

Table 1 Pathophysiology of excessive blood TSH

1. Permanent hypothyroidism
1-1. Central hypothyroidism (hypothalamic and/or pituitary origin)
Anomaly, genetic defects, etc.
1-2. Primary hypothyroidism (thyroid origin)
Dysgenesis (agenesis, hypogenesis, ectopic thyroid gland, etc.)
Dyshormonogenesis
1-3. Peripheral thyroid hormone insufficiency
Thyroid hormone resistance, thyroid hormone transporter abnormality (MCT8 defects), etc.
1-4. Subclinical congenital hypothyroidism
Others
Loss of function mutations of TSH receptor gene
Pseudohypoparathyroidism
2. Transient hypothyroidism (primary)
Severe iodine deficiency
Iodine excess
Administration of anti-thyroid drugs to mother
Loss of function mutations of DUOX2 gene, loss of function mutations of DUOXA2 gene
3. TSH-producing pituitary adenoma
4. Transient infantile hyperthyrotropinemia
5. Interference for TSH measurements
Anti-TSH antibody, anti-mouse IgG antibody (HAMA), etc.

hormone deficiency causes secondary growth hormone deficiency and impaired osteogenic maturation, resulting in growth disorder and osteoporosis in the early adult phase.

Several causes of peripheral thyroid hormone deficiency have been determined as the pathology of hypothyroidism: thyroid hormone receptor abnormalities (resistance to thyroid hormone, RTH; thyroid hormone receptor α/β abnormalities), abnormal thyroid hormone transporter (monocarboxylate transporter 8, MCT8) in the brain; and abnormal activation of thyroid hormone (selenocysteine insertion sequence-binding protein 2, SBP2).

Diseases and conditions presenting with increased thyroid-stimulating hormone (TSH) levels are shown in Table 1. These include CH and other conditions. CH is classified into CH requiring continuous treatment; and transient and subclinical CH (definitions given below) (1, 6, 8–12). However, it can be difficult to differentiate the two types because transient CH may involve a morphological or genetic abnormality of the

thyroid gland (13–18).

b. Transient CH

Patients with transient CH have continuous normal thyroid function after a transient increase in TSH and decreased FT4 concentrations (1, 6). The incidence in North America is 5% to 10% in children positive for CH in mass screening, or 1/50,000 (1). However, transient CH accounted for 40% of CH-positive cases in mass screening from 1981 to 2002 in France (19). Transient CH may occur due to the following causes.

1) Iodine deficiency: Iodine deficiency is rarely found in Japan. In Europe, iodine deficiency is frequently found in premature infants due to maternal iodine deficiency (19).

2) Effect of antithyroid drugs administered to mothers with Graves' disease: Antithyroid drugs administered to mothers inhibit fetal thyroid hormone synthesis. This condition continues from several days to 2 wk after birth. Neonates delivered by mothers with Graves' disease may have transient CH due to inhibition

of the hypothalamic-pituitary system caused by exposure to excessive thyroid hormone in the fetal phase (20).

3) Transfer of inhibiting antibodies from the maternal body: TSH may be inhibited due to transfer of TSH receptor-binding antibody (TSBA_b) from mothers with thyroid disease (9, 14, 21, 22). The action of TSBA_b continues for 3 to 6 mo after birth. Harada *et al.* conducted mass screening in about 570,000 neonates for 13 yr from 1981 to 1994 in Hokkaido and found one case of transient CH due to transfer of maternal TSBA_b (14). In a study in Niigata from 2002 to March 2010, 4 subjects had transient CH due to maternal TSBA_b, and the incidence was 1/40,000 (22).

4) Low birth weight infant: Low birth weight infants frequently have transient CH (1, 6, 10, 23–25). More details on low birth weight infants are given in other sections.

5) Iodine excess: Iodine deficiency is extremely rare in Japan, which is the leading iodine-consuming country in the world. Transient CH due to iodine excess is often found in Japan, and there are many case reports (6, 26, 27). A fetus before 36 wk of gestational age cannot suppress iodine uptake in the thyroid gland when exposed to iodine and has low excretion of iodine from the kidney; consequently, the fetus is likely to be affected by iodine excess. Iodine excess may be induced by disinfection with an iodine preparation, oily contrast media used for hysterosalpingography, food containing a high level of iodine, seasonings, and gargles. However, the incidence of transient CH is low, and the condition does not occur in most pregnant women who undergo hysterosalpingography using oily contrast media (28, 29). Thus, other environmental or genetic factors may be involved in the onset of transient CH due to iodine excess.

6) Dual oxidase 2 (DUOX2) and dual oxidase maturation factor 2 (DUOXA2) abnormalities: DUOX2 is an enzyme that produces H₂O₂, which is required for iodide organification in the thyroid gland. DUOXA2 is required to stimulate DUOX2

action. Transient CH develops due to loss-of-function mutations in both alleles of the DUOX2 gene (16, 17) and mutation in both alleles of the DUOXA2 gene (30).

The intellectual quotient (IQ) of subjects with transient CH is low in areas with iodine deficiency (31, 32). Therefore, similar to persistent CH, transient CH is a hypothyroid condition, and thyroid hormone replacement therapy is required. A case in which the cause is uncertain is difficult to differentiate from subclinical CH, which is defined below. Such a case is followed up carefully by a CH specialist when possible.

c. Subclinical CH

Subclinical CH is also referred to as compensated hypothyroidism. The pathology has been identified in mass screening with TSH as an indicator. Subclinical CH has no symptoms, i.e., it is a subclinical disease, but some patients may have a low thyroid hormone level, and these cases are diagnosed as mild CH (1, 5, 6, 10, 33). Since these cases are called subclinical CH in some countries, the Guidelines for subclinical CH include cases diagnosed as having mild CH. However, there is no evidence for differentiation of subclinical and mild CH, and studies of this issue are required. Hypothyroidism may suddenly manifest in the neonatal stage, and it is subsequently difficult to define such a case as subclinical CH. Therefore, infants in such cases should be very carefully followed up from birth until 3 mo.

Some infants with subclinical CH have morphological abnormalities (semilobar deficiency, swelling, hypoplasia) in the thyroid gland and mutations of thyroperoxidase (TPO) and thyroid-stimulating hormone receptor (TSHR) genes (15). Patients with slightly high TSH may subsequently be diagnosed with persistent CH (34–36). However, there are no global criteria for the range of abnormal TSH, and diagnosis depends on the discretion of the clinician. In a survey of pediatric endocrinologists,

infants with TSH ≥ 10 mIU/L at <6 mo after birth (excluding neonates) and those with TSH ≥ 5 mIU/L at 12 mo after birth were considered to have abnormalities and to require treatment (37, 38). However, there is currently no evidence showing that the intelligence prognosis of these children is improved by therapy, and thus treatment should be conducted carefully (39).

Nishiyama *et al.* found that many patients diagnosed with transient CH due to excessive uptake of iodine-containing food also had elevated TSH during follow-up and were diagnosed with subclinical CH (40). Thus, the effect of dietary iodine may be involved in subclinical CH in Japan.

