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Graves' Disease Following the Occurrence of Hypothyroidism

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Three patients with hypothyroidism of 15-48 months' duration developed Graves' disease while on thyroid hormone replacement therapy. In one patient, the hyperthyroid phase was preceded by ophthalmopathy and nonsuppressible 24-hour radioactive iodine uptake (RAIU). Eventually, all had hyperthyroid findings with elevated thyroid hormone levels, high 24-hour RAIU, and a diffuse uniform uptake of RAI by the enlarged thyroid. All subjects had negative antithyroglobulin and antimicrosomal antibody titers. Two had demonstrable long-acting thyroid stimulator (LATS) in their sera. All three were followed for 5-36 months while on propylthiouracil therapy prior to surgery or RAI administration. Both LATS-positive patients underwent bilateral subtotal thyroidectomy. Classical changes of Graves' disease were found on histopathological examination of resected tissues.

The occurrence of Graves' disease after a period of hypothyroidism is an unusual phenomenon. Since 1930, the English literature describes almost 80 patients with Graves' disease following use of thyroid extract or synthetic thyroid hormone (1-11). However, only 24 had substantial evidence that suggested prior hypothyroidism, and of the 24, 14 had well-documented evidence to support the diagnosis (6-16). In the majority of patients, obesity was the primary indication for thyroid hormone therapy (1-3). Attention was therefore focused on the possible association of prior thyroid extract therapy and the subsequent development of "exophthalmic goiter" with hyperthyroidism. Not until 1967 were autoimmune mechanisms considered a possible cause of hyperthyroidism in this subset of patients (4). This report deals with three cases of Graves' disease following unequivocal hypothyroidism which can be best explained on the basis of autoimmune mechanisms.

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Dr. Guansing died suddenly during the summer shortly before this special issue went to press. He received his training in medicine and endocrinology at Henry Ford Hospital and trained as an Endocrinology Fellow under the direction of Dr. Smith in 1968-69.—Ed. Note.

Patients and Methods

Three patients with a history of hypothyroidism were referred to The Medical College of Wisconsin for manifestations of hyperthyroidism while they were on thyroid hormone replacement therapy.

The clinical history and physical findings during the disease period were reviewed, as well as the laboratory procedures performed before and during thyroid hormone therapy. The diagnosis of hypothyroidism was verified in all three patients with the determination of serum protein-bound iodine (PBI) and/or serum thyroxine (T_4) levels together with T_3-resin uptake (T_3RU). Initial 24-hour radioactive iodine uptake (RAIU) tests were performed on two patients before therapy.

All three patients were seen one to three months after their thyroid hormone medication had been discontinued. A complete history and thorough physical examination were made on each patient and appropriate thyroid function studies were performed. Serum triiodothyronine (T_3) and T_4 were measured by standard radioimmunoassay procedures (17,18). Serum T_3RU values were determined with a commercially available kit (Abbott Laboratories, North Chicago, IL) except when otherwise indicated. The free thyroxine index (FTI) was calculated for each of the subjects (19). Radioimmunoassay for serum TSH was carried out with commercially available materials (Beckman Company, Fullerton, CA). Thyroid antibodies were checked with the hemagglutination techniques for antithyroglobulin and antimicrosomal antibody determinations (20,21). An im-

munofluorescent antibody technique was also employed for patients 2 and 3 (22). Werner's suppression test was used in patient 3, with 50% suppressibility of RAIU as the minimal criterion for response (23). The presence of a long-acting thyroid stimulator (LATS) in serum was verified by Bioscience Laboratories (Van Nuys, CA) using the McKenzie method (24). RAI uptake and scans were performed for all three subjects.

Propranolol, a beta-adrenergic block agent, was given for symptomatic relief, and propylthiouracil (PTU) was administered in appropriate doses to the patients over a period of 5-26 months. Subsequently, bilateral subtotal thyroidectomy was performed on two patients, and RAI therapy was instituted on the third.

Results

Hypothyroid phase

Table I summarizes some of the clinical and laboratory features of the three patients.

