Hypothyroidism after Thyroidectomy for Graves's Disease: A Search for an Explanation

M. VAN WELSUM, T. E. W. FELTKAMP, M. J. DE VRIES, R. DOCTOR, J. VAN ZIJL, G. HENNEMANN

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Summary

Out of 38 patients who had undergone subtotal thyroidectomy for Graves's disease seven to 20 years previously 15 developed hypothyroidism. In these 15 patients autoantibodies against thyroid cytoplasm were significantly more frequent than in the 23 euthyroid patients, though there was no difference in the prevalence of autoantibodies against thyroglobulin. Histological examination of the thyroid tissue removed at operation showed that significantly more plasma cells and lymphoid follicles with germinal centres were present in patients who subsequently developed hypothyroidism than in those who remained euthyroid. No differences in the amount of lymphocytic infiltration were seen in hypothyroid and euthyroid patients.

The results suggest that B lymphocytes play a part in the development of postoperative hypothyroidism in Graves's disease. It is proposed that Graves's disease and Hashimoto's disease are different aspects of the same basic autoimmune process.

Introduction

It is now clear that in a substantial number of patients hypothyroidism may develop after partial thyroidectomy for Graves's disease. Reports give overall incidences of hypothyroidism from 35% to 49%.¹⁻³ The factors responsible for this complication are ill defined.

In patients with Graves's disease with lymphocytic infiltration of the thyroid hypothyroidism tends to develop after partial thyroidectomy.^{4,6} Greene⁷ reported that the presence of lymphoid follicles with germinal centres is more relevant to postoperative hypothyroidism than lymphocytic infiltrations alone, and Hargreaves and Garner⁸ found that hypothyroidism does not occur in the absence of germinal centres. A relation has also been found between the presence of thyroid autoantibodies, especially antimicrosomal antibodies, at operation and the subsequent development of hypothyroidism.^{4,9,10} One group³ considered the size of the thyroid remnant left at operation to be important in the development of hypothyroidism, but an earlier report could not establish such a relation.¹¹

In the present study of patients who underwent partial thyroidectomy for Graves's disease we compared the histological findings in specimens taken from the euthyroid and hypothyroid patients at thyroidectomy. We also compared the two groups of patients for the presence of autoantibodies to thyroid antigens 12 years after thyroidectomy.

Medical Faculty, Erasmus University, Rotterdam, The Netherlands
M. VAN WELSUM M.D., Research Fellow, Internal Department III
M. J. DE VRIES, M.D., Professor of Pathology, Department of Pathology II
R. DOCTOR, Ir., Biochemist, Internal Department III
J. VAN ZIJL, Ing., Physicist, Department of Nuclear Medicine
G. HENNEMANN, M.D., Reader, Department of Nuclear Medicine

Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands

T. E. W. FELTKAMP, M.D., Head of Department

Patients and Methods

Thirty-eight patients (36 women) who had undergone subtotal thyroidectomy seven to 20 years (mean 11.8 years before) were included in the study (mean age 52.6 years). No patient was having any form of treatment known to influence serum thyroid hormone levels.

Apart from clinical examination the following determinations were made: total thyroxine (T-4) (Tetrasorb), normal values 6.8-14.4 $\mu\text{g}/100\text{ ml}$; total triiodothyronine (T-3) by a radioimmunoassay,¹² normal values 80-205 ng/100 ml; thyroid-stimulating hormone (TSH) by the method of Odell *et al.*,¹³ normal values 2.5-8.4 $\mu\text{U}/\text{ml}$. Antibodies to thyroid colloid and cytoplasm were shown in 1/10 diluted serum with the indirect immunofluorescence technique.¹⁴ If antibodies to thyroid colloid were found the passive haemagglutination method was performed to determine antibodies to thyroglobulin (Wellcome Research Laboratories, Beckenham, England). A titre 1/320 was considered positive and lower titres dubious. The complement fixation test was performed on all sera to measure antibodies to microsomal antigens (Wellcome Research Laboratories, Beckenham, England). A titre 1/4 was considered positive. Histological examination of the operation specimens was carried out by two of us (M. J. de V. and G. H.). From each removed thyroid two or three microscope slides were available for examination. Focal and diffuse lymphocytic infiltration were separately graded from 0 to 3, and both scores were added (when there was maximal lymphocytic infiltration of both types a final score of 6 was reached). The presence of plasma cells and lymphoid follicles with germinal centres was also noted.

Results

The results are shown in the table. The patients were divided in two groups on the basis of the T-4 serum concentration. They were considered euthyroid when the T-4 was equal or greater than 6.8 $\mu\text{g}/100\text{ ml}$ and hypothyroid when a lower

Data on 38 Patients operated on for Graves's Disease. Mean Values are $\pm$ S.D.