Based on a survey of Japanese experts, infants with TSH ≥ 10 mIU/L at <6 mo after birth and those with TSH ≥ 5 mIU/L at 12 mo after birth were considered to have abnormalities and were diagnosed with subclinical CH. An untreated patient with subclinical CH should be carefully followed up with a thyroid function test. A treated patient may be reevaluated after suspension of treatment and diagnosed again.

d. Transient infantile hyperthyrotropinemia

Transient infantile hyperthyrotropinemia is defined as follows: 1) The patient has high serum TSH (determined in a specialized test facility, excluding a high concentration in filter blood in mass screening) and blood thyroid hormone always within the normal range corresponding to age. 2) TSH returns to the normal range in the infant stage (excluding an excessive response in a thyrotropin-releasing hormone (TRH) stimulation test). 3) No cause of hypothyroidism (maternal administration of antithyroid drugs, inhibiting TBII, fetal imaging, maternal/neonatal exposure to massive iodine) is found. 4) No abnormality in thyroid echography or scintigraphy; or in uptake. 5) All substances interfering with the TSH assay are excluded (6).

This condition is referred to as transient infantile hyperthyrotropinemia because in infants with thyroid hormone within the normal range

and increased TSH, it is difficult to differentiate subclinical CH from resistance to pituitary thyroid hormone in the initial stage (41). It is currently difficult to differentiate this condition from subclinical CH, and follow-up by experts is required when possible. A patient diagnosed with transient infantile hyperthyrotropinemia should be followed up because a subsequent increase in TSH may occur and result in hypothyroidism (6).

2. Neonatal Mass Screening

2-1. Effectiveness of neonatal mass screening

Recommendation

- 2-1-1. CH mass screening should be conducted as part of a series of neonatal mass screenings. 1 (Consensus)
- 2-1-2. Prefectures and major city governments that conduct mass screening should establish procedures for screening for inborn errors of metabolism and a practical treatment protocol to provide rapid and appropriate treatment for neonates who are positive in mass screening. 1 (Consensus)

Explanation

Before the start of neonatal mass screening, CH was diagnosed from clinical symptoms including 12 checklist items: prolonged jaundice, constipation, umbilical hernia, poor body weight gain, dry skin, sluggishness, macroglossia, hoarseness, cold extremity, edema, wide posterior fontanelle; and goiter. However, these symptoms are nonspecific, and early detection and diagnosis of CH from clinical symptoms were difficult, often resulting in the disease being overlooked. Therefore, many patients presented with typical CH symptoms and then had delayed psychomotor development (42, 43). Nakajima *et al.* surveyed 497 patients with cretinism who were treated for 5 yr from January 1973 to December 1977 (43). The age at the start of treatment was within 1 mo after birth in 6.8%

of patients and within 3 mo after birth in 19.8% of patients. Mental retardation with an IQ < 75 was present in 43% of patients, while 33.3% of patients had an IQ \geq 90; that is, about two-thirds had mental retardation or borderline mental retardation after treatment. An IQ \geq 90 was found in 28.2% of children who were aged \geq 1 yr at the initial visit, but an IQ \geq 90 was found in 59.3% of children aged < 3 mo at the initial visit, which was significantly better. Regarding body growth and development, the incidence of severe short stature (< -3SD) decreased from 45% to 11.8% as a result of treatment, but about 30% of patients had a short stature (< -2SD). These results indicate the importance of early diagnosis and treatment based on mass screening.

Naruse *et al.* developed a radioimmunoassay (RIA) for TSH measurement in dry filter blood in 1975 and started mass screening for CH using this measurement, which is more effective than T4 measurement (42). CH was added to the public program of neonatal mass screening for phenylketonuria, and screening was conducted at public expense (4, 42). In the late 1980s, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed and widely utilized for mass screening (44). At present, almost 100% of neonates undergo mass screening. The intelligence prognosis of patients with CH has been significantly improved by mass screening, and few patients now have irreversible mental retardation or growth failure (3, 5, 45–47).

2-2. Current status of neonatal mass screening

Recommendation

2-2-1. CH mass screening is performed using TSH measurement. Filter blood drawn from the external marginal part of the foot pad at 4 to 6 d of age should be used as a sample. Filter blood TSH should be presented as a whole blood concentration. However, if TSH is presented as a serum concentration, TSH as the whole blood concentration should also be added.

A neonate with TSH exceeding 15–30 mIU/L in his/her first blood sample should immediately be referred to a hospital designated by the local government for a detailed examination. (Note 1-1) 1 (●●●)

2-2-2. If TSH is 7.5–15 mIU/L, a recalled blood sample should be tested at the facility that performed the first blood test. If the TSH in the recalled blood test is higher than the cutoff level of the test facility, the neonate should undergo a detailed examination. (Note 1-2) 1 (●●○)

(Note 1-1) The incidences of CH, transient CH and false-positive findings change with the cutoff levels. Therefore, an appropriate cutoff level for each area should be determined based on previous results. To prevent a delay in treatment due to diagnosis requiring a second blood test, the cutoff level for the first blood test should be set in a detailed examination.

(Note 1-2) A third blood test is performed in some areas to limit the number of subjects requiring a detailed examination. It is important for a test facility to give a full explanation and instructions to parents without prolonging the mass screening step using filter blood. Expert opinion is that the age at the time of the second blood test should be at least 14 d.

Additional notes: precautions in mass screening

1) The blood sampling age for low birth weight infants and neonates in a neonatal intensive care unit (NICU) may be significantly older. Blood sampling is performed at the designated age of 4 to 6 d if possible because CH mass screening is not affected by feeding. For precautions for low birth weight infants, see other items.

2) Early detection requires routine validation of transport of samples from blood sampling facilities, measurement in test facilities, information on abnormal results, a second blood sampling for subjects who are positive in mass screening, notification of a visit to a facility for a detailed examination, and smooth reception in medical facilities.

3) Iodine-containing disinfectants used in the perinatal period increase the positive rate. Countermeasures are difficult, but the situation

should be recognized. If there is no difference in performance between disinfectants, iodine-containing disinfectants should not be used.

2-2-3. Mass screening with simultaneous measurement of TSH and FT4 can identify central CH, but mass screening with TSH alone cannot identify this condition. 2 (●●●)

2-2-4. Some cases of CH are not detected in mass screening. 1 (●○○)

Explanation

The previous guidelines recommended that a subject with TSH > 30 mIU/L (whole blood) in his/her first blood sample should immediately undergo a detailed examination (6). In the United States, TSH \geq 30 mIU/L is also generally used as the threshold for a detailed examination (1, 10, 48). Based on the 1998 guidelines, > 30 mIU/L in the first blood test is used to indicate the need for a detailed examination in many regions in Japan, but this is not followed nationwide (42, 49, 50). Minamitani *et al.* conducted a survey of 47 test facilities in 2008 (that is, after publication of the 1998 guidelines) to understand the conditions of mass screening (50) and compared the results with those of the 1995 survey by Niimi *et al.* (48). In 2008, the percentage of facilities that used a TSH level > 30 mIU/L (whole blood) to indicate the need for an immediate detailed examination was 89.4%, while it was 52.9% in 1995. Of the patients with TSH \geq 30 mIU/L in their first blood test, 138 were diagnosed with CH, and the predictive value of 56.8% was higher than that in 1995. Based on the assumption that the TSH cutoff level was decreased to 30 mIU/L in test facilities with a previous cutoff > 30 mIU/L, the number of detailed examinations increased by 0.75 patients per facility, and the rates of detailed examinations and detection of CH in these examination increased by 0.002% and 3.6%, respectively (50).

