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Familial Aggregation Study of Hashimoto's Thyroiditis

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ABSTRACT Data for the present study were collected at the Institute of Nuclear Medicine and Allied Sciences. Unit of study was the family and all family members of a patient with Hashimoto's thyroiditis were included. Patients were school children between 5 to 16 years. Using a radioimmunoassay method, which depends on the interaction between antibody and radiolabeled autoantigen, this study on the assessment of the inheritance patterns of TG and MC autoantibodies was carried out on 20 families (87 individuals) with Hashimotos' thyroiditis. In families where both parents were normal the prevalence of TG antibody was 11.1% in sons and 45.45% in daughters but increased to 15.38% and 62.22%, respectively if either of the parents had this antibody. The prevalence of MC antibody was 0% in sons and 54.54% in daughters if both parents were normal but increased to 7.69% and 81.25% in daughters, respectively if either of the parents had this antibody. The present study clearly shows the aggregation of antithyroglobulin antibodies and antimicrosomal antibodies in families studied.

INTRODUCTION

Hashimoto's thyroiditis is extremely common in clinical practice. The original description of this kind of thyroiditis was first reported in 1912 in four middle-aged Japanese women in whom the thyroid gland was enlarged and appeared to have transformed in to lymphoid tissue (*Struma lymphomatosa*) (McConahey et al., 1962). One of the clinical questions is to define what constitutes a diagnosis of Hashimoto's thyroiditis. It is an autoimmune disease in which there is:

a) A goitre
b) Evidence of humoral autoimmunity to thyroid antigens and
c) Characteristic lymphocytic infiltration of the thyroid (Fisher, 1974).

Frequently other members of the family have autoimmune thyroid disease or circulating antithyroid antibodies. There would be no doubt about the diagnosis if the patient had all of the above features. According to Fisher and Oddie(1974), the following five markers are required for the diagnosis: goitre, scintigraphic findings, increased TSH, thyroid antibodies and a positive percholate discharge test.

Clinically significant thyroiditis occurs in approximately 1 per 2000 population, but other epidemiological studies have shown an incidence of the disease up to 69 per 100,000 (Furszyfer et al., 1972). Although the disease is seen to occur predominantly in women in the fourth or fifth decade of life, it may occur at any age (Bastenie and Ermans, 1972; Volpe and Clarke, 1973; Hayashi et al., 1985). Approximately two-thirds of the goitres observed in childhood and adolescence prove to be lymphocytic thyroiditis if biopsied (Ling et al., 1969; Fisher et al., 1975).

It is generally accepted that the Hashimoto's thyroiditis is caused by a disturbance of the autoimmune system (Volpe, 1978; Doniach et al., 1979). This is based on the observation of the elevated plasma gamma globulin levels, abnormal serum flocculation tests and the presence of antithyroid antibodies in patients with chronic lymphocytic thyroiditis (Luxton and Cooke, 1956; Doniach and Roitt, 1957; Amino et al., 1976). Positive antimicrosomal antibody titre greater than 1:100 or antithyroglobulin antibody greater than 1:20,000 are only found in patients with Hashimoto's thyroiditis and Graves' disease (Volpe, 1978; Doniach et al., 1979). Some patients with Hashimoto's thyroiditis are found to have titres to 1 in several millions; conversely, this test is negative in about 10% of proven cases (Roitt and Doniach, 1960; Irvine, 1975). By radio immunoassay these antibodies have been detected in virtually all patients with Hashimoto's thyroiditis (Mori and Kriss, 1971).

Thyroid radioactive iodine uptake (RAIU) may be normal, elevated or suppressed in patients with lymphocytic thyroiditis, depending on the stage of the disease at the time of presentation

(Volpe and Row, 1965). Thyroid scintigraphy reveals a wide range of patterns, the most common being a non-homogenous distribution of the radiotracer or a pattern suggestive of 'hot' or 'cold' nodules (Fisher et al., 1975; Paull et al., 1975).

