Congenital Iodide Organification Defect Accompanied by a Large Nodular Goiter: A Case Report

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Abstract

A girl who had a nontoxic diffuse goiter with a congenital organification defect of iodide was first seen at the age of 8 years, and since then she has been followed up for a long period. The nodularity of the thyroid gland had gradually progressed, because of intermittent failure of ingestion of thyroid hormone preparation which was followed by excess TSH secretion. 18 years later, a nodular goiter developed and the patient underwent subtotal thyroidectomy.

In order to prevent the development of nodular change in the thyroid gland in this disorder, supplemental thyroid hormone medication should be started as soon as the diagnosis is confirmed, and the therapy should be carried out regularly.

Nontoxic goiter is an enlargement of the thyroid due to repeated or congenital hyperplasia in response to a deficiency of thyroid hormone. There is a great variety of causes and of pathologic manifestations. Depending on the etiologic factors causing the deficiency, thyroid stimulation and hyperplasia may be mild or severe. One of the causes of a deficient output of thyroid hormone is inborn errors of iodine metabolism.

We have observed a case of nontoxic diffuse goiter with an inherited defect in thyroid hormone biosynthesis for 18 years. This patient developed a nodular goiter later. This is the first case we have experienced. To the best of our knowledge, there have been no reports similar to this case in the past decade in Japan. Thus we describe the case in detail here.

Case Report

The female patient (E. O.) was first seen at the Pediatric Endocrinology Clinic of Chiba University Hospital in 1960 at the age of 8 years with large diffuse goiter (Shichijo’s criteria grade 4) (Shichijo, 1953). She was the second child of healthy parents. She was born by cephalic presentation at 36 weeks’ gestation. Pregnancy and delivery had been normal, as had been the neonatal period. Birth weight was 2,250 g and length 47 cm.

The family was closely intermarried. The genetic chart is shown in Fig. 1. Her elder sister and one of her younger brothers
died in early infancy. Her younger brother had a goiter (Shichijo's criteria grade 3), but he was euthyroid. There was no family history of thyroid disease, deafness, or mental abnormality, except her younger brother.

She had a goiter since infancy. Her growth and development were normal, and she was clinically euthyroid. Her intelligence was normal and her physical examination results were otherwise normal.

At the initial visit, the thyroid gland was diffusely enlarged without palpable nodules. The serum PBI was 7.0 µg/dl (normal 4.0–8.0 µg/dl) and the 24 hour thyroidal ¹³¹I uptake was 56.4% (normal 10–40%).

According to these findings, she was suspected of having nontoxic goiter due to an inherited defect in thyroid hormone biosynthesis, and several clinical studies were performed.
Clinical Studies

1. Potassium thiocyanate (KSCN) discharge

$^{131}$I was given orally. After 24 hours thyroidal uptake was measured, and then a 1.0 g dose of KSCN was given orally. One hour later, epithyroidal counts were measured.

2. Deiodination of L-diiodotyrosine (DIT)

The in vivo metabolism of DIT was studied by the methods of Stanbury and co-workers (Stanbury et al., 1956 a, b). A dose of 25 µC of $^{131}$I-DIT in 2.1 µg of DIT was given intravenously. Urine was collected without catheterization at 0–1 hour and 1–2 hour after administration. Samples were applied directly to a paper, chromatographed in a descending system of butanol-acetic acid-water, and counted on a strip counter.

The distribution of labeled compounds was measured and the amount of $^{131}$I-DIT excreted was calculated as a percentage of the administered dose.

3. Deiodination of L-monoiodotyrosine (MIT)

The test method used was similar to that for DIT. A dose of 30 µC of $^{131}$I-MIT in 7.7 µg of MIT was given intravenously.

4. Chromatographic analysis of thyroid biopsy specimen

This test was performed at 24 hours after $^{131}$I administration. The thyroid biopsy specimen was digested by trypsin-pancreatin. After digestion, the sample was applied to a paper, chromatographed in a descending system of butanol-acetic acid-water, and counted on a strip counter (Nakajima et al., 1965).

Results

1. KSCN discharge

According to our criteria, decline in thyroid radiiodine content by more than 20% of the 24-hour value was considered abnormal (Niimi et al., 1970).

After administration of KSCN, an immediate and striking fall in the concentration of radioactive iodine in the thyroid gland was observed. By 1 hour the count had fallen to 62.2% of the previous level (Fig. 2).

2. Deiodination of DIT

According to our criteria, excretion of DIT more than 1% of the total dose in urine within the first 2 hours after administration was considered abnormal (Nakajima et al., 1968). Only a small fraction of the $^{131}$I-DIT (0.06% dose) was excreted in the urine in this patient.

3. Deiodination of MIT

In our experience with this test in normal subjects, radioactivity less than 0.3%
of the administered dose is excreted as $^{131}$I-MIT in urine.

The patient excreted less than 0.07% of the total $^{131}$I-MIT in urine within the first 2 hours after administration.

There are some reports which were considered as showing two defects on thyroid hormone biosynthesis in a patient (Mosier et al., 1958; Kobayashi et al., 1965; Nagao et al., 1965). Then in addition to the KSCN discharge test, examination for deiodination of DIT and MIT was performed on this patient. But we could not find any abnormality of deiodination of DIT and MIT.

