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# FAMILIAL STUDIES OF AUTOIMMUNE THYROIDITIS*

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## INTRODUCTION

We would like to review the evidence which has accumulated over the last few years suggesting that autoimmune thyroid disease is an inherited condition.

The term autoimmune thyroid disease (AIT disease) is generally accepted to include Hashimoto's disease and spontaneous myxoedema which are variants of the same condition. Graves' disease should also be included in the group of AIT diseases since antibodies to various thyroid constituents can be detected in about 85% of cases and also because long-acting thyroid stimulator (LATS), which is probably the causative agent in Graves' disease, is a $\gamma$-globulin and likely to be an antibody to some thyroid constituent.

TABLE 1. Clinical features of autoimmune thyroid disease

| |
|---|
| Exophthalmos, lid retraction, ophthalmoplegia |
| Goitre |
| Hyperthyroidism |
| Hypothyroidism |
| Vitiligo |
| Thyroid acropachy |
| Pretibial myxoedema |

Persons with AIT disease may be quite normal superficially. Abnormalities may be detected only by most careful clinical examination and laboratory investigations. Diagnosis of AIT disease depends upon satisfaction of clinical (Table 1), immunological and biochemical criteria.

A number of patients who are clinically normal have high levels of thyroid antibodies and sensitive immunological tests can pick up many patients with autoimmune thyroiditis

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(Table 2). We have included LATS in this list because of the strong evidence that it is an antibody.

TABLE 2. Immunological features of autoimmune thyroid disease

| |
|---|
| Thyroglobulin antibodies |
| Microsomal antibodies |
| Second colloid antibodies |
| Anti-nuclear antibodies |
| Long-acting thyroid stimulator |

Biochemical tests may occasionally be abnormal in patients without clinical thyroid disease or circulating antibodies (Table 3). The thyroid may release an iodoprotein or iodinated peptides which can easily be detected. There may be a defect in organification of iodine detected by the perchlorate test or the intrathyroidal iodine pool may be low.

TABLE 3. Biochemical features of autoimmune thyroid disease

| |
|---|
| Iodoprotein or iodinated peptides in circulation |
| Defective organification of iodine |
| Low intrathyroidal iodine pool |

These clinical, biochemical and immunological abnormalities usually occur together, but in certain instances only laboratory investigation will reveal the patient with subclinical AIT disease. Previous studies on the inheritance of AIT disease were hampered because clinical features only were taken into account and many patients with the subclinical condition were missed.

The main criteria suggesting genetic factors in diseases of unknown aetiology are:

*Familial incidence*

A greater frequency of the abnormality in relatives than in the general population. This point will be considered principally in this paper.

*Familial incidence in same functional system*

Dr Doniach and Dr Roitt will deal with the familial incidence of pernicious anaemia and of thyroiditis.

*Twin studies*

Dr Buchanan and his colleagues will consider this point.

The first question which must be decided is whether there is a greater frequency of AIT disease in relatives of patients with the disease than in the general population? Rundle (1961) obtained a family history of thyroid disease in 22% of his thyrotoxic patients com-

pared with 5·5% in controls. Bartels (1941) also found clinical thyroid disease in 21·3% of the sibs of patients with Graves' disease.

Our initial family study dealt with the incidence of thyroid antibodies in the siblings of patients with AIT (Hall, Owen & Smart, 1960). The only criteria for selection of the propositi was that they should have high levels of thyroid antibodies and have at least one sib available for study. Thirty-nine siblings of eleven propositi were examined. Similar results have since been obtained in a larger series (Hall, 1962) and Drs Doniach and Roitt have also confirmed these findings (Doniach, Nilsson & Roitt, 1965; Doniach, Roitt & Taylor, 1965).

All available siblings were contacted and examined for clinical thyroid disease and thyroid antibodies (both thyroglobulin and complement-fixing antibodies). The results of the study are analysed under the following headings:

(1) Incidence of antibodies in siblings.
(2) Titre of antibodies in siblings.
(3) Clinical thyroid disease in siblings.
(4) Mode of inheritance.

*Incidence of antibodies in siblings*

Eighteen of twenty-nine female and four of ten male sibs had one or other thyroid antibody in the circulation, giving an overall incidence of 56%. In the general population the incidence of antibodies in women does not exceed 25% and in men does not exceed 13% (Dingle *et al.*, 1966). Thus the incidence of antibodies in the siblings of patients with AIT disease is higher than that in the general population.