The Tokyo Metropolitan Government set the TSH cutoff level for CH at 25 mIU/L (51) and found

that 35 patients who underwent mass screening needed an immediate detailed examination; 28 of these patients then started treatment, while 7 were untreated. Sixteen patients with persistent CH continued treatment, 7 were diagnosed with an unknown disease type, 7 were diagnosed with transient hypothyroidism, and 5 were found to be normal. A TSH cutoff of 30 mIU/L for a detailed examination would have resulted in delayed treatment for 5 patients. The Chiba Prefectural Government set the TSH cutoff level for a detailed examination at 15 mIU/L (whole blood), and patients with persistent CH were found among subjects with TSH of 15–30 mIU/L detected in mass screening (52).

The survey by Minamitani *et al.* showed that 73.2% and 62.3% of CH patients had TSH \leq 30 mIU/L in filter blood in their first and recalled blood tests, respectively, and these rates were higher than those in 1995 (50). In a study in Italy, TSH cutoff levels of 12 and 20 mIU/L resulted in incidences of CH of 1/1,816 and 1/2,654, respectively (53). Follow-up showed that the incidence of orthotopic CH increased, and about 20% of cases were transient CH; however, about 40% were mild subclinical CH with increased TSH (5.0–9.9 mIU/L) due to discontinuation of treatment. In a study in Argentina, the incidence of CH increased from 1/2,904 to 1/2,412 when the TSH cutoff level was decreased from 15 to 10 mIU/L (54). The incidence of hypoplasia and ectopic CH decreased, while the incidence of orthotopic CH increased. In a study with the first cutoff level at 6 mIU/L in the United Kingdom, TSH in the recalled blood test also increased in term infants (55). However, an extreme decrease in cutoff level is not a standard for severe CH requiring immediate treatment, and the meaning of mass screening at this level has been questioned (39). Therefore, there is a need to determine how to unify the TSH cutoff levels in the first and recalled blood tests in mass screening in Japan.

In almost all Japanese facilities, TSH is determined in mass screening. In North America,

mass screening has been performed with T4 measurement in the first sample, followed by TSH measurement, but mass screening with TSH measurement is currently more common due to improved sensitivity of the TSH assay. In facilities in some regions in Japan, TSH and FT4 are simultaneously measured, and the effectiveness of this procedure has been shown (56–58). TSH+FT4 measurement permits identification of pituitary (secondary) and hypothalamic (tertiary) hypothyroidism (central CH). The incidence of central CH from 2000 to 2004 in Sapporo was 1/13,872 births (59), and the incidence in Kanagawa was recently reported as 1/30,000 births (58). The FT4 cutoff in Kanagawa was set at 0.7 ng/dL (serum), which was slightly low, and therefore the sensitivity may be low (58). A study in the Netherlands in 2005 reported an incidence of 1/16,404 births (60).

If central CH is detected in mass screening, complication of other anterior pituitary hormone deficiencies can be diagnosed earlier (1, 55–62). The incidence of central CH is lower than that of primary CH; but is similar or higher than that of phenylketonuria (60), and the costs of TSH measurement and detection of central CH were reported to be \$6353 and \$11,206 per CH patient, respectively, which were considered to be appropriate for cost-benefit perspective (60). In mass screening in Japan, Adachi et al. found that the cost when FT4 was added to the current system increased only by the cost of reagent for FT4 measurement; therefore, the increased detection of CH improved the cost-benefit ratio from 4.96 to 3.82 (63). The rate of recalled blood tests after simultaneous blood sampling of FT4 and TSH is about 1%, whereas that after TSH mass screening is about 0.3% (1). It remains uncertain whether both measurements are useful because TSH mass screening has sufficient sensitivity for detection of severe CH of thyroid origin.

Some CH cases are not detected in mass screening. In a national survey in 1999, Inomata *et al.* identified 35 patients with CH who were

not found in mass screening, with an incidence of about 1/750,000 (64). The causes of failure to identify these patients included delayed TSH elevation, measurement-related problems; and paperwork. Nagasaki *et al.* performed a thyroid function test on patients' siblings after diagnosis of CH and found that siblings of several patients had CH (65). Therefore, a child with high TSH in the first mass screening and normal TSH in the second test should be carefully followed up with tests that include family consultation.

2-3. Handling of premature and low birth weight infants Recommendation

- 2-3-1. Premature neonates and low birth weight infants (< 2,000 g) should undergo a second mass screening [1] one mo after birth, [2] when their body weight reaches 2,500 g, or [3] at discharge from the hospital, even if data in the first mass screening at age 4-6 d is within the normal range. 1 (●●●)
- 2-3-2. Infants with delayed TSH elevation in the second mass screening should undergo a detailed examination. 1 (●●●)
- 2-3-3. Hypothyroxinemia in low birth weight infants should not be treated with levothyroxine sodium (L-T4). 2 (●○○)

Explanation

The feedback system of the hypothalamic-pituitary-thyroid axis matures with gestational age and is mature at birth; however, the system is not mature in premature and low birth weight infants (66). Hypothyroxinemia without increased TSH is sometimes caused by administration of dopamine, high-dose steroid therapy, undernutrition; and exchange transfusion (67). CH with delayed TSH elevation, which is diagnosed as CH at a later stage when TSH in the first filter blood sample is less than the cutoff level, is common in premature and low birth weight infants (34, 68, 69). Therefore, a neonate with a birth weight of < 2,000 g should undergo a second mass screening at one mo after

birth, when his/her body weight reaches 2,500 g, or at discharge from the hospital (70).

A survey by Kamitaki *et al.* showed that 150 of 391 infants who underwent a second blood test underwent a detailed examination, of which 51 were diagnosed with CH (71). In a report from the Kanagawa Prefectural Government, 1,184 patients underwent a second blood test in 2000, and 5 were diagnosed with CH (72). Other studies show incidences of delayed TSH elevation in the second blood test of 1/58 in extremely low birth weight infants and 1/95 in low birth weight infants, with 3 infants treated with thyroid hormone (73). In a further study, 48 of 2,117 infants with increased TSH in their second blood test were diagnosed with transient hypothyroidism, and 2 mo later, 18 were still being treated with thyroxine (74). These CH patients do not always need life-long treatment, but patients with positive results in their second blood test should undergo a third blood test or a detailed examination at a test facility following procedures established by local governments that conduct mass screening.

