A study of triplets with Hashimoto's thyroiditis

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Summary

Genetic predisposition to Hashimoto's thyroiditis is suggested by its striking aggregation in families and its occurrence in twins. The manifestations range from overt clinical and biochemical hypothyroidism to the detection of thyroid autoantibodies in healthy, symptom-free individuals and their relatives. So far as the authors are aware, the finding of Hashimoto's thyroiditis in identical triplets has not previously been reported and they therefore present the cases of Faith, Hope and Charity, 63-year-old triplet sisters.

Introduction

The aetiology of Hashimoto's thyroiditis is uncertain. Immunological and genetic factors are certainly involved although their significance and relationship remains to be clarified (Doniach, 1975). Family studies (Bartels, 1941; Hall, Owen and Smart, 1960), familial predisposition to other associated autoimmune diseases (Doniach, Roitt and Taylor, 1965), the association with chromosomal abnormalities (Fialkow *et al.*, 1971) and the reports of monozygotic twins with autoimmune thyroid disease (Irvine *et al.*, 1961; Hennen and Dodinval, 1965; Hassan *et al.*, 1966; Jayson *et al.*, 1967; Thornham, Nutt and Clark, 1976) all point to an underlying hereditary defect.

The recognition of genetic linkage between the murine major histocompatibility complex (H2) and predisposition to experimental autoimmune thyroiditis (Vladutiu and Rose, 1971) has led to an extensive search in man for associations between antigens of the histocompatibility (HLA) system and the organ-specific disease states. Diseases in which viral and autoimmune processes have been implicated have been particularly associated with the HLA system (McDevitt and Bodmer, 1974). It is surprising therefore that so far no correlation has been shown between Hashimoto's thyroiditis and specific HLA antigens (Bode, Dorf and Forbes, 1973; Farid,

Barnard and Marshall, 1976; Chopra *et al.*, 1977). This is difficult to explain since familial aggregates can show both Graves' disease and Hashimoto's thyroiditis; Graves' disease being associated with an increased frequency of HLA B8 (Farid *et al.*, 1976) and HLA DW3 (McMichael *et al.*, 1975) in Caucasians and HLA BW35 in Japanese patients (Grumet *et al.*, 1975).

The presentation of triplets with Hashimoto's thyroiditis, in whom monozygosity has been established, further emphasizes the role of heredity factors in this disease process.

Patients and methods

Faith (F) was noted to have a goitre at puberty. At the age of 34 years, while pregnant, her goitre enlarged further and 6 months after delivery she underwent partial thyroidectomy. No histology is available. She was well until 10 years later when, because of increasing tiredness and return of her goitre, she was investigated and found to be hypothyroid. She was started on thyroxine replacement therapy (0.2 mg daily) with subsequent resolution of the thyroid enlargement and has since remained well and symptom free. Hope (H) underwent partial thyroidectomy at the age of 35 years for a large goitre. No histology is available. She has remained symptom-free without medication. Charity (C) developed a goitre at puberty which subsequently enlarged. She underwent partial thyroidectomy at the age of 34 years and has remained clinically and biochemically euthyroid without medication. Histology showed diffuse lymphocytic infiltration with formation of lymphoid follicles.

Serum thyroxine (T_4) was measured by radioimmunoassay in unextracted serum (Evered *et al.*, 1976) and thyrotrophin (TSH) by a double antibody radioimmunoassay (Hall, Amos and Ormston, 1971) using MRC Human TSH Standard 68/38.

Thyroglobulin and microsomal autoantibodies

were measured by the tanned red cell method (Roitt and Doniach, 1967b; Bird and Stephenson, 1973) and blood groups, serum proteins and red cell enzymes were determined by standard serological and electrophoretic procedures (Race and Sanger, 1968; Giblett, 1969). HLA cell surface antigens of the A and B loci were detected by a microcytotoxicity technique (Mittal *et al.*, 1968) as modified by Kissmeyer-Nielsen and Thorsby (1970).

Results

The biochemical and serological thyroid results for the triplets are shown in Table 1. All 3 show the same phenotype in each of the 20 genetic polymorphic systems (24 loci) of the blood cell antigens (including histocompatibility antigens), red cell enzymes and serum proteins (Table 2). From these results the probability that these triplets are uniovular is 0.999999786. This probability is calculated from the formulae in Table 3, derived following the general principles of twin zygosity (Smith and Penrose, 1955).