4. Chromatographic analysis of thyroid biopsy specimen

It was possible to demonstrate the presence of a considerable amount of T4 and T3 in the biopsied thyroid specimen taken out at 24 hours after administration of radioiodine, although a small amount of MIT and DIT were also demonstrated. Percent distribution of labeled material was as follows; I$^-$ 20.8%, MIT 8.9%, DIT 14.9% and T4+T3 55.4%. The MIT/DIT ratio was 0.6 and the iodotyrosine/iodothyronine ratio was 0.43.

In our experience with this method in a congenital hypothyroidism which was suspected of involving the failure of coupling of iodotyrosines, the MIT/DIT ratio was high (1.1) and the iodotyrosine/iodothyronine ratio was extremely high (43.8). The above results therefore imply that the thyroid gland in this patient has normal ability to couple MIT and DIT into T4 and T3.

5. Histological findings

Histopathological examination revealed that the thyroid tissue consisted of well formed follicles of varying sizes which were lined with cuboidal epithelium and contained colloid. In some areas papillary hyperplasia was observed. There was no significant lymphocytic infiltration.

Clinical Course

Based on the above results, the defect in thyroid hormone biosynthesis in this patient was thought to be present at the organification process of iodide, and thyroid hormone therapy was instituted.

In response to the administration of thyroid hormone preparation, her goiter started to decrease in size. Because drug ingestion was somewhat irregular, however, her thyroid gland increased and decreased in size accordingly. In 1964, her goiter decreased in size significantly and became barely palpable. Unfortunately, in subsequent years she was on and off the prescribed medication and her goiter progressively increased in size.

In 1967, her goiter became enlarged again and a palpable nodule developed in the left lobe. From this time, her goiter failed to decrease in size in response to the administration of thyroid hormone preparation. Thyroid scanning with $^{131}$I did not show any cold area.

In 1975, a nodule was palpated in the right lobe and one more nodule became palpable in the following year. These nodules were round and firm.

Tests for antithyroglobulin antibody and antimicrosome antibody performed several times during this interval consistently gave negative results.

Throughout the following period she remained clinically euthyroid. The $^{131}$I-T3 resin uptake and serum T4 levels stayed within the normal range (T4 4.6–8.3 μg/dl : normal 4.5–13.5 μg/dl). After the radioimmunoassay of TSH became available, her serum TSH levels were determined and were found to be below the normal limit (<2–6 μU/ml : normal <2–8 μU/ml).

She was then married and had taken 100–150 mg/day of desiccated thyroid regularly for 6 months from the spring of 1977, but no decrease in the size of the goiter
was observed. Surgical therapy was therefore advised and bilateral lobes of the thyroid were resected, removing 104 g of nodular tissues (right lobe 65 g, left lobe 39 g) at Ito Hospital in the fall of 1977. Since then she has taken 50 mg/day of desiccated thyroid. Histopathological study and assay of peroxidase activity were carried out on the resected thyroid specimens.

Studies on the Surgically Resected Tissues

1. Histopathological study
Some follicles were largely filled with colloid, while some others showed a microfollicular patterns with focal epithelial hyperplasia. The lesions were not encapsulated, but had irregular areas of fibrosis. (Fig. 3)

2. Assay of peroxidase activity
Enzyme activity was assayed by 2 different methods (guaiacol and iodide assay) (Hosoya et al., 1982; 1983).

Enzymatic studies demonstrated very low peroxidase activity compared to the normal thyroid. In particular, no peroxidase activity could be demonstrated in the iodide assay. (Table 1)

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<th>Table 1. Thyroid peroxidase activity</th>
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<td>Guaiacol activity</td>
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<td>mGU/mg prot.</td>
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Discussion

Nodular goiter in patients with congenital dyshormonogenesis is generally preceded by diffuse thyroid hyperplasia, and nodule formation may be the result of any long continued low grade, intermittent stimulation of the thyroid gland. But how diffuse hyperplasia is transformed into a nodular process is not clear (Fujimoto, 1983). The disease process has conventionally been described as having three stages: 1) the diffuse hyperplastic, 2) the colloid accumulation, and 3) the nodular phase (DeGroot et al., 1975; Meissner, 1978; Studer et al., 1979). The hyperplastic phase of the nontoxic goiter is the initial one. As the process continues, it enters a second phase characterized by an excessive accumulation of colloid in the follicles. The epithelia become low cuboidal or flattened with involution. This phase of nontoxic goiter is often termed colloid goiter. The nodular phase gradually develops as nontoxic goiter and continues over many years. Among those who have nodular goiter, there are patients who have a congenital iodine metabolism defect (DeGroot and Stanbury, 1975).

In the case presented here, a disturbance of thyroid hormone synthesis due to the organification defect of iodide was noted. In order to maintain a euthyroid state, TSH was secreted excessively, producing a goiter from infancy. At the time of her initial examination at the age of 8 years, she was euthyroid, but her goiter became quite large. The histopathology of the thyroid biopsied at that time was that of colloid goiter.

Since the excessive stimulation of TSH decreased in response to the administration of thyroid hormone preparation, her goiter temporarily decreased in size. Because of irregular ingestion of thyroid hormone preparation thereafter, TSH stimulation of the thyroid persisted intermittently, and nodularity gradually progressed over a period of several years until a nodular goiter developed.

Since nontoxic diffuse goiter appears to develop into a nodular goiter if it is left without proper treatment, supplemental therapy with thyroid hormone preparation should be given to the patients, beginning as early as possible and not intermittently throughout their lives.

References