Patient 1 was found to have an "adolescent goiter" 14 months before clinical hypothyroidism developed. Her serum PBI at the time was 6.2 μg/dl (n =2.5-6.7 μg/dl), and the T_3RU was 29.1% (n =25-35%). Then at age 11 she developed progressive weight gain, cold intolerance, sluggishness, dry skin, coarse scalp hair, puffy eyelids, and persistence of thyromegaly. Her serum PBI decreased to 1.3 μg/dl with a T_3RU of 20%. When desiccated thyroid was started at a maintenance dose of 3 gr/day, all of her symptoms improved, she gained weight, and her goiter disappeared. Menarche began at age 12 with normal menstrual cycles. The desiccated thyroid was gradually decreased and finally discontinued after 35 months when she developed signs of hyperthyroidism.

Patient 2 presented with signs and symptoms of hypothyroidism, but no thyromegaly was found. On 2-3 gr of desiccated thyroid daily, all signs and symptoms disappeared until 48 months later when he developed hyperthyroidism.

Patient 3 presented with mild symptoms of cold intolerance and tiredness at age 54 but few physical findings. He did not have thyromegaly. He was treated with 0.2 mg of L-thyroxine until 15 months later when he developed gynecomastia, exophthalmos, and diplopia without signs and symptoms of hyperthyroidism. The L-thyroxine was promptly discontinued.

None of the patients were taking any iodide preparation. Family histories revealed that the mother of the first patient had required thyroid medications for approximately three months during her mid-thirties. She is now euthryoid and without any evidence of goiter. Patient 2 did not have a family history significantly related to hyperthyroidism. The father of patient 3 had undergone surgery for a goiter which was benign.

Hyperthyroid phase

Table II illustrates the salient clinical and laboratory findings at the time hyperthyroidism developed, and Table III shows other laboratory procedures performed during the initial phase.

Patient 1 developed a progressive weight loss of 11 pounds in two months with generalized weakness, increased nervousness, irritability, and heat intolerance. She was normotensive with a tachycardia of 90/minute. There was lid-lag and diffuse thyromegaly with soft to firm consistency. She had an estimated weight of 60 gm. A bruit was present over the goiter. Her skin was moist, and fine tremors of both hands were observed. The remainder of her physical examination was within normal limits. Results of the laboratory studies are shown in Table II. Over the next 35 months her serum TSH levels varied from 4.1 μU/ml to 10.9 μU/ml, depending on the amount of PTU medication she was taking.

Patient 2 presented with a progressive weight loss of 30 pounds and severe weakness of the lower limbs. On physi-

TABLE I
Clinical Findings During the Hypothyroid Phase

Patient	Sex	Age of onset (years)	Presenting symptoms	PBI (2.5-6.7 μg/dl)	T_4 (5.5-14 μg/dl)	T_3RU	24-hour RAI uptake (10-35%)
1	F	11	"Adolescent" goiter preceded hypothyroidism x 14 months; weight gain; cold intolerance	1.3	—	20% (25-35%)	1%
2	M	12	Fatigue; cold intolerance; puffy eyes	1.5	1.0	—	4%
3	M	54	Cold intolerance	—	1.8	35% (43-60%)	

TABLE II
Clinical and Laboratory Features During the Hyperthyroid Phase

Patient	Sex	Age of onset (years)	Salient findings	Serum T_4 (4-11.5 μg/dl)	Serum T (70-215 ng/ml)	T_3RU (25-35%)	TSH (<10 μU/ml)
1	F	14	Diffuse goiter; tremors; tachycardia	19.4	380	42%	2.2
2	M	16	Diffuse goiter; tachycardia; severe myopathy	27.4	570	44%	6.4
3	M	56	Mild thyromegaly, exophthalmos and diplopia; gynecomastia	14.5	—	41%	3.8

cal examination, he was tachycardic at 110/minute, with a normal blood pressure (124/80 mmHg). Lid-lag was bilateral. A diffuse goiter was found. The remainder of the physical findings were within normal limits except for severe pelvic girdle muscle weakness with lesser involvement of the distal musculature. Electromyography showed low voltage with polyphasic potentials consistent with myopathy. Cerebrospinal fluid findings were normal. Table II shows the results of the laboratory findings. At the end of 10 months his serum TSH decreased to 2.8 μU/ml together with a return to normal of both serum T_4 and T_3. Skull x-rays showed a normal sella turcica.