Hypothyroxinemia requires differentiation from CH with delayed TSH elevation. More than 50% of low birth weight infants before 30 wk of gestational age have hypothyroxinemia, and the more premature the infants, the severer the thyroxine decrease. In comparison with the decrease in thyroxine, FT4 is slightly decreased. Therefore, evaluation using blood FT4 is preferable to avoid the effect of decreased blood thyroxine-binding globulin (TBG) (75). Hypothyroxinemia is difficult to differentiate from CH with delayed TSH elevation; therefore, careful follow-up is required. Infants with hypothyroxinemia usually return to normal within 6 to 10 wk after birth and develop normally without treatment. Many studies show that L-thyroxine (L-T4) has a poor effect on severe hypothyroxinemia (76–78), and administration of L-T4 to premature infants in Japan has been suggested to cause late onset circulatory collapse (79, 80). The evidence is incomplete, but the

Guidelines recommend that hypothyroxinemia in low birth weight infants should not be treated with L-T4.

3. Diagnosis and Severity of CH in a Detailed Examination

Recommendation

- 3-1. CH should be diagnosed from the results of neonatal mass screening, clinical symptoms, imaging and thyroid function tests in a detailed examination. 1 (Consensus)
- 3-2. The severity of CH can be evaluated using the following items:
 - 1) Clinical evaluation of thyroidism using the following checklist: 1) prolonged jaundice, 2) constipation, 3) umbilical hernia, 4) poor body weight gain, 5) dry skin, 6) sluggishness, 7) macroglossia, 8) hoarseness, 9) cold extremity, 10) edema, 11) wide posterior fontanelle, and 12) goiter.
 - 2) The approximate standards for the serum FT4 level are most severe, < 0.4 ng/dL; severe, 0.4 to < 0.7 ng/dL; and moderate, 0.7 to < 1.5 ng/dL. The normal range for FT4 differs among test facilities (see Explanation below).
 - 3) Thyroid ultrasonography.
 - 4) Distal femoral nucleus. 1 (●●●)
- 3-3. Infants with TSH \geq 10 mIU/L at < 6 mo after birth or TSH \geq 5 mIU/L at 12 mo after birth have abnormalities and can be defined as cases of subclinical CH. (Expert opinion)
- 3-4. If serum thyroglobulin (Tg) is low (< 10 ng/mL), thyroid agenesis and Tg deficiency are suspected as indicators of severe CH. 1 (●●○)

4. Criteria for Initiation of CH Treatment

Recommendation

- 4-1. Criteria for starting treatment immediately
 - 1) If a case has \geq 2 items on the checklist, the thyroid gland cannot be identified by ultrasonography; or goiter is found, treatment should be started immediately.

- 1 (●●●)
- 2) If serum TSH is ≥ 30 mIU/L or TSH is 15–30 mIU/L with low FT4; despite no findings in 1), Treatment should be started immediately. Attention should be paid to the different normal ranges of FT4 among test facilities (see Explanation below). 1 (●○○)
- 3) If filter blood TSH is ≥ 30 mIU/L or TSH is < 30 mIU/L, there is ≥ 1 checklist item, or no distal femoral nucleus appears, treatment should be started immediately. 2 (●○○)
- 4-2. If no clinical symptoms are found, blood thyroid hormone is within the normal range, and serum TSH is < 15 mIU/L, a thyroid function test should be performed again. If TSH is > 10 mIU/L at 3 to 4 wk after birth, initiation of treatment should be considered. Even if treatment is started, administration of L-T4 may be discontinued at 3 yr of age and not restarted, and a thyroid function test should be performed again. It should then be determined whether to make an accurate diagnosis, including a disease-type diagnosis. If a patient is untreated, a thyroid function test should be performed again 1 to 2 wk later, and the patient should be followed up. 2 (●○○)

Explanation

1. Diagnosis and severity determination

1) Interview and examination at the first hospital visit

Family history: thyroid disease, particularly maternal pathology and thyroid disease, drugs used for treatment, interview regarding excessive intake of iodine-containing food, maternal thyroid function as required, thyroidal autoantibody, urine total iodine measurement.

Medical history: fetal imaging, exposure to massive iodine-containing disinfectants, nutrition.

Consultation: checklist as follows: 1) prolonged jaundice, 2) constipation, 3) umbilical hernia, 4) poor body weight gain, 5) dry skin, 6) sluggishness, 7) macroglossia, 8) hoarseness, 9)

cold extremities, 10) edema, 11) wide posterior fontanelle, and 12) goiter.

2) Tests at the first visit

Serum TSH and FT4 must be measured. Thyroid ultrasonography is performed when possible. The position and size of the thyroid gland should be determined by ultrasonography. For patients in the early infant stage, the easiest way is to measure the maximum transverse diameter (81) at the cross section at which the thyroid isthmus thickness is at its maximum. The normal values of the maximum transverse diameter are 23.5 ± 1.6 mm at < 1 mo after birth and 25.6 ± 1.6 mm at 1 mo after birth (81). However, ultrasonography cannot be performed easily in some test facilities; and this should not delay treatment in cases diagnosed based on mass screening, clinical symptoms and endocrine tests in detailed examinations.

A patient with ≥ 2 items on the checklist after consultation and examination is considered to have a severe condition (6, 82). Delayed appearance of the distal femoral nucleus in a mature infant at ≥ 38 wk gestational age indicates a severe condition, and a distal femur edge radiograph should be obtained. Lack of a bilateral or unilateral distal femoral nucleus in the radiograph indicates a lack of thyroid hormone in the fetal stage (82–85). Tamaru *et al.* and overseas groups have examined the normal size of the distal femur edge nucleus (83–85). If the thyroid gland cannot be identified by ultrasonography or goiter is found, the condition is severe (1, 6).

Serum Tg is low in patients with thyroid aplasia and Tg synthesis abnormality (12); and is abnormally high in patients with impaired thyroid hormone synthesis and hypothyroidism due to iodine excess (12). Tg is relatively high in an ectopic thyroid gland; but low in patients with maternal-derived antithyroglobulin (anti-Tg). Measurement of anti-Tg antibody is required if serum Tg is low.

3) Severity based on thyroid hormone level

The Guidelines classify serum FT4 < 0.4 ,

0.4 to < 0.7; and 0.7 to < 1.5 ng/dL as indicating most severe, severe and moderate cases, respectively, based on expert opinion. Inomata *et al.* defined serum FT4 < 0.7 ng/dL as severe and serum FT4 > 1.0 ng/dL as mild (6). The previous Japanese guidelines recommended treatment if FT4 is \leq 1.5 ng/dL, even if TSH is only slightly elevated (6). The European Society for Paediatric Endocrinology recently proposed a consensus of FT4 < 0.4, 0.4 to < 0.8, and 0.8 to 1.2 ng/dL for most severe, severe and moderate cases, respectively (12). However, no unified FT4 assay is used nationwide in Japan, and the normal range of FT4 differs among test facilities. There is also no normal range for neonates and infants. Therefore, diagnosis of moderate to most severe hypothyroidism using FT4 is based on each physician's experience.