	Hypothyroid	Euthyroid	P
No. of patients	15	23	
Mean T-4 ($\mu\text{g}/100\text{ ml}$)	5.0 $\pm$ 1.47	9.36 $\pm$ 1.91	
Mean T-3 (ng/100 ml)	125 $\pm$ 49.4	173 $\pm$ 61.8	<0.025†
Mean TSH ($\mu\text{U}/\text{ml}$)	42.5 $\pm$ 44.7	8.9 $\pm$ 3.89	<0.001‡
Mean period after thyroidectomy (yrs)	13.2 $\pm$ 4.7	10.9 $\pm$ 4.6	N.S.
Mean age (yrs)	50.9 $\pm$ 10.79	53.3 $\pm$ 15.5	N.S.
Mean score of focal + diffuse lymphocytic infiltration	2.86 $\pm$ 1.55	2.38 $\pm$ 1.66	N.S.
No. with plasma cells	10	5	<0.05§
No. with lymphoid follicles with germ centres	10	5	<0.05§
No. with autoantibodies against thyroglobulin present*	5	1	N.S.
No. with dubious result of passive haemagglutination test†	3	1	N.S.
No. with autoantibodies against cytoplasm*	7	1	<0.01§
No. with positive result of complement fixation test	7	1	<0.01§

N.S. = Not significant

*Detected with fluorescence antibody technique.¹⁴

†Titres <1/320.

‡Students *t* test.

§ χ^2 Test

value was found. It seems that 39% of the patients operated for Graves's disease became hypothyroid, the mean T-4 being 5.0 $\mu\text{g}/100$ ml. In the euthyroid group the mean T-4 was 9.36 $\mu\text{g}/100$ ml. The mean T-3 and the mean TSH were significantly different in both groups. There was no significant difference in the mean age and the mean period after thyroidectomy of both groups. Also no difference was found in the mean score of the diffuse plus focal lymphocytic infiltration. The occurrence of plasma cell infiltration and lymphoid follicles with germinal centres in both groups was significantly different ($P < 0.05$). These phenomena were seen more often in the hypothyroid group. Between the two groups no difference was seen in the frequency of circulating autoantibodies against thyroglobulin (fluorescence technique and passive haemagglutination test). By contrast, there was a difference ($P < 0.01$) in the prevalence of autoantibodies against thyroid cytoplasm (fluorescence technique and complement fixation test). These autoantibodies occurred more often in the hypothyroid patients.

Discussion

Our results confirm the findings of others¹⁻³ that hypothyroidism is a frequent complication of thyroidectomy for Graves's disease. We classified hypothyroidism on the basis of a subnormal T-4 level, though it may be argued that the TSH serum level is perhaps a more sensitive index. In recent publications,^{15,16} however, the significance of a raised TSH level after treatment with ¹³¹I for hyperthyroidism in otherwise clinically euthyroid patients with normal T-4 levels has been questioned. The finding of a positive relation between autoantibodies against thyroid cytoplasm and hypothyroidism after thyroidectomy has already been described by others.^{4,9,10}

In contrast to earlier workers^{4,6} we found no relation between the mean score of diffuse plus focal lymphocytic infiltration and hypothyroidism after thyroidectomy. This might have been the result of the biochemical criteria we used to diagnose hypothyroidism. Most of our hypothyroid patients had no or only slight clinical signs of hypothyroidism, in contrast to the patients studied by others.

The association of lymphoid follicles with germinal centres with postoperative hypothyroidism has been described,^{7,8} and we showed a correlation also between the presence of plasma cells and a final hypofunction of the thyroid. We therefore suggest that plasma-cell and other bursa-dependent (B) cellular infiltration is important in the pathogenesis of thyroid destruction in Graves's disease. The importance of B lymphocytes in the development of autoimmune thyroiditis is strongly supported by the observations on chickens of the "obese strain"^{17,18} and by the observations on chickens of the thyroiditis in neonatally thymectomized irradiated Wistar rats.¹⁹

Strong indications for a direct cytotoxic effect of anti-thyroid antibodies in vivo have never been found.²⁰ Recently, however, in electronmicroscopical studies on thyroid tissue of patients with Hashimoto's disease follicular membrane deposits resembling antigen-antibody complexes of the immune complex nephropathies have been seen.²¹ These deposits appeared to be essentially associated with plasma cells closely abutting the follicles, whereas in areas with a predominantly lymphocytic infiltrate no such follicular membrane deposits were present. Though electron dense deposits were not seen in the thyroids of patients with Graves's disease immunofluorescence staining methods clearly showed immunoglobulin and complement deposits on the follicular basement membrane, confirming recent studies in a large group of patients with Graves's disease.²² Though possibly these complexes lead to tissue damage, it is also possible that the antibodies favour conditions in which non-specific lymphocytes or that non-phagocytic monocytes cause tissue destruction.^{23,24}

Several observations point to a partial thymic-dependent (T) lymphocytic deficiency in autoimmune diseases like autoimmune thyroiditis.^{25,26} Such a deficiency might lead to an uncontrolled hyperreactivity of certain B lymphocytes.

