

LABORATORY METHODS

The following methods were used in each laboratory: *Birmingham* C3 and C4—turbidometric method on the Kone CD analyser using monospecific antisera (Kallestadt Ltd) and SPS-01 (Sheffield) as a standard; C1 esterase inhibitor single radial immunodiffusion with monospecific antisera (Atlantic); TGA and TMA as Sheffield; free T4—radioimmunoassay

(Amerlex); thyroid stimulating hormone—immunoradiometric assay (Hoechst).

Cambridge C3, C4, and C1 esterase inhibitor—single radial immunodiffusion using polyclonal antisera (Atlantic); TGA and TMA by passive haemagglutination (Thymune G and Thymune M tests, Wellcome).

Cardiff C3 and C4—rate nephelometry using a Beckman Auto ICS and Beckman calibrator and Beckman antisera; C1 esterase inhibitor—Laurel rockets (electroimmunodiffusion) with Atlantic antisera and standards.

Charing Cross Hospital TGA and TMA—haemagglutination (Wellcome and Fujirebio reagents); T4 was measured by an in-house antibody radioimmunoassay. Thyroid stimulating hormone was measured by an in-house immunoradiometric assay.

Glasgow TGA and TMA—passive haemagglutination (Thymune G and Thymune M tests, Wellcome); C3, C4, and C1 esterase inhibitor—single radial immunodiffusion.¹²

Newcastle TGA and TMA as Sheffield; antigenic C3 and C4—laser nephelometry (Beckman); C1 esterase inhibitor—radial immunodiffusion using commercial antisera and calibrant (Atlantic).

Sheffield C3 and C4—immunoturbidometric assays, SPS-01 calibrant; C1 esterase inhibitor antigenic—single radial immunodiffusion, SPS-01 calibrant, functional C1 esterase inhibitor—haemolysis inhibition (Cordis Laboratories Inc); TGA and TMA—haemagglutination (Fujirebio reagents); thyroid stimulating hormone in-house radioimmunoassay.

The lower limit of normal for T4 was 60 nmol/l in all assays: the upper limit of normal for thyroid stimulating hormone was 6 mU/l, except at Charing Cross Hospital where the upper limit was 2.8 mU/l.

The results for the patients with hereditary angioedema were compared with those obtained from a survey of a large community, Whickham, by Tunbridge *et al.*¹³ They selected every sixth name from the electoral register and from a sample of 3538 names they obtained results from 2779 people.

Spontaneous clinically overt hypothyroidism—that is, clear clinical features of hypothyroidism with a low T4 and raised thyroid stimulating hormone—was found with a prevalence of 10/1000 women and less than 1/1000 men. TMA were scored as positive if present at a titre of 1/100 or more and were found in 2% of men and 7.6% of women. TGA at a titre of 1/20 or more was present in 0.9% of men and in 3% of women. The Whickham study confirmed earlier findings that thyroid antibodies were more common in women than men and that they were also more common in the older age groups.

Statistical analyses were carried out using the χ^2 test with Yates's correction, the Kolmogorov-Smirnov two sample test, and the Mantel-Haenszel procedure with Yates's correction.

Results

The sera deficient in C1 esterase inhibitor from 94 patients were made available. Three of the samples came from patients with an acquired deficiency of C1 esterase inhibitor. Table 1 summarises the findings in the 91 patients with hereditary angioedema. Ages ranged from 2 to 78 years. There were 30 males and 61 females. Eighty one patients had type 1 deficiency; 10 had type 2. Forty six of the 91 patients were related (17 families varying in size from two to 10). Table 2 gives details of those with thyroid abnormalities.

Three unrelated patients, aged 53, 23, and 32 had myxoedema. One (case 4), a known case of hereditary angioedema receiving danazol, had presented with anaemia which proved to be pernicious anaemia. He was found to have thyroid antibodies, and three months later his T4 and thyroid stimulating hormone concentrations became abnormal. Of the two other hypothyroid patients, one (case 1) was the mother of a known case of hereditary angioedema (case 2). The mother had asymptomatic C1 esterase inhibitor deficiency but was noted to have a croaky voice when she accompanied her daughter to the clinic. Her T4 concentration was at the lower limit of normal (60 nmol/l), but she had a raised thyroid stimulating hormone of 23 mU/l. The third patient (case 5), who was receiving danazol had presented with the signs of hypothyroidism at the age of 18 when her T4 concentration was 17 nmol/l, thyroid stimulating hormone > 50 mU/l.