2. Criteria for starting treatment

If a case has \geq 2 items on the checklist, appearance of the distal femoral nucleus is delayed, the thyroid gland cannot be identified by ultrasonography, or goiter is found, treatment should start immediately without waiting for the results of serum tests. Niimi *et al.* evaluated findings and thyroid function of subjects who were positive in mass screening at the first medical examination (81). Of patients who undergo an immediate detailed examination, those who meet the following criteria probably have hypothyroidism and should receive immediate treatment: 1) filter blood TSH \geq 30 mIU/L and 2) \geq 1 item on the checklist or no appearance of the distal femoral nucleus even if filter blood TSH < 30 mIU/L, blood TSH \geq 20 mIU/L in the second test, or blood TSH in the second test is \geq 15 but < 20 mIU/L higher than that in the first test.

If no symptoms in the checklist or a distal femoral nucleus is found; but serum TSH is \geq 30 mIU/L, TSH is 15–30 mIU/L and FT4 < 1.5 ng/dL even though the patient has not undergone thyroid ultrasonography; or if a test facility determines that FT4 is lower than that in normal infants, the patient should be treated

(6, 10, 12). There is no evidence-based study on the treatment policy for patients without clinical symptoms, serum FT4 within the normal range, and serum TSH higher than the normal range (\geq 5 to < 15 mIU/L). If TSH does not return to normal at 3 to 4 wk after birth, treatment is often started (expert opinion). However, some patients remain untreated, undergo thyroid function tests; and are carefully followed up. In such cases, it is difficult to differentiate among subclinical CH, transient infantile hyperthyrotropinemia, and persistent CH. As described in the section on subclinical CH, it has been suggested that infants with TSH \geq 10 mIU/L at <6 mo after birth and TSH \geq 5 mIU/L at 12 mo after birth should be followed up carefully and treated. However, it is unclear if 12-mo-old infants with TSH \geq 5 mIU/L should be treated, and follow-up without treatment may be appropriate. Evidence is required for this decision. If treatment is started, it may then be suspended if the patient is determined to be hyperthyroid. If treatment continues, it should be discontinued at the age of 3 yr and not restarted; at this time, the thyroid system should be reevaluated, and a formal diagnosis, including a disease-type diagnosis, should be considered.

5. CH Treatment and Monitoring

Recommendation

- 5-1. Treatment should be started with levothyroxine sodium (L-T4) at 10 μ g/kg/d once a day, or at 15 μ g/kg/d for most severe patients. 1 (●●●)
- 5-2. A patient with moderate/subclinical CH can be treated with L-T4 at 3–5 μ g/kg/d. (Expert opinion)
- 5-3. Oral administration of L-T4 is possible in the morning or evening, or before or after a meal. L-T4 should be taken at the same time every day. For neonates and infants, L-T4 should be administered with a small amount of water, breast milk or milk. Substances inhibiting L-T4 absorption include soy milk,

iron preparations, calcium, stomachics and ion exchange resins. These agents should not be taken simultaneously with L-T4. 1 (●○○)

5-4. The target serum FT4 and T4 levels should be > 50% of the normal range by age. The target for TSH should be the normal range by age. 1 (●●○)

5-5. Follow-up is required at 1, 2 and 4 wk after initial administration, at 1-mo intervals until 1 yr of age, and then at 3- to 4-mo intervals until the adult stage. 1 (●○○)

Explanation

Treatment with levothyroxine sodium (L-T4, Thyradin S®) should be started at 10 µg/kg/d, or at 15 µg/kg/d for most severe CH (6, 10, 12, 86). Moderate and subclinical CH should be treated at 3–5 µg/kg/d because these patients often become hyperthyroid after receiving L-T4 at 10 µg/kg/d (expert opinion). It is important to pay attention to thyroid hormone and clinical symptoms and prevent underdose and overdose, regardless of the dose. L-T4 at 15 µg/kg/d can still cause overdose in severe patients with orthotopic CH including DUOX2 abnormality, and a dose of 10 µg/kg/d is sufficient (expert opinion). Many severe patients return to normal with administration of FT4 and T4 within 3 d and TSH within 2–4 wk at 10–15 µg/kg/d (47, 86). Early normalization of thyroid hormone is important for the intelligence prognosis (5, 44–46, 86–88).

IQ improved after introduction of mass screening in Japan. The mean IQ in the first nationwide survey (1991) (44) was 97.5 ± 14.8 (n = 81), and that in the second survey (1994) was 99.9 ± 13.7 (n = 151) (46). An overseas survey at the time patients became adults showed a marked decrease in IQ in severe patients. The dose at the start of treatment was 5–8 µg/kg/d, and treatment initiation was sometimes delayed. An initial dose of 10–15 µg/kg/d is now recommended, and treatment should start within 2 wk after birth. This protocol has steadily improved the outcome of intelligence in CH infants. In Japan, the most

recent national survey of children with CH was performed in 2003 (5). The subjects were children who were found to have CH from 1994 to 1999. The mean age at the first visit was 17.3 d (limited to direct examination), and the initial dose was ≥ 10 µg/kg/d in more than a half of severe patients. DQ/IQ at 1 to 5 yr old ranged from 104.1 to 107.3, excluding patients with serious complications, indicating better results than those in the earlier surveys described above.

After the initial dose, the appropriate maintenance dose per body weight gradually decreases with age: 5–10 µg/kg/d in the infant phase, 5–7 µg/kg/d at 1–5 yr of age, and 4–6 µg/kg/d at age 5–12 yr (89). The indicators for treatment in the previous Japanese guidelines were serum TSH in the normal range and FT4 at the upper limit of the normal range by age (6). The doses proposed by the American Academy of Pediatrics and the European Society for Paediatric Endocrinology are almost the same as those in Japan and are from 50% of the normal range to the upper limit of the normal range (10, 12). Therefore, based on the above doses, the doses are adjusted to maintain TSH and FT4 within these ranges. Some patients have serum TSH of 10–20 mIU/L, and their levels do not normalize despite initial treatment; however, many of these cases are treated with a low dose of drugs, and an increased dose should be considered. There are also rare children with a reduced inhibitory effect of FT4 on TSH (90, 91). Therefore, patients should be carefully examined to confirm whether administration is excessive due to TSH within the normal range.

Regarding monitoring intervals in Japan, thyroid function is usually evaluated by blood sampling at 1, 2 and 4 wk after starting treatment. Patients are then followed up at 1-mo intervals until 1 yr of age, and at 3- to 4-mo intervals from the age of 3 yr until adolescence (6). Results at one facility showed that patients were monitored once a mo from 6 mo after birth until 1 yr of age, but that 35% of patients did not reach the TSH and FT4 target ranges with

CH treatment; therefore, it was proposed that patients be followed up more frequently until 1 yr of age and that the dose should be adjusted (92). It is desirable to shorten the follow-up interval to every month if the L-T4 dose is revised, thyroid hormone levels are abnormal; and there is poor compliance (6, 10, 12). Patients in the adult stage are usually followed up at an interval of 6 mo to 1 yr in Japan, and follow-up at this interval is reasonable (89).