Discussion

The sisters are well, all having undergone partial thyroidectomy in the past for large goitres and only one has required subsequent thyroxine replacement therapy. Although clinically euthyroid they all have significant titres of antithyroglobulin antibodies and

one has a significant antimicrosomal-antibody titre, indicating the presence of autoimmune thyroid disease (AITD).

Early studies of close relatives of patients with AITD (Hall *et al.*, 1960; Hall, Saxena and Owen, 1962) suggested a dominant mode of inheritance of thyroid antibodies. Further evidence for a genetic predisposition to AITD came with the description of Hashimoto's thyroiditis in 2 pairs of uniovular twins (Irvine *et al.*, 1961). Because of criticism of subject selection techniques used in the study of AITD families (Masi, Hartmann and Shulman, 1965; Mulhearn, Masi and Shulman, 1966) a re-assessment of the work was carried out (Roitt and Doniach, 1967a) which reconfirmed the familial aggregation.

TABLE 3. Relative chances against uniovularity in triplets

Without dominance (3 genotypes distinguishable):

all AA $p^2 + \frac{1}{2}pq^2 + \frac{1}{16}q^2$

all Aa $1\frac{1}{2}pq + \frac{1}{2}p^2 + \frac{1}{2}q^2$

all aa $q^2 + \frac{1}{2}pq + \frac{1}{16}p^2$

With dominance (2 phenotypes distinguishable):

A+ $p^2 + 4p^2q + \frac{59}{16}pq^2 + \frac{1}{2}q^3$

$1 + q$

A- $\frac{1}{16}p^2 + \frac{1}{2}pq + q^2$

Where p = frequency of allele A,

q = frequency of allele a

and $p + q = 1$

TABLE 1. Biochemical and serological thyroid investigations

Patient	Serum thyroxine nmol/l	Serum TSH mu./l	Anti-microsomal antibody titre	Anti-thyroglobulin antibody titre
F	123*	1	negative	1:320
H	100	undetectable	1:400	1:1250
C	81	2.2	negative	1:320
Normal	60-150	6		

*Receiving thyroxine 0.2 mg daily.

TABLE 2. Results of the genetic polymorphisms investigated*

Blood groups		Red cell enzymes	
ABO	O	ADA	1-1
Rhesus	CCDee	PGM	2-1
MN	MSMs	PGM2	N
P	P1+	AP	BA
Kell	kk	LDH	N
Duffy	Fy (a-b+)	Est-D	1-1
Kidd	Jk (a-b+)	AK	1-1
Lutheran	Lu (a-b+)	MDH	N
Lewis	Le (a-)		
Xg	Xg (a+)		
HLA		C3	
A11, A28, 5B, B8		S	

*These were identical for the 3 sisters

The mode of inheritance has been difficult to evaluate (Hall, Dingle and Roberts, 1972) but does not appear to be due to simple Mendelian, single gene inheritance, particularly as matings between autoantibody negative individuals have produced offspring with AITD. It appears more likely to be multifactorial; a mode of inheritance in which the liability is partly genetic, brought about by the cumulative effect of a number of interacting polygenes, and partly environmental; a complicating factor in familial similarity is the common environment shared by close relatives and particularly twins and triplets so that environmental factors could also be involved. It is well known that environmental stimuli such as viruses and drugs (Leading Article, 1970; Bucknall, 1977) can induce autoantibody production. However, the studies of genetic polymorphisms indicating that the triplets are identical provide further evidence for the importance of genetic factors in the development of AITD.

Studies in mice have demonstrated linkage between the H2 complex and AITD (Vladutiu and Rose, 1971) and in man there is an association between

HLA B8 and HLA DW3 in Caucasians and HLA BW35 in Japanese patients with Graves' disease. However, no such associations have been demonstrated between any HLA antigen and Hashimoto's thyroiditis, despite the occurrence of this condition and Graves' disease in the same families. Although no conclusions can be drawn from the results of HLA typing in the triplets other than that they are identical, it is nevertheless of interest that the triplets were positive for the HLA B8 antigen. Previous studies (Chopra *et al.*, 1977) have shown a considerable increase in this antigen in Hashimoto's thyroiditis although it lacked statistical significance. This latter study showed a highly significant correlation between HLA AW30 and Hashimoto's thyroiditis but this antigen was not tested for in the triplets.

Hashimoto's thyroiditis is likely to have a multifactorial aetiology. Family studies have not been able to define a clear pattern of inheritance. Twin studies require a far greater number of such patients than are presently available. Genetic predisposition is established although the influence of the environment is still uncertain particularly in cases such as the present one where both genetic and environmental factors are shared.

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