Table 1 Summary of findings in all patients with hereditary angioedema

	No of patients		
	Total	Males	Females
Hereditary angioedema	91	30	61
Type 1	81	27	54
Type 2	10	3	7
Clinically overt hypothyroidism	3	1	2
Thyroglobulin antibodies (TGA)	8	0	8*
Microsomal antibodies (TMA)	12	1	11*
Low T4	5/23	3/9	2/14
Raised thyroid stimulating hormone	5/35	2/15	3/20
Pernicious anaemia	1	1	0
ANF positive	0/14		
Benign IgG paraprotein	1	0	1

Includes one patient under 18 years.

Men							
Age	18-24	25-34	35-44	45-54	55-64	65-74	74+
Group with hereditary angioedema (No %)	3 (11.1)	7 (25.9)	5 (18.5)	7 (25.9)	3 (11.1)	2 (7.4)	0
Whickham group (No %)	110 (8.6)	233 (18.1)	255 (19.8)	290 (22.6)	210 (16.3)	130 (10.1)	57 (4.4)
Kolmogorov-Smirnov two-sample test, p =	0.264						
Women							
Group with hereditary angioedema (No %)	11 (22.0)	15 (30.0)	8 (16.0)	5 (10.0)	5 (10.0)	4 (8.0)	2 (4.0)
Whickham group (No %)	128 (8.6)	323 (21.6)	275 (18.4)	240 (16.1)	266 (17.8)	182 (12.1)	80 (5.3)
Kolmogorov-Smirnov two-sample test, p <	0.025						

Table 4 Prevalence of thyroid antibodies in different groups

	Whickham	Hereditary angioedema	Unrelated hereditary angioedema (procedure 1)	"Random" hereditary angioedema (procedure 2)	Non-familial hereditary angioedema	Familial hereditary angioedema
Males						
TGA (No %):	11/1285 (0.9)	0/27	0/13	0/20	0/13	0/14
TMA (No %):	26/1285 (2.0)	1/27 (3.7)	0/13	1/20 (5)	0/13	1/14 (7.1)
Females						
TGA (No %):	45/1494 (3.0)	7/50 (14.0)	4/33 (12.1)	5/38 (13.1)	4/28 (14.3)	3/22 (13.6)
TMA (No %):	113/1494 (7.6)	10/50 (20.0)	7/33 (21.2)	8/38 (21.1)	7/28 (25.0)	3/22 (13.6)

TMA in female patients with hereditary angioedema.

Because the prevalence of thyroid antibodies is related to age, the age distributions in both groups were compared for each sex by means of a two sample Kolmogorov-Smirnov test. The distributions in the males were similar while those of the females varied ($p < 0.025$). This was due to the fact that there was a greater proportion of patients with hereditary angioedema in the younger age groups (table 3). To allow for the differences in the age distributions an age stratified χ^2 analysis of the prevalence of thyroid antibodies was carried out using the Mantel-Haenszel method, with Yates's correction (χ^2_{MHY}). No significant differences between male patients in either group were found, but the prevalences of TGA and TMA were increased in the females with hereditary angioedema (TGA, χ^2) and χ^2_{MHY} 23.665, $p < 0.001$; TMA, χ^2 and χ^2_{MHY} = 10.93, $p < 0.001$) (tables 4 and 5).

To assess whether the increased proportion of

female patients with hereditary angioedema and thyroid antibodies was due to familial factors two alternative procedures were carried out on the group of 77 patients with hereditary angioedema over 18. Firstly, any patient related to any other in this group of 77 was removed. There remained, however, five women who were members of a family group but who were the only members of the family aged 18 or over. Secondly, all but one of the members of a family were eliminated on a random basis using a table of random permutations of 10 numbers.

The first procedure removed 32 related individuals from 12 families and left 13 men and 33 women among whom were four with TGA and seven with TMA—all women (table 4). When the unrelated female patients with hereditary angioedema were compared with the Whickham females using the Mantel-Haenszel method, the proportion of patients with hereditary angioedema and TGA was greater than expected (χ^2 and χ^2_{MHY} = 8.63, $p < 0.01$), as was