Though the above arguments suggest that B cells play an important part, probably a deficiency of T lymphocytes is not the only mechanism controlling the B lymphocytes. If the leucocyte migration test reflects the T lymphocyte mediated immunity probably this type of immunity is also involved in thyroid autoimmune disease.²⁷

Volpe *et al.*²⁸ suggested that Graves's disease is a disease of delayed hypersensitivity induced by T lymphocytes situated within the thyroid gland and stimulating the thyroid cell directly, thereby causing thyroid hyperfunction. They supposed that these T lymphocytes could also stimulate B lymphocytes within the thyroid gland to produce long acting thyroid stimulator (LATS). In this model LATS is postulated to be an epiphenomenon secondary to primary events within the thyroid gland. That LATS is not directly related to the hyperfunction of the thyroid gland in Graves's disease is suggested by several recent studies.²⁹⁻³² Our results, suggesting the B lymphocytic activity is related to the development of hypothyroidism after thyroidectomy for Graves's disease, does not contradict the hypothesis that Graves's disease is primarily caused by an abnormality of T lymphocytes. One could postulate that in Graves's disease T lymphocytic stimulation of the thyroid cells prevails over stimulation of B lymphocytes producing thyroid autoantibodies, thereby causing late hypothyroidism. In addition, in Hashimoto's disease—which has been suggested to be closely related to Graves's disease or even caused by the same basic autoimmune process³³—B lymphocytic activity is much more pronounced, possibly causing early hypothyroidism, while the stimulation of the thyroid cells by T lymphocytes is much less pronounced so that only transient or no hyperthyroidism is produced.

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Requests for reprints should be addressed to G. Hennemann, Department of Internal Medicine III, Dijkzigt Hospital, Erasmus University, Rotterdam, The Netherlands.

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Medical History

A Memorable Decade in the History of Neurology 1874-84—II

J. D. SPILLANE

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Richard Caton 1842-1926

THE PIONEER OF ELECTROENCEPHALOGRAPHY

Richard Caton had been a medical student with Ferrier at Edinburgh, and they were both founding members of the Physiological Society in 1876. Caton had examined the electrical activity of nerve-muscle preparations and tried to discover whether similar changes in electrical potential occurred in the brain. His experiments were conducted on rabbits and monkeys in Liverpool where he had been appointed lecturer in physiology. He discovered that not only were there changes with sensory stimulation, but that "feeble currents of varying direction passed through the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter and one on the surface of the skull. The electric currents of the grey matter appear to have a relation to its function."⁴⁹ In this first publication (1875) he noted the electrical changes which occurred when Ferrier's topographical zones were in action. He sought to demonstrate his results at a meeting of the Royal Society in 1875, but was not successful. It was at that very meeting that Ferrier's own new experiments were demonstrated.

In his second paper in 1877⁵⁰ Caton concluded that "all the brains examined have shown evidence of the existence of electric currents" and he considered that these currents were related to cerebral activity because they varied with the degree of alertness of the animal, whether it was awake or asleep, and because he noted that the currents were abolished by anaesthesia and ceased at death. Caton was primarily engaged in studying the localization of sensory functions in the brain and he succeeded in noting the effects of visual and probably tactile stimulation, but not with auditory and olfactory stimulation. He observed what is known as intermittent photic stimulation. "I tried the effect of alternate intervals of light and darkness . . . I found that light caused negative variation almost invariably." Brazier⁵¹ comments that this was the "gaslight era" and the mention of flame as a source of light in his experiments exemplifies the skill and degree of success which these Victorian physiologists managed to achieve. Caton thought that "the study of these currents may prove a means of throwing further light

FIG. 1—Richard Caton, Lord Mayor of Liverpool, 1907

on the function of the hemispheres." He said "I obtained more definite results when experimenting on Ferrier's motor and sensory areas."

In 1887 Caton attended the Ninth International Medical Congress in Washington, U.S.A., and read a paper on "Researches on Electrical Phenomena of Cerebral Grey Matter."⁵² He thought "it was well received but not understood by most of the audience." Brazier⁵¹ comments that "this pebble that Caton dropped into the pool in Washington in 1887, was to produce no ripple in this country until 1930, when the first American publication on the electrical activity of the brain appeared." The Russian journal *Vrach* published an abstract of his paper but, in Brazier's words "this abstract was no more successful in catching the eye of Russian and Polish workers than those in the English language were in attracting the attention of Caton's countrymen."

In 1890, in the pages of the *Centralblatt für Physiologie*, Beck of Cracow and Marxow of Vienna were arguing their case for

Newport, Pembrokeshire

J. D. SPILLANE, M.D., F.R.C.P., President, Association of British Neurologists