*Titre of antibodies in siblings*

The titre of antibodies was also higher in both male and female siblings compared with persons of the same age and sex in the general population. The thyroglobulin antibody titre was 1:640 or more in 30% of the male and 50% of the female sibs compared with 4% and 13% of age and sex matched controls.

*Clinical thyroid disease in siblings*

Clinical thyroid disease was found in 33% of the siblings. This was usually a non-toxic goitre due to AIT disease and occasionally myxoedema or thyrotoxicosis. This incidence of clinical thyroid disease is certainly higher than in the general population in the Newcastle area where goitres are found in about 10% of the female population and myxoedema and thyrotoxicosis much less frequently.

*Mode of inheritance*

Can we obtain evidence that this familial pre-disposition is inherited? Does the incidence of antibodies in the siblings fit with any genetic pattern? In fact the incidence of antibodies among siblings (56%) is close to the theoretical expectation of 50% for dominant inheritance.

*Parent study in thyroiditis.* In the original study few parents were available since AIT disease usually occurs in middle age. Therefore the parents of nineteen children with histologically proven Hashimoto's disease were examined (Hall, Saxena & Owen, 1962). Dominant transmission with complete penetrance would require that one or other of the parents of all these children should have shown evidence of autoimmune disease. Actually positive

thyroid antibodies were detected in one or other parent in seventeen of nineteen families which is quite compatible with dominant transmission with incomplete penetrance. The incidence of antibodies in parents was also significantly higher than in age and six matched controls.

*Parent study in Graves' disease.* A similar study has recently been carried out by Saxena (1965) on twelve children with Graves' disease. In ten of eleven families where both parents could be traced one or other parent had evidence of clinical thyroid disease or circulating antibodies, which again is compatible with dominant transmission.

## FAMILY PEDIGREES

We will now deal with some family pedigrees of autoimmune thyroid disease. Thier *et al.* (1965) described a large family with AIT disease, many of whom were dead, not tested or not seen. Eliminating the irrevelant details from their pedigree we obtain the result shown on Fig. 1, which is quite compatible with dominant transmission through several generations.

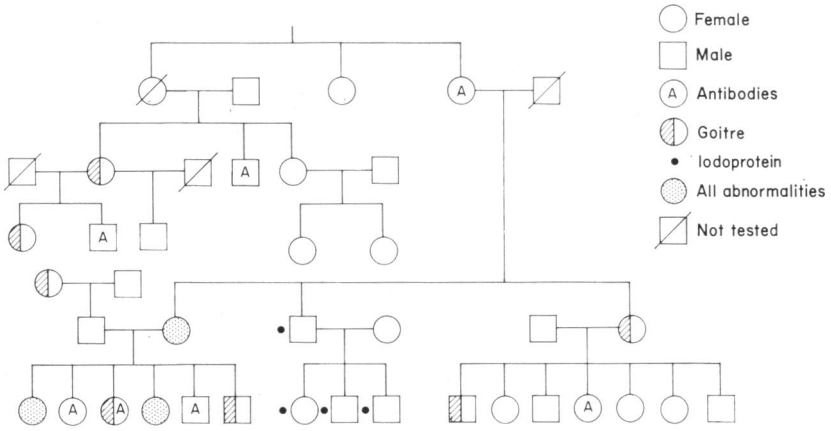


FIG. 1. Pedigree of 'R' family (Thier *et al.*, 1965).

A disturbing finding in their study was the low incidence of thyroid antibodies in patients with clinical thyroid disease. This suggests either that the tests were insensitive or the family unusual.

In 1962, Van Wyk *et al.* described a large family with 'simple goitre' from North Carolina (Fig. 2). Thyroidectomies were carried out on three patients and the histological examination of the glands showed thyroiditis. Antibody tests were carried out on six goitrous members of the kindred and positive results were obtained in five. Iodinated peptides were present in the circulation of some goitrous patients. There can be little doubt that this family suffered from AIT disease. Several of the members became hypothyroid after iodine administration, a not uncommon event in patients with Hashimoto's diseae. Van Wyk *et al.* (1962) concluded that the goitre in this family probably resulted from inheritance of a single autosomal gene, although sex linkage could not be ruled out. Penetrance was not complete in either sex but was low in males and high but incomplete in females.

A family which DeGroot and one of us (DeGroot *et al.*, 1962) studied in Boston reveals the dissociation which can occur between the various features of AIT disease (Fig. 3).