Fine needle aspiration cytology (FNAC) of the thyroid is a relatively benign and simple procedure, which yields important diagnostic information of thyroid pathology. However, up to 30% of cytological specimens prove to be unsatisfactory for histological diagnosis (Miller, 1982).

In family studies the frequency of the disease in the relatives of the proband or index case compared with the disease frequency in the normal population. If there is evidence of familial clustering, the pedigrees are inspected and the disease distribution in the relatives is compared with the expectations for various genetic hypotheses (Vanderpump et al., 1995).

Hashimoto's thyroiditis is more common than the Graves' disease but with a similar sex ratio. Coresspondingly, however, less is known about its genetics. Furthermore, some patients with Graves' disease progress to Hashimoto's thyroiditis, suggesting that both diseases are part of the spectrum of thyroid autoimmunity (Kurihara et al., 1993). Evidence for a genetic predisposition to auto antibody production was first provided by Hall and his colleagues in 1967 who showed that auto antibodies were present in 56% of the siblings of probands with autoimmune thyroid disease, which is close to the theoretical figure of 50% expected if the tendency to produce antibody was being inherited in a dominant fashion. Evans et al (1967) concluded that although there was a marked tendency for antibodies to cluster in families, several genes were probably involved.

The hereditary nature of Hashimoto's thyroiditis has now been explained in part by the demonstration of linkage between HLA-B8 and DR3 atropic Hashimoto's thyroiditis and between HLA-DR5 and goitrous thyroiditis. The HLA-DR5 increases the probability of Hashimoto's thyroiditis by five folds (Chopra et al., 1977). The associations between the MHC and autoimmune thyroid disease are difficult to interpret. They are weak compared with many HLA associated diseases and in pedigree studies both autoantibody and overt disease don't show genetic linkage with the MHC locus. It may be that the disease is multiallelic. An alternative hypothesis is that the genes in the MHC region could code for disease severity as opposed to disease susceptibility, an idea supported by the observation that individuals with the B8 DR3 haplotype have an enhanced immune response (Vanhaelst et al., 1972).

Family studies are difficult to carry out and need to be interpreted with caution. Unlike simple inherited conditions such as cystic fibrosis, where individuals are clearly affected or normal, in many benign thyroid diseases it is not always clear who is actually affected. This is exemplified in family studies of autoimmune thyroiditis. Graves' disease and Hashimoto's thyroiditis frequently coexist in the same family. Hashimoto's thyroiditis is rare before the third decade of life and has a predilection for the women. Furthermore, the lower disease rates in men may mean that it is impossible at any age to detect whether or not a man is a carrier. A different problem occurs with individuals who appear to be affected but do not have the disease genotype (phenocopies). This could occur, for example, in families with autoimmune thyroid disease if one of the family members had hyper or hypothyroidism resulting from a non-autoimmune cause.

METERIALS AND METHODS

Data for the present study were collected from 20 families (87 individuals) of patients at the Institute of Nuclear Medicine & Allied Sciences. Unit of study was the family and all family members of a patient with Hashimoto's thyroiditis were included. Patients were school children between 5 to 16 years. Data were collected with the help of a pre-tested and revised questionnaire. Detailed pedigrees were drawn for each family.

First of all the subjects were examined clinically by a medical specialist. Goitre was graded clinically as per WHO classification. All subjects with goitre were subjected to fine needle aspiration studies to get a cytomorphological diagnosis of the disease. In addition, estimation of

serum T3, T4, TSH and thyroid antibody titres were carried out. Serum triiodothyronine (TT3), thyroxine (TT4) and thyroid stimulating hormone (TSH) levels were estimated using radio immunoassay kits supplied by the Bhaba Atomic Research Centre, Mumbai. The normal ranges of TT3, TT4 and TSH were 70- 220 ng/dl, 5-13.5 mg/dl and less than 10 mU/ml, respectively. Antithyroglobulin and antimicrosomal antibodies were measured by the tanned red cell haemagglutination technique (TRCA) using commercially available kits from Burroughs Wellcome, England. Antibody titres above 1: 640 for thyroglobulin and 1:1600 for microsomal were considered significant.