Patient 3 initially presented with exophthalmos, diplopia, and unilateral gynecomastia without galactorrhea. Werner's suppression test showed an initial 24-hour RAIU of 30% and a subsequent value of 38% at the end of 10 days of triiodothyronine, 75 μg/day in three divided doses (Table III). One month later he developed manifestations of hyperthyroidism. He lost 12 pounds and was found to be mildly tachycardic (HR=90/minute). Eye findings included marked limitation of upward gaze and limited lateral gaze bilaterally. Hertel exophthalmometry at base 100 was 23 mm OD and 22 mm OS. A small goiter was found. Except for unilateral gynecomastia, physical findings were otherwise unremarkable. Both testes were of normal size. Laboratory studies showed elevation of serum T_4 to 14.5 μg/dl, T_3RU at 41%, and the FTI to 6.9. Three months later, while on PTU, he became euthyroid with both serum T_4 and T_3RU decreasing to 5.2 μg/dl and 25%, respectively, and serum TSH remaining normal at 3.8 μU/ml. On the fourth month his TSH increased to 18 μU/ml. PTU was discontinued. Excision of the gynecomastia revealed normal breast tissue, and skull x-rays showed a normal sella turcica.

As shown in Table IV, appropriate doses of propranolol and/or PTU were administered to the three patients for a period of 5-36 months. Bilateral subtotal thyroidectomy was recommended to patients 1 and 2 (who were still in their teens) at the end of one year of PTU therapy. At the request of patient 1 and her family, this was done three years later. At surgery, 170 gm of thyroid tissue was resected; on histological examination, it showed pseudopapillary proliferation of tall columnar cells with some islands of lymphoid nodules scattered throughout. Actual lymphocytic infiltration was not observed. Patient 2 had a bilateral subtotal thyroidectomy after 12 months of PTU therapy. Histological findings were almost identical except for the weight of the tissue removed (160 gm). Patient 3 received 10 mCi of RAI as ablative therapy when hyperthyroidism recurred at six months, after PTU had been discontinued for 30 days. All three patients were euthyroid on L-T_4 replacement therapy 26-72 months after these procedures.

Discussion

Graves' disease following hypothyroidism is an unusual sequence of events that is not well recognized. In these three patients the clinical history and laboratory findings indicated hypothyroidism preceding hyperthyroidism.

TABLE III
Other Laboratory Findings During Hyperthyroidism

Patient	LATS	Anti-Tg	Anti-M	24-hour RAI uptake (10-35%)	Thyroid scan
1	(+)	(−)	(−)	51%	Enlarged with uniform uptake
2	(+)	(−)	(−)	79%	Enlarged with uniform uptake
3	ND	(−)	(−)	30% 38%*	"Normal" size uniform uptake

*After 10 days of T_3, 75 μg/day

ND = not done

LATS = long-acting thyroid stimulator

Anti-Tg = antithyroglobulin antibody

Anti-M = antimicrosomal thyroid antibody

TABLE IV
Treatment Procedures During Thyrotoxic Phase

Patient	First treatment	Duration (months)	Second treatment	Findings*
1	PTU, 100 mg qid; propranolol, 20 mg qid	36	Bilateral subtotal thyroidectomy	170 gm thyroid with pseudopapillary proliferation of columnar cells; lymphoid nodules
2	PTU, 150 gm qid; propranolol, 40 mg qid	12	Bilateral subtotal thyroidectomy	160 gm thyroid with similar histology as in No. 1
3	PTU, 100 mg tid	5	10 mCi radioactive iodine	—

*Typical of Graves' disease

PTU = propylthiouracil

Their low serum PBI and T_4 values and the definitely decreased 24-hour RAIU confirmed this diagnosis. However, as with most cases of hypothyroidism, the exact cause was not apparent. Aside from patient 1, whose small goiter occurred before the clinical findings of hypothyroidism were evident, the other two patients did not show any clues of "silent" or spontaneously resolving thyroiditis, subacute thyroiditis (which usually leads to transient hypothyroidism and, in rare instances, to permanent hypothyroidism), or of Hashimoto's thyroiditis, which has been implicated as the most frequent cause of this disorder. No patient had a history of prior hyperthyroidism. While goiter in childhood has been ascribed primarily to Hashimoto's thyroiditis (27), the subsequent antithyroglobulin and antimicrosomal antibody titers in our patients did not confirm this impression, although the relative insensitivity of the procedures employed might account for the negative results. The immunofluorescent procedure, which is more sensitive but less specific for detecting thyroid antimicrosomal antibody, was also negative in two subjects (28). Since these studies were performed two to four years after the patients developed myxedema, significant titers might have been present at an earlier time. However, despite the development of significant thyromegaly and the presence of appropriate antigens during the hyperthyroid phase, no anamnestic response in terms of higher and significant antithyroglobulin and antimicrosomal antibody titers was observed. Furthermore, since histological findings in two patients were not characteristic of Hashimoto's thyroiditis, it is doubtful that this disorder accounts for the initial phase of hypothyroidism. The possibility, however, of antibody-mediated TSH-receptor blockade as an initial event could not be ruled out.