Pediatric endocrinologists in Japan frequently administer L-T4 (Thyradin S®) as powder to neonates. However, if only tablets are available, the tablets may be ground into powder. Once a patient is old enough to take tablets, tablets may be administered. Thyradin S® is provided as 5 kinds of L-T4 tablets (12.5, 25, 50, 75 and 100 µg), which makes it easy to adjust the dose. However, 12.5- and 75-µg tablets have no score line, and therefore these tablets cannot be divided. Two levothyroxine sodium® tablets (25 and 50 µg) are available. Pediatric endocrinologists indicate that replacement of powders with tablets rarely induces significant changes in the thyroid hormone level in treatment of CH. The potency of Thyradin® (dry thyroid powder) is variable, and Thyradin® should not be used for CH treatment.

For neonates and infants, it is possible to administer drugs dissolved in a small amount of water, breast milk or formula. Substances inhibiting L-T4 absorption include soy milk, iron preparations, calcium, stomachics, and ion exchange resins (10). The Pharmaceutical Affairs Committee of the Pediatric Endocrine Society in the United States indicated that it is difficult to administer drugs to fasting neonates and infants; and that administration after feeding can improve compliance (93). The Society suggested that the dose can be set based on a thyroid hormone test if the administration time is constant (93). There is no study showing that fasting administration causes poor compliance after the neonate age, but empirically it is assumed that fasting administration may affect

patients. Therefore, it is recommended that drugs be taken after a meal at constant intervals (93). A clinical study in adults showed the efficacy of administration before sleep (94), but there is no similar study in children. The European Society for Paediatric Endocrinology recently proposed the consensus that L-T4 should be taken at the same time, including while fasting, after a meal, or in the morning or evening (12). Therefore, the Guidelines recommend that neonates and infants should not always take L-T4 while fasting, but older infants and adults should always take L-T4 at a certain time, with the dose method depending on the circumstances of the patient.

6. Examination of Other Anomalies and Symptoms Complicating CH

Recommendation

6-1. A thorough examination of symptoms is required in cases of CH complicated with cardiac malformation and delayed psychomotor development. 1 (●●○)

Explanation

CH patients are more likely to be complicated with congenital anomalies, particularly cardiac malformation including atrial septal defect, and other diseases with delayed psychomotor development, in comparison with the general population (95, 96). A study in Japan showed that 14.6% of patients with primary CH were complicated with cardiac malformation and congenital anomalies in the nervous and muscular systems (97). This study also showed that female patients were frequently complicated with cardiac malformation and congenital anomalies in the nervous and muscular systems, while male patients had significantly more congenital anomalies in the gastrointestinal and urinary systems. Therefore, a patient with primary CH should be examined for symptoms and manifestations associated with these congenital anomalies.

Patients with Down's syndrome often have

mild TSH elevation in the neonatal stage and thereafter (98, 99), and increased blood TSH cannot always be identified in neonatal mass screening. Patients with Down's syndrome also have a lower FT4 level than the normal range (98). Therefore, if a patient with Down's syndrome has increased blood TSH, it is necessary to determine whether the patient has true CH (100). Pendred syndrome (with or without goiter) and pseudohypoparathyroidism also cause mild or moderate TSH elevation at the neonatal stage, and these cases may be found in neonatal mass screening (101, 102). These two diseases are included in diseases to be differentiated from orthotopic CH (see the sections on genetic counseling and genetic diagnosis).

7. Diagnostic Imaging of the Thyroid Gland

Recommendation

- 7-1. Imaging should be performed to examine the cause of CH. 1 (●●●)
- 7-2. Thyroid ultrasonography should be performed as part of the first detailed examination when possible. 2 (●●●)
- 7-3. Thyroid scintigraphy can be performed only when feasible and is unnecessary in the neonatal stage, in which treatment is given the priority. When the disease type is determined, L-T4 is withdrawn, and performance of thyroid scintigraphy should be considered. 2 (●○○)

Explanation

Imaging using thyroid ultrasonography and scintigraphy is useful to determine the causes of CH. Real-time ultrasonography can be used in the neonatal phase. It is preferable to use a high-frequency (> 10 MHz) probe because the thyroid gland is a superficial organ. This method can differentiate dysgenesis from impaired synthesis, and it should be used in the first detailed examination when possible (1, 6, 10, 12, 81). However, there may be a delay in performing ultrasonography at some test facilities. If

ultrasonography is difficult to implement, diagnosis should be based on mass screening results, clinical symptoms and endocrine tests in a detailed examination, and treatment should not be delayed (6).

Onishi *et al.* showed that ultrasonography can differentiate between orthotopic CH and thyroid dysgenesis (81). Of 23 patients who were not confirmed to be orthotopic, 6 and 16 were diagnosed with thyroid aplasia and as ectopic, respectively, and one patient who was diagnosed as ectopic was found to be normal using scintigraphy. An ectopic thyroid gland can also be diagnosed by color Doppler ultrasonography at a rate of 90% (103). However, the specificity of ectopic diagnosis by ultrasonography differs among studies and ranges from 0% to 21% (104–106). In such cases, tissue is present at the site of the thyroid gland, and ultrasonography misidentifies this as an orthotopic thyroid gland (107, 108). Therefore, it may be difficult to diagnose a neonate as ectopic using ultrasonography.

Thyroid scintigraphy is reliable for definitive diagnosis of dysgenesis (ectopic, hypoplasia and aplasia) (109–111). In impaired thyroid hormone synthesis, isotope uptake returns to normal or is enhanced by thyroid scintigraphy, resulting in an enlarged thyroid. In such a case, impaired organification is evaluated by a perchlorate discharge test. Impaired organification is diagnosable by thyroid scintigraphy. However, if a patient has an abnormal iodide symporter, which is equivalent to impaired thyroid hormone synthesis, uptake is not recognized by thyroid scintigraphy. In such a case, aplasia should be examined by ultrasonography because uptake deficiency also occurs due to a TSH β genetic abnormality, a TSH receptor inactivated mutation, and an abnormal iodine symporter (111, 112).

Regarding the implementation and timing of thyroid scintigraphy, European and US guidelines recommend that scintigraphy be performed in the neonatal stage prior to

treatment because thyroid dysgenesis can be definitely diagnosed and an orthotopic thyroid with normal uptake can suggest transient CH (10, 12). However, scintigraphy is not generally used for CH diagnosis in the neonatal stage in Japan. The 1998 Guidelines for Mass Screening of Congenital Hypothyroidism in Japan specified performance of scintigraphy to diagnose the disease type at an age ≥ 3 yr (6). Therefore, the current Guidelines conform to this policy.