The propositus, a teenage girl, had histologically proven Hashimoto's disease, as had another sister and a brother. Another brother had positive thyroid antibodies without clinical thyroid disease and a sister was clinically and serologically normal. All members of the sibship had an iodinated protein in their plasma. The father had a goitre and CA2 antibody. The mother had thyroglobulin antibodies but no clinical thyroid disease. The high incidence of thyroid disease in this family was compatible with inheritance of the trait from both parents.

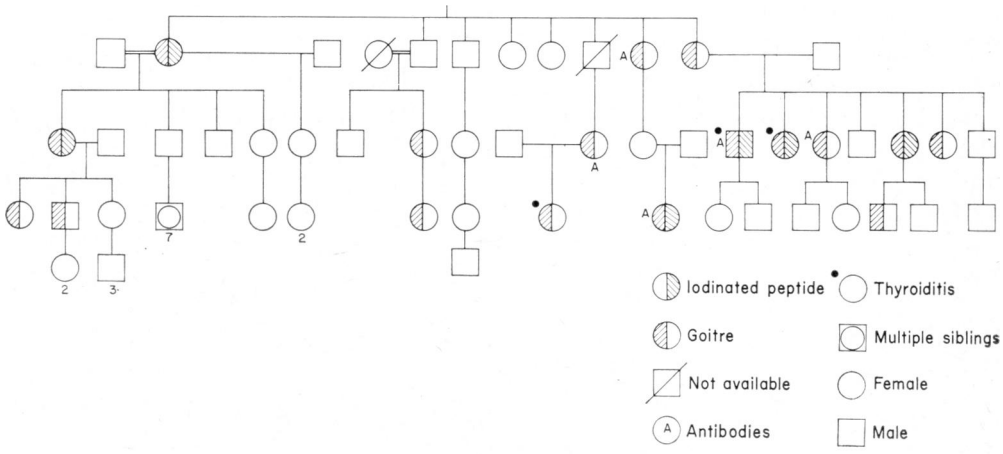


FIG. 2. 'S' Segment, 'H' kindred (Van Wyk *et al.*, 1962).

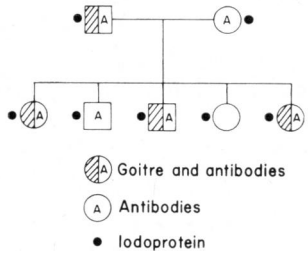


FIG. 3. 'M' family (De Groot *et al.*, 1962).

This dissociation of effects does not invalidate our hypothesis that a dominant gene is responsible. Variation in the kind of effect produced by the same gene or gene complex in different individuals has long been known, and has been designated variability in specificity. Alternatively this may be an example of variability in expression, in which the severity or degree of manifestation of symptoms varies from one individual to another.

## CONCLUSIONS

The evidence is now very strong that autoimmune thyroiditis is a familial disorder. The incidence approaches 50% in siblings and there is almost invariably an abnormality in one or other parent of an affected patient. This is compatible with dominant inheritance.

It seems probable that many environmental factors act on genetically predisposed individuals to produce clinical thyroid disease. Emotional stress, iodine deficiency, hormonal factors such as puberty and pregnancy and viral infections may all play a part in the development of overt thyroid disease.

## GENERAL DISCUSSION

DR LAWRENCE. I was very interested in the age distribution of the thyroid antibodies in your population sample. Have you any ideas as to the reason for this distribution? It wasn't just an increase with age, was it? You find the maximum about 60–69 years.

DR HALL. This is true. The number of patients we had in the older age groups was fairly low. I would doubt whether the slightly lower incidences in the older age groups was, therefore, significant. In the eighties we only had eight or nine patients.

DR LAWRENCE. I was a little bit confused in studying your slides. Could you say if there was father and son transmission?

DR HALL. In the family described by Van Wyk *et al.* (1962) from North Carolina there was no father to son transmission. These authors concluded that the goitre in this family probably resulted from inheritance of a single autosomal gene though sex linkage could not be ruled out. We have certainly observed father to daughter transmission in a number of cases. We have not observed father to son transmission, but clinical autoimmune thyroid disease is fairly rare in males anyway.

DR LAWRENCE. The second point is that in pooling your data you showed us the incidence of familial antibodies. I wonder how many times you have seen an individual with autoimmune disease and made a search back for say two or three generations and found no evidence of antibody?

DR HALL. Usually in the family of a patient with thyroid disease antibodies and/or thyroid disease are also found in other generations.

