

—Report on Experiments and Clinical Cases—

The Longitudinal Course of Two Cases with Cretinism Diagnosed After Adolescence

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Abstract

In Japan, mass screening tests on newborns for Cretinism have been performed since 1984. Cretinism is a very rare condition. We report the clinical course and complications of longitudinal thyroid hormone replacement therapy (liothyronine sodium: T3) of two women with Cretinism and ectopic thyroid gland for the past 33 years until 2001.

They were born in April 1951 (Case 1) and in January 1952 (Case 2). On admission in June 1968, they were 17 and 16 years old. They had short stature, mental retardation, macroglossia, saddle nose, retardation of bone maturation, edematous face, coexistence of permanent teeth and deciduous teeth, abdominal distention, hypotonia, anemia, hypophosphatemia and hypercholesterolemia.

After admission, Case 2 had an appendectomy for appendicitis. She was found to have a right ovarian cyst, but was not operated upon. Later, the right ovarian cyst disappeared during thyroid hormone replacement therapy. The complication in this case was NIDDM. Over secretion of thyroid hormone in for example, hyperthyroidism sometimes induces NIDDM.

On their admission, a levothyroxine sodium (T4: Thyradin S) was unavailable in Japan, so we had no choice but to treat them with liothyronine sodium for thyroid hormone replacement therapy. We suspect that liothyronine sodium replacement therapy probably induced NIDDM. They experienced improved bone maturation, anemia, hypophosphatemia and hypercholesterolemia, but their intellectual and mental disabilities were not improved.

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Key words: Cretinism, complications, ovarian cyst, NIDDM, ectopic thyroid gland

Introduction

Yamamoto and Fujino encountered two patients with Cretinism with sublingual thyroid gland in June 1968¹. They were born in April 1951 (Case 1) and in January 1952 (Case 2). They were 16 and 17 years old, and had short stature, mental retardation,

macroglossia, saddle nose, retardation of bone maturation, edematous face, coexistence of permanent teeth and deciduous teeth, abdominal distention, hypotonia, anemia, hypophosphatemia and hypercholesterolemia. They had not been treated for Cretinism before admission. Thyroid gland scintigraphy showed a hot spot in the sublingual region. After the diagnosis of Cretinism, thyroid

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hormone (liothyronine sodium: T3) replacement therapy was started. After replacement therapy, clinical symptoms including short stature, anemia, hypercholesterolemia, hypophosphatemia, etc. improved gradually. In Japan, mass screening of newborns for Cretinism have been performed since 1984. Cretinism is a very rare condition. We report the clinical course and complications of thyroid hormone replacement therapy in these two cases for the 33 years until 2001.

Case Presentation

Case 1: Y. N. born in April 1951, 17 years old female on admission.

Perinatal history was normal. Head control was shown at 3 months, sitting alone at 9 months, standing with holding in 1.5 years old. Anterior fontanel was closed at 3 years old. She had not taken any medication until the 1968 hospitalization. When she entered our hospital, her height was 98 cm, and her weight was 17 kg. The other clinical symptoms were short arms and legs, edematous face, saddle nose, macroglossia, coexistence of permanent teeth and deciduous teeth, and abdominal distension. She could hardly speak, and showed echolalia. IQ was suspected to be below 30. Laboratory data showed anemia, hypercholesterolemia, hypophosphatemia, and decreased PBI (protein binding iodine: 1.8 micro g/dl (normal child data: 4~8 micro g/dl)). EEG showed low voltage theta waves. ECG showed low voltage and flat T waves. She had only three Carpal bones and an immature pelvis (**Fig. 1**). Thyroid gland scintigraphy showed a hot spot in the sublingual region. Therefore, thyroid hormone (liothyronine sodium: T3) replacement therapy was started with a diagnosis of Cretinism with sublingual thyroid gland in 1968. Her anemia, hypercholesterolemia, and hypophosphatemia improved gradually. Her menarche appeared after 4 years of therapy. After therapy for 3 years, bone age developed, and the nasal sinus, lumbar spine, and femoral head matured (**Fig. 2**). After 7 years (25 years old), her height was 131 cm, maximally. But her mental deficits remained unchanged. Now, in 2001, one year after the menopause she is 50



Fig. 1 Pelvis X-ray photography of Case 1 in 1968. The bone maturation is poor.



Fig. 2 Pelvis X-ray photography of Case 1 after 3 years thyroid hormone replacing therapy (1971). Bilateral femoral heads are noticed.

years old, and has taken 60 micro-grams of liothyronine sodium every day since 1971. She can sit alone on the bed. Her height is 128 cm, and there are no deformities except scoliosis.

Case 2: I. M. born in January 1952, 16 years old female on admission.

Perinatal history was normal. Head control was shown at 4 months, sitting alone at 7 months, and standing with holding at 10 months. She could not speak at all, and could not walk alone. At 16 years old, she had her first menstruation before admission. Until entered our hospital in 1968, she had not taken any medication. When entered our hospital, her height was 115 cm, and her weight was 24.5 kg. Her bone age and chronological age were almost the same. She was poorly developed and had never spoken. She could walk with support and excrete by herself. Her appearance was with the same features

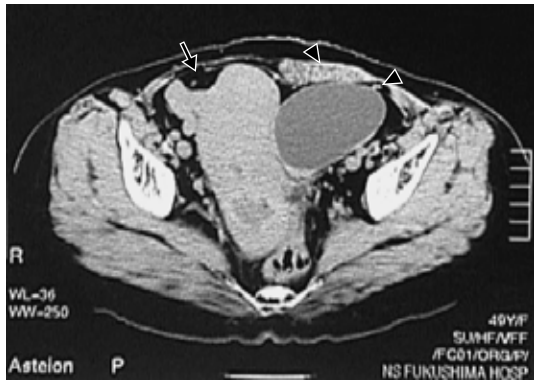


Fig. 3 Abdominal plain CT of Case 2 in 2001. Left monocystic ovary (triangle) and uterine tumor (arrow) are showed.