As an alternative mechanism for the development of hypothyroidism in these patients, TSH deficiency, with subsequent development of hyperthyroidism, has been described in one case study (7). However, several factors in our three patients weaken these possible explanations: the subsequent menarche and normal menstrual periods after thyroid hormone therapy in patient 1, the normal skull x-rays of patients 2 and 3, and the appropriate changes in the circulating levels of TSH in all three patients during thionamide therapy, and subsequent surgery in the first two subjects.

Immune-complex disease could also be implicated in the evolution of this problem. Although circulating immune complexes have been demonstrated for many thyroid disorders, their pathogenetic significance has not been made clear except in glomerulonephritis (29,30).

The evolution of Graves' disease is clearly evident in all patients. Classically, it consists of three components which occur simultaneously or independently: hyperthyroidism, infiltrative ophthalmopathy, and pretibial dermopathy (31). Patients 1 and 2 presented with hyperthyroidism only. Their physical findings, thyroid scans, and presence of LATS, a type of thyroid-stimulating immunoglobulin (33), all suggested Graves' disease; histological findings bore this diagnosis out. In patient 3, Graves' disease presented with the infiltrative ophthalmopathic component followed by the hyperthyroid phase. Whether this was the ophthalmopathy of Hashimoto's or of Graves' disease is a moot point, since it has been described in both disorders (33,34). The negative Werner's suppression test during the patient's initial euthyroid phase suggests the presence of a thyroid-stimulating immunoglobulin that caused a sufficient increase in thyroid hormone levels to suppress TSH secretion. TSI determinations, which could have confirmed this possibility, were not performed in this individual. However, the elegant studies of Solomon, et al (35) indicate that in euthyroid Graves' disease the relationship of thyroid-stimulating immunoglobulins to thyroid nonsuppressibility is complex.

While the thyroid disorder in our three patients undoubtedly evolved from a hypothyroid to a hyperthyroid phase,

we still do not understand the sequence of events. The evolution of Hashimoto's thyroiditis to Graves' disease is one consideration, which is supported by previous reports of the concurrence of Graves' disease and Hashimoto's thyroiditis in the same patient (32), the occurrence of these disorders in identical twins (36-38) and in families (39), and "Hashitoxicosis" (34,40). Our patients may represent a variant of Hashimoto's thyroiditis without the classic serological and histological findings. Since both disorders are considered to be autoimmune, the hypothesis of Volpe (41) could be modified to explain this evolution. The defect in immune surveillance (T-lymphocyte system), which could be spontaneous, stress- or viral-induced, permits organ-specific "T" lymphocytes to survive. They then interact with complementary antigen (thyroid gland, orbital tissue, or pretibial skin in Graves' disease) to cause a cell-mediated immune process in the target site. It is possible that a cytotoxic, destructive process, probably mediated by "T" or killer (K) lymphocytes directed at the thyroid gland, led to initial hypothyroidism in our patients. Subsequently, with continuing exposure of "B" lymphocytes to TSH receptors on thyroid cell plasma membrane, specific thyroid-stimulating immunoglobulins (TSI) were formed (42-45), perhaps aided by "helper" T lymphocytes as well. The presence of LATS, one type of TSI, in two patients, lends credence to this hypothesis, since TSI could then lead to a continuous stimulation of residual thyroid gland tissue that would cause sufficient hyperplasia and growth to account for the eventual hyperthyroid phase in our patients. However, for this situation to occur, the cytotoxic component of this dual immune response must for some reason fail so that the cytotrophic effect can prevail.

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