8. Reevaluation of Thyroid Function for Differentiation of Transient and Persistent CH and Disease-type Diagnosis

Recommendation

- 8-1. The thyroid system should be reevaluated after L-T4 withdrawal and the disease type should be diagnosed at 3 yr of age or older. 1 (●●●)
- 8-2. Reevaluation including disease-type diagnosis is required for patients who have received continuous treatment with L-T4 without determination of the cause of CH and for low birth weight infants treated with L-T4. 1 (●●○)
- 8-3. Disease-type diagnosis can be performed if the causes of impaired thyroid hormone synthesis, aplasia or hypoplasia are not determined by genetic tests. 2 (●○○)

Explanation

Reevaluation or disease-type diagnosis is required after L-T4 withdrawal, including differentiation of transient from persistent CH if definite causes of CH have not been identified, particularly for patients diagnosed with orthotopic CH by ultrasonography (6, 10, 12). It has been shown that 10% to 30% of patients diagnosed with orthotopic at the neonatal stage and given thyroxine have transient CH (10, 19, 113). Low birth weight infants diagnosed with CH and given thyroxine may have transient CH, and thus reevaluation and disease-type diagnosis are required. These should be conducted upon

completion of neuronal development at or after 3 yr of age (114).

Even if the diagnosis is aplasia, hypoplasia or ectopic thyroid gland by ultrasonography at the neonatal stage, images should be examined again by ultrasonography. Diagnosis of an ectopic thyroid gland may be difficult, as mentioned above, and thyroid scintigraphy is required for an accurate diagnosis. If CH is suspected due to a specific genetic mutation, neonatal goiter, impaired thyroid hormone synthesis, family history; or other characteristic symptoms before the age of 3 yr and confirmed by genetic diagnosis, reevaluation and disease-type diagnosis may not be necessary. However, it is preferable to determine the diagnosis independently.

The procedures for disease-type diagnosis are as follows: replace L-T4 with one-fourth the dose of liothyronine sodium for 4 wk (t.i.d.), measure ^{123}I thyroid uptake after withdrawal for 7–10 d, determine the saliva/blood iodine ratio, and perform a perchlorate discharge test, scintigraphy, serum TSH, FT4, FT3 and Tg measurements, and a TRH stimulation test. A definite diagnosis of aplasia, hypoplasia, ectopic thyroid gland, defect of hormone organification; and iodine concentration deficiency can be performed.

A patient who is normal in reevaluation or disease-type diagnosis is considered to have transient CH; but should be followed up because hypofunction may develop again. A patient diagnosed with transient infantile hyperthyrotropinemia will have increased TSH at a later stage that results in hypothyroidism, and such a patient should also be followed up (6).

9. Long-term Prognosis

9-1. Psychomotor development

Recommendation

- 9-1-1. Intelligence should be evaluated if mental retardation is found. Careful follow up is required for a patient with a mild developmental disorder and learning

disability. 1 (●●●)

9-1-2. Appropriate interventions are required for a patient with a developmental disorder and learning disability. 1 (●○○)

Explanation

As described in the section on treatment, the recommended initial dose of L-T₄ was 5–8 µg/kg/d in early mass screening, and the start of treatment was often delayed until 4–5 wk after birth. CH patients treated in this way had an IQ that was lower by 6–20 points in comparison with controls, and the prognosis was particularly poor in severe children with blood T₄ < 5 µg/dL at their initial visit. In Japan, the mean IQ in the first nationwide survey was 97.5 ± 14.8 (n = 81) (45), and that in the second survey was 99.9 ± 13.7 (n = 151) (46).

Patients have been treated with an initial dose of 10–15 µg/kg/d for the last 10 yr, with treatment starting within 2 wk after birth, and this approach has steadily improved the outcome of intelligence in CH infants (47). The latest nationwide survey in CH children in Japan published in 2003 (5), and it found that children discovered to have CH from 1994 to 1999 were 17.3 d old at their first visit (limited to direct examination) and that the initial dose was ≥ 10 µg/kg/d in more than a half of severe patients. The DQ/IQ at 1–5 yr of age was good, ranging from 104.1 to 107.3. As described above, serious intellectual disability due to CH has almost been eradicated; however, children with severe hypothyroid conditions during pregnancy may still have a mild IQ decrease.

Patients with severe CH also have problems with cognitive ability, behavior and attention deficit in adolescence and adulthood (5, 47). Furthermore, cognitive ability and school outcomes of severe patients are related to the starting time and dose of thyroxine (5, 115–118). Problems related to attention deficit may be linked to the transient thyroid hormone excess induced by an increased initial dose, resulting in adverse effects on the central nervous system

(119), but there is no definitive evidence for this. Asakura *et al.* examined emotion and behavior in 47 Japanese patients with persistent CH and 16 patients with transient CH (based on disease-type diagnosis) aged 4–15 yr and found no differences from healthy controls (120). An evaluation of QOL of Japanese adults with CH showed that patients identified in mass screening and treated appropriately led a normal social life (121).

9-2. Adult height, adolescence and fertility Recommendation

9-2-1. Information should be provided to show that a good adult height can be attained by appropriate treatment and good drug compliance. 1 (●●●)

9-2-2. Information should be provided to show that good adolescent growth and fertility can be obtained with appropriate treatment and good drug compliance. 1 (●●●)

9-2-3. Information should be provided that indicates no difference in QOL between adult CH patients and the general population. 1 (●●○)

Explanation

The adult height of CH patients identified in mass screening has been studied in many countries, including Japan (122–125). Kanagawa Children's Medical Center conducted an analysis of CH patients and found no difference in adolescent growth patterns, based on age at the start of adolescence, peak growth rate; and age at peak growth rate, in comparison with reference data for the general population; and no significant correlation between adult height and severity of hypothyroidism or the age of starting treatment (123). Sato *et al.* analyzed height and body weight in 2341 CH patients (1030 males and 1311 females) registered in the Medical Aid Program for Chronic Pediatric Disease of Specified Categories in 2002 and found neither short stature nor obesity and normal growth and

constitution (124).

After the QOL of adult CH patients was examined in Japan, similar studies were conducted in two other countries. A study in the Netherlands showed that the QOL of patients who were born in 1981–1982 after mass screening started was relatively low (126), with the higher the severity, the stronger the tendency for a lower QOL. A study of QOL in patients after mass screening started in France indicated that the QOL of CH patients slightly decreased (127). It is possible that these subjects were patients when mass screening started and that they may have received a small L-T4 dose, delayed start of treatment; and suboptimal follow-up. The data in the Netherlands and France showed a slight decrease in QOL, in contrast to the results in Japan. This difference may also depend on the evaluation methods and differences in health-care conditions. Further studies are required in Japan to evaluate differences in QOL due to a high dose of L-T4 and early treatment; compared with earlier treatment after mass screening. A recent study in France also showed that the reproductive potential of females with severe CH was lower than that of normal women (128), and this also requires further examination.