DR LAWRENCE. Yes, but I mean what about a normal population? In other words did you ever find individuals who had no family history of thyroid disease or no family incidence of antibodies?

DR HALL. In our original family study we almost invariably found antibodies in one or other relative.

DR HOLBOROW. Has Dr Hall any idea from his studies whether the abnormality which is genetically expressed has anything to do with the antigens in the thyroid or with antibody producing system?

DR HALL. I do not think we have definite evidence either way. As far as the thyroid is concerned no abnormality has been detected in the thyroglobulin molecule as a cause for autoimmunization, but, of course, minor abnormalities in such a large molecule would be very difficult to detect. Most evidence suggests that the abnormality lies in the immune apparatus.

DR HOLBOROW. Do you think genetic studies of this type can give you any indication?

DR HALL. Yes, I think they can. If you have a family in which a patient has, say, pernicious anaemia and also has Hashimoto's disease it is rather difficult to imagine that there is an abnormality in the stomach antigen and also the thyroid antigen. It is easier to think that there is something wrong with the immune apparatus (Irvine, 1964).

DR O'BRIEN. We each have two grandparents, four great grandparents and innumerable cousins, and 10–20% of normal people have thyroid autoantibodies. Would it be fantastically unusual if you did not find antibodies somewhere in the family tree?

DR HALL. Yes, I quite agree. All I would say is that when we studied the parents of children with thyroiditis we found a much higher incidence of thyroid antibodies in the parent than in the general population.

DR O'BRIEN. Who were all these normal people walking around with these antibodies?

DR HALL. Minor degrees of autoimmune thyroiditis are quite common and very often asymptomatic.

DR BUCHANAN. Familial aggregation of a disease does not necessarily imply genetic transmission. If we did not know that syphilis, for instance, was an infective disease, we might conclude from family studies that it, and the Wassermann antibody, showed father to son transmission.

DR HALL. Well, I agree we must interpret the results of our studies with caution and all I would say is that they are compatible with genetic transmission, but I take your point, and they are almost certainly influenced by environmental factors.

## REFERENCES

BARTELS, E.D. (1941) Heredity in Graves' disease. *Op. Dom. Biol. hered. hum. Kbh.*, p. 2. Munksgaard, Copenhagen.

DEGROOT, L.J., HALL, R., MCDERMOTT, W.V. & DAVIS, A.M. (1962) Hashimoto's thyroiditis: a genetically conditioned disease. *New Engl. J. Med.* **267**, 267.

DINGLE, P.R., FERGUSON, A., HORN, D.B., TUBMEN, J. & HALL, R. (1966) Incidence of thyroglobulin antibodies and thyroid enlargement in a general practice in North-East England. *Clin. exp. Immunol.* **1**, 277.

DONIACH, D., NILSSON, L.R. & ROITT, I.M. (1965) Autoimmune thyroiditis in children and adolescents. II. Immunological correlations and parent study. *Acta paediat. scand.* **54**, 260.

DONIACH, D., ROITT, I.M. & TAYLOR, K.B. (1965) Autoimmunity in pernicious anemia and thyroiditis: a family study. *Ann. N.Y. Acad. Sci.* **124**, 605.

HALL, R. (1962) Immunologic aspects of thyroid function. *New Engl. J. Med.* **266**, 1204.

HALL, R., OWEN, S.G. & SMART, G.A. (1960) Evidence for genetic predisposition to formation of thyroid autoantibodies. *Lancet*, **ii**, 187.

HALL, R., SAXENA, K.M. & OWEN, S.G. (1962) A study of the parents of patients with Hashimoto's disease. *Lancet*, **ii**, 1291.

IRVINE, W.J. (1964) Thyroid autoimmunity as a disorder of immunological tolerance. *Quart. J. exp. Physiol.* **49**, 324.

RUNDLE, F.F. (1941) A study of the pathogenesis of thyrotoxicosis. *Lancet*, **ii**, 149.

SAXENA, K.M. (1965) Inheritance of thyroglobulin antibody in thyrotoxic children. *Lancet*, **i**, 583.

THIER, S.O., BLACK, P., WILLIAMS, H.E. & ROBBINS, J. (1965) Chronic lymphocytic thyroiditis: report of a kindred with viral, immunological and chemical studies. *J. clin. Endocr.* **25**, 65.

VAN WYK, J.J., WYNN, J.O., DEISS, W.P., ARNOLD, M.B. & GRAHAM, J.B. (1962) Genetic studies in a family with 'simple' goiter. *J. clin. Endocr.* **22**, 399.