Those subjects who were diagnosed having CLT (chronic lymphocytic thyroiditis) were called with their family members for the check up. Estimation of serum T3, T4, TSH and thyroid antibody was also carried for all family members of the affected individual.

RESULTS

Out of the 20 families studied (Tables 1-4), 75%, i.e., 15 families had aggregation of autoimmune thyroid disease (having positive antibodies). Out of the 36 parents (4 males could not be included due to death or divorce) studied, 14 parents presented with autoimmunity (Table 5). Out of the 31 sibs examined, 9 had positive antibodies (Table 7). Out of the total number of mothers studied 60% of mothers presented with autoimmunity, while only 12.5% of fathers had aggregation of antibody (Table 6). Out of the total number of sisters investigated, 54.55% had autoantibodies present but out of brothers, only 10% had this (Table 7).

Out of the total number of parents with autoimmunity 85.7% were mothers and only 14.3% are fathers. Out of the total number of sibs with

Table 1: Index cases by age and sex (n = 20)

Sex	*Age in years*			
	< 10 years	*10-14 years*	*14-18 years*	*Total*
Males	-	1	1	2
Females	1	8	9	18
Total	1	9	10	20

Table 2: Family members of index cases

Sex	*Parents*	*Siblings*	*Total*
Males	16	20	36
Females	20	11	31
Total	36	31	67

Table 3: Autoimmune status of index cases

Sex	*FNAC*	*ATG*	*AMC*
Males	2	1	1
Females	18	12	15
Total	20	13	16

FNAC = Fine needle aspiration cytology
ATG = Antithyroglobulin
AMC = Antimicrosomal

Table 4: Thyroid status of Index cases

Sex	*Euthyroid*	*SCH*	*Hypothyroid*
Males	1	1	-
Females	5	9	4
Total	6	10	4

SCH = Sub clinical hypothyroid

Table 5: Autoimmune status of parents

Sex	*N*	*AMC*	*%*	*ATG*
Males	16	2	12.5	2
Females	20	12	60.0	7
Total	36	14	38.8	9

Table 6: Thyroid status of parents

Sex	*Hyper-thyroid*	*Euthyroid*	*SCH*	*Hypo-thyroid*	*Total*
Males	1	14	1	-	16
Females	5	9	4	2	20
Total	6	23	5	2	36

SCH = Sub clinical hypothyroid

Table 7: Autoimmune status of siblings

Sex	*AMC*	*ATG*
Males	1	1
Females	4	3
Total	5	4

Table 8: Thyroid status of siblings

Sex	*Hyper-thyroid*	*Euthyroid*	*SCH*	*Hypo-thyroid*	*Total*
Male	3	14	3	-	20
Female	-	7	4	-	11
Total	3	21	7	-	31

autoimmunity 75% were sisters and only 25% were brothers.

DISCUSSION

The present study clearly shows the aggregation of antithyroglobulin antibodies and antimicrosomal antibodies in families studied for aggregation of Hashimotos' thyroiditis. According to Evans et al. (1969) although there was a marked tendency for antibodies to cluster in families, several genes were probably involved.

Using a radioimmunoassay method, which depends on the interaction between antibody and radiolabeled autoantigen, this study on the assessment of the inheritance patterns of TG and MC autoantibodies was carried out on 20 families (87 individuals) with Hashimotos' thyroiditis. In families where both parents were normal the prevalence of TG antibody was 11.1% in sons and 45.45% in daughters but increased to 15.38% and 62.22%, respectively if either of the parents had this antibody. The prevalence of MC antibody was 0% in sons and 54.54% in daughters if both parents were normal but increased to 7.69% and 81.25% in daughters, respectively if either of the parents had this antibody.

Segregation analysis demonstrates that the inheritance of these antibodies is consistent with dominant Mendelian inheritance in female offspring but not among male offspring. These observations suggest that the tendency to produce these antibodies is being inherited as a dominant characteristic in women but with incomplete penetrance in men. Although this analysis provides strong support for vertical transmission, it cannot distinguish between the single gene and multifactor models.

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