Table 5 Results of age stratified χ^2 analysis

	Hereditary angioedema v Whickham	Unrelated hereditary angioedema v Whickham (procedure 1)	"Random" hereditary angioedema v Whickham (procedure 2)	Hereditary angioedema non-familial v familial
Males				
TGA:				
χ^2_{MHY}	0.435	0.189	0.836	—
p	> 0.5	> 0.5	> 0.25	—
TMA:				
χ^2_{MHY}	0.01	0.16	0.007	0.021
p	> 0.7	> 0.5	> 0.9	> 0.7
Females				
TGA:				
χ^2_{MHY}	23.665	8.63	15.40	0.027
p	< 0.001	< 0.01	< 0.001	> 0.75
TMA:				
χ^2_{MHY}	10.93	8.65	9.98	0.721
p	< 0.001	< 0.01	< 0.01	> 0.25

the proportion with TMA (χ^2 and $\chi^2_{\text{MHY}} = 8.65$, $p < 0.01$) (table 5). The second "random elimination" procedure left 20 men and 38 women of whom one man and eight women had TMA while five women had TGA (table 4). The proportion of male patients with hereditary angioedema and TGA in this group was not significantly different from that in the Whickham group. The female patients with hereditary angioedema, however, again had a greater than expected number with TGA and TMA (TGA, χ^2 and $\chi^2_{\text{MHY}} = 15.40$, $p < 0.001$; TMA, χ^2 and $\chi^2_{\text{MHY}} = 9.98$, $p < 0.01$) (table 5).

As a further check 36 patients with hereditary angioedema who were members of a family group and who were 18 years or older, were compared with the 41 non-familial patients and no significant differences in the prevalence of thyroid antibodies were apparent (tables 4 and 5).

Discussion

There were significantly increased prevalences of TGA and TMA in female patients with hereditary angioedema. No increase was shown in men. With the expected low prevalence rates in men of 2% for TMA and 0.9% for TGA, however, considerably more than the 30 male patients in this series would have been required to show significant differences. The probability of detecting a difference of a given magnitude, if it really existed, is reflected by the power of a statistical test. With a power of 80%, to show that men with hereditary angioedema had twice the rates of the Whickham group men would require some 1000 patients for TMA and over 2000 for TGA.

The excess of thyroid antibodies in women with hereditary angioedema was not accompanied by any corresponding increase in spontaneous clinically overt hypothyroidism. This could reflect the fact that the group with hereditary angioedema contained a greater proportion of young women than the Whickham group. A minor degree of hypothyroidism, manifest as a raised thyroid stimulating hormone, was twice as common over the age of 45 years as in those under this age¹³ in the Whickham group.

The increased prevalences of thyroid antibodies in women with hereditary angioedema could be: fortuitous; spurious due to the fact that both disorders are familial,¹⁴ and this study includes 46 related patients in 17 families; the result of an association between hereditary angioedema and the predisposition to develop thyroid antibodies.

A fortuitous association seems highly unlikely with the age stratified χ^2 comparisons of both groups of women, giving probabilities under the null hypothesis of less than 0.001 for both TGA and TMA. The prevalence of thyroid antibodies is related to age, so it is

worth noting again that there was a higher proportion of patients with hereditary angioedema in the younger age groups which would have been expected to result in a lower prevalence of thyroid antibodies in the women with hereditary angioedema.

Removal of all related, or all but one randomly selected member of a family, still left a group which had increased prevalences of TGA and TMA. In addition, a comparison of unrelated and related patients with hereditary angioedema showed no difference. It seems unlikely, therefore, that familial factors could explain the findings.

An explanation for the increased prevalence of thyroid autoantibodies and perhaps thyroid autoimmune disease in hereditary angioedema is not immediately apparent. Likewise, the reason for the association between immune complex diseases and various complement deficiencies including hereditary angioedema is not yet clear. C2 and C4 are HLA encoded complement components so the possibility of a closely linked disease susceptibility gene has been considered. C1 esterase inhibitor deficiency, however, is not linked to HLA, and there is evidence to suggest that immune complex disease can arise in complement deficiency disorders as a consequence of impairment of the recognition arm of the classical pathway and persistence of immune complexes.¹⁵ In hereditary angioedema absence of functional C1 esterase inhibitor leads to unrestrained action of C1s and low C2 and C4 values. This secondary reduction of C2 and C4 may give rise to erythematous-like syndromes in the same way as genetic deficiencies of C2, C4, and other complement components.

Although the association of hereditary angioedema with immune complex disease can be explained, the cause of production of thyroid antibodies is less clear. It would, however, be interesting to know whether thyroid antibodies are more prevalent in other complement deficiencies and especially in homozygous C2 and C4 deficiencies, in which a high proportion of subjects have systemic lupus erythematosus.

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