Fig. 4 Abdominal contrast enhanced CT after 4 months of plain CT (Fig. 3). The size of the left monocystic ovary and uterine tumor are not changed. Uterine tumor is enhanced by contrast medium, and it is suggestive of a myoma.

as case 1, and PBI was decreased mildly (3.7 micro g/dl). Thyroid gland scintigraphy showed a hot spot in the sublingual region. Therefore, a diagnosis of Cretinism with sublingual thyroid gland was made, and thyroid hormone (liothyronine sodium: T3) replacement therapy was started in 1968. After admission, she had an appendectomy for appendicitis. She was found to have a right ovarian cyst, but it was not operated upon. Now, in 2001, a half year after menopause she is 50 years old. Her height is 131 cm, and she has taken 40 micro-gram of liothyronine sodium every day since 1975. But her mental deficit remains unchanged. She was found to have glucosuria in February 2001. Her blood glucose before meals was 178 mg/dl, and 2 hours after, 270 mg/dl. Her insulin level before meals was 3.54 micro U/ml, and 2 hours after, 13.8 micro U/ml. A diagnosis of NIDDM was made. An abdominal echography did not show any tumor in the liver or pancreas, and the right ovarian cyst had disappeared. But, we found a giant tumor in the uterus and a left ovarian cyst (Fig. 3). Alfa-fetoprotein, CEA, CA 125 and HCG were in almost the normal range. After 4 months, abdominal contrast enhanced CT suggested the giant uterine tumor to be a myoma (Fig. 4). Diet therapy (1,400 kcal/day), and glibenclamide (sulfonylurea) had been started for NIDDM. After one year, her glucosuria was negative, and the blood glucose before meals was 127 mg/dl, and 2 hours after, 128 mg/dl.

Discussion

Cretinism has been a very rare condition since 1984, when neonatal screening started in Japan. We report the longitudinal clinical course and complications of Cretinism. In the literature, thyroid hormone levels are higher in cases of ectopia than in athyreosis at diagnosis². Our two cases survived until adolescence. We started thyroid hormone (Thyronamin: T3) replacing therapy after adolescence, and their bone maturation, body height, anemia, etc. improved. But, their psychological and intellectual development did not improve, as the cases in previous reports³. Triiodothyronine (T3) binds with T3 nuclear receptor (T3-R) in the target organ. The promoter of T3 regulating gene in the target cell has thyroid hormone response element (TRE) sequence. T3-R and retinoid X receptor (RXR) heterodimer binds with TRE directly, and proliferates or matures the target cell. Cretinism results in a short stature, and immature epiphysis. Progenitor cells and immature chondrocytes are the major T3 target cells in the epiphyseal growth plate. T3 inhibits chondrocyte clonal expansion and cell proliferation while simultaneously promoting hypertrophic chondrocyte differentiation⁴. Thyroid hormone replacement therapy activates the epiphyseal growth plate. Besides, T3-R has been demonstrated in oligodendrocytes. T3 increases

morphological and functional maturation of postmitotic oligodendrocytes as indicated by a well-developed network of branched processes⁵. Thyroid hormone therapy after adolescence does not improve mental retardation in Cretinism. T3 probably promotes the maturation of oligodendrocytes in the developing brain.

The bones in Case 2 matured better than in Case 1, and menarche in Case 2 was faster than in Case 1. It is suggested that Case 2 discharged thyroid hormone more than Case 1.

Case 2 had a right ovarian cyst about 30 years ago, but it was not detected in 2001. A case of ectopic thyroid with congenital hypothyroidism presented bilateral multicystic ovaries without marked precocious puberty has been reported. The cystic ovaries disappeared after thyroid hormone therapy⁶. Several mechanisms have been considered, such as increased ovarian sensitivity to gonadotropins, or high levels of TSH acting via the FSH receptor causing gonadal stimulation⁷. Therefore, we thought the left monocystic ovary and myoma were not related to thyroid hormone therapy, but were symptoms of senility. Thyroid hormone decreases glucose sensitivity to insulin in the liver, and increases peripheral glucose metabolism. Usually, patients treated for Cretinism are not associated with NIDDM. A brother of Case 2 died by unknown nephropathy, but may have had DM. Case 2 has been improved by diet therapy and medication without a decrease in thyroid hormones. In 1968, levothyroxine sodium (T4: Thyradin S) was unavailable, so we had no choice but to treat our cases with liothyronine sodium for thyroid hormone replacement therapy. But, we have treated our

cases with liothyronine sodium carelessly after levothyroxine sodium was available. The serum TSH level of Case 2 is very low now, and we think we may have given her excessive liothyronine sodium therapy. We suspect that liothyronine sodium replacement therapy probably induced NIDDM. It is difficult to control internal thyroid hormone with liothyronine sodium, so it should not be used.

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