10. Genetic Counseling and Diagnosis of CH

Recommendation

- 10-1. Genetic counseling can be provided that includes information indicating that thyroid dysgenesis is often sporadic and the risks for recurrence are low. 2 (●●○)
- 10-2. It can be made clear that the disease is due to dysgenesis or impaired hormone synthesis. 2 (●○○)
- 10-3. If iodine excess is excluded and impaired hormone synthesis is the definitive diagnosis, about 50% of cases develop due to autosomal recessive genetic abnormality. Therefore, it should be explained that the probability of morbidity in another child is up to 25%. 2 (●●○)

Explanation

Nonfamilial thyroid dysgenesis is almost always sporadic (129, 130), but unknown genetic factors may exist because the incidence of familial dysgenesis is more than 15-fold higher than that of sporadic cases (131). The first relative of a patient with thyroid dysgenesis may have normal thyroid function, but often has anomalies associated with fine thyroid malformation (132). Genes causing CH and characteristic findings due to genetic anomalies are listed in Table 2. Symptomatic thyroid dysgenesis and TSH resistance with and without various complications develop due to mutation of *NKX2-1*, *FOXE1*, *PAX8*, *NKX2-5*, *TSH-R* and *GNAS* (pseudohypoparathyroidism 1a). Impaired hormone synthesis develops due to mutation of *SCL5A5/NIS* (iodide transport defect), pendrin (*SCL26A4/PDS*, Pendred syndrome), thyroglobulin (*TG*), thyroid peroxidase (*TPO*), *DUOX2*, *DUOX2A*, and iodotyrosine deiodinase (*IYD/DEHAL1*) (133). These mutations indicate autosomal recessive inheritance. Heterozygous mutation of *DUOX2* and homozygous mutation of *DUOX2A* can cause transient CH in the neonatal stage (16, 17, 30). Pendred syndrome is associated with deafness (101); however, other genetic abnormalities in impaired hormone synthesis do not lead to other disorders.

In Japanese patients, the detection rate of genetic abnormality in thyroid dysgenesis and impaired hormone synthesis is about 20% (134, 135). Therefore, if there are findings that suggest the specific abnormalities above, genetic analysis may be considered; however, genetic tests are available only at the research level. Neurologic symptoms and respiratory disease require attention in patients with *NKX2-1* mutations (136). *PAX8* mutations are complicated with renal and urologic disease; therefore, echography should be performed (137). *SLC26A4/PDS* mutations require a careful audiometric examination. *TPO* or *TG* mutations infrequently lead to cancer from goiter in the adult stage (138, 139). If a *GNAS* mutation is detected, endocrine

Table 2 Characteristic findings and genes related to congenital hypothyroidism and thyroid hormone insufficiency

	Function	Gene	Chromosome	Genetics	Characteristic findings
1. Thyroid dysgenesis					
TTF1	Transcription factor	<i>NKX2-1</i>	14q13	AD	Respiratory failure, chorea
TTF2	Transcription factor	<i>FOXE1</i>	9q22	AD	Cleft palate, spiky hair, choanal atresia
NKX2.5	Transcription factor	<i>NKX2.5</i>	5q35	AD	Persistent foramen ovale
PAX8	Transcription factor	<i>PAX8</i>	2q13	AD	Unilateral kidney aplasia (rare)
TSH receptor	Receptor	<i>TSHR</i>	14q31	AD/AR	No characteristic findings
2. Central hypothyroidism					
TSH β	TSH	<i>TSHB</i>	1p13	AR	Isolated TSH deficiency, hypogenesis of thyroid
TRHR	TRH receptor	<i>TRHR</i>	8q23	AR	Low TSH and PRL responses after TRH stimulation
IGSF1	Unknown	<i>IGSF1</i>	Xq25	X-linked recessive	TSH and PRL deficiency, testicular enlargement, delayed puberty
Combined pituitary hormone deficiency (CPHD)	Transcription factors, growth factors, etc.				
3. Dyshormonogenesis					
NIS	Active iodide transport	<i>SLC5A5</i>	19p13	AR	Reduced uptake of iodide, reduced ratio of iodide of saliva to serum
Pendrin	The passive efflux of iodide	<i>SLC26A5</i>	7q31	AR	Bilateral sensorineural hearing loss (associated with vestibular dysfunction), multinodular goiter
TG	Matrix for hormone synthesis	<i>TG</i>	8q24	AR	Goiter, undetected or very low serum TG
TPO	Organization	<i>TPO</i>	2p25	AR	Organization defect
DUOX2	Hydrogen peroxide generation	<i>DUOX2</i>	15q15	AR/AD	Permanent or transient, partial organization defect
DUOXA2	Hydrogen peroxide generation	<i>DUOXA2</i>	15q15	AR	Partial organization defect
Iodotyrosine deiodinase (IYD)	Recycling of intrathyroidal iodine	<i>DEHAL1</i>	6q25	AR	Goiter, undetected by neonatal mass screening
4. Thyroid hormone insufficiency					
TR β	Thyroid hormone receptor	<i>THRB</i>	19p13	AD	High T4, high T3, no suppression of TSH, tachycardia, goiter
TR α	Thyroid hormone receptor	<i>THRA</i>	3p24	AD	Growth retardation, constipation, delayed bone maturation, psychomotor developmental delay
MCT8	Thyroid hormone transporter	<i>SLC16A2</i>	Xq13	X-linked recessive	Low T4, high T3, severe developmental delay, nystagmus
SBP2	Thyroid hormone metabolism defect	<i>SECISBP2</i>	9q22	AR	High T4, low T3, normal TSH, developmental delay

function should be examined (140).

In Japanese patients, if iodine excess is excluded and impaired hormone synthesis is the definitive diagnosis, about 50% of cases have an autosomal recessive genetic abnormality (135). In such cases, it should be explained that the probability of morbidity of another child is up to 25%. However, the genetic cause is only identified in 10% to 20% of all CH cases, even when using sophisticated genetic analyses.

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Appendix

1. Development process

1-1. Understanding current conditions

A forum for clinical questions was organized by the Japanese Society for Pediatric Endocrinology from October 10 to 30, 2012.

1-2. External evaluation

The draft guidelines were made openly available on a website for members of the Japanese Society for Pediatric Endocrinology from December 6, 2013, to January 5, 2014, to solicit opinions, and a revised draft was developed on March 30, 2014, based on the received opinions. The validity of the guidelines was discussed in the Guidelines Committee, including external members, and revisions were made based on the proposal of the Guidelines Committee (April 22, 2014). This revision was

approved by the Board of the Society on May 23, 2014, and published online in Japanese (http://jspe.umin.jp/medical/files/CH_gui.pdf).

1-3. Consultation with relevant societies

Solicitation of clinical questions from the Japanese Society for Mass Screening was performed from October 10 to 30, 2012, by sending e-mails to members of the society. The draft guidelines were published on a website for members of the Japanese Society for Mass Screening from December 6, 2013, to January 5, 2014, for solicitation of opinions. A revised draft was developed on March 30, 2014, with consideration of the received opinions.

2. Revision schedule

The Guidelines are planned to be revised within 3 years after disclosure. In particular, issues for which no evidence is currently available are scheduled to be discussed and revised as required if a relevant study providing evidence is published. The committee for revision will be organized by the board of the Japanese Society for Pediatric Endocrinology. If new conditions occur that may have critical effects on the Guidelines, the board of the Japanese Society for Pediatric Endocrinology may decide to revise the Guidelines immediately as "Recommendations."

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