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Special Report

Guidelines for Newborn Screening of Congenital Hypothyroidism (2021 Revision)

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Abstract. Purpose of developing the guidelines: Newborn screening (NBS) for congenital hypothyroidism (CH) was started in 1979 in Japan, and early diagnosis and treatment improved the intelligence prognosis of CH patients. The incidence of CH was once about one in 5,000–8,000 births, but has been increased with diagnosis of subclinical CH. The disease requires continuous treatment and specialized medical facilities should conduct differential diagnosis and treatment in patients who are positive by NBS to avoid unnecessary treatment. The Guidelines for Mass Screening of Congenital Hypothyroidism (1998 version) were developed by the Mass Screening Committee of the Japanese Society for Pediatric Endocrinology in 1998. Subsequently, the guidelines were revised in 2014. Here, we have added minor revisions to the 2014 version to include the most recent findings. Target disease/conditions: Primary congenital hypothyroidism**.** Users of the Guidelines: Physician specialists in pediatric endocrinology, pediatric specialists, physicians referring pediatric practitioners, general physicians, laboratory technicians in charge of mass screening, and patients.

Key words: congenital hypothyroidism, newborn screening, guideline

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Introduction

Thyroid hormones are essential for neurodevelopment in the fetal and early neonatal phases. Congenital hypothyroidism (CH) causes neuronal migration disorder due to thyroid hormone deficiency and serious CH delays psychomotor development. CH is preventable by early detection and treatment. Newborn screening (NBS) is performed worldwide and is useful for detection of CH (1, 2). NBS for CH was developed in 1979 in Japan and has been effective (3–5). Guidelines for Mass Screening of Congenital Hypothyroidism were developed by the Japanese Society for Pediatric Endocrinology in 1998 (6, 7). Subsequently, the incidence of CH has increased in several regions and eutopic, slightly impaired synthesis has also increased (8, 9). Details regarding the prognosis of adult CH and several genetic causes have also emerged. The American Academy of Pediatrics published clinical guidelines for CH in 2006, and the European Society for Paediatric Endocrinology held a meeting to reach a clinical and therapeutic consensus on CH and revise previous guidelines in 2010 (10, 11), publishing new guidelines in 2014 (12). In Japan as well, based on new data from Japanese and foreign studies, we have published the Guidelines for Mass Screening of Congenital Hypothyroidism (2014 revision) (13).

Novel findings that have since become available and the revisions to the European Society for Paediatric Endocrinology guidelines (14) have prompted us to publish the Guidelines for Newborn Screening of Congenital Hypothyroidism (2021 revision). The 2021 revision includes updates regarding the diagnostic and treatment guidelines for primary CH. The guidelines on central CH were summarized as a column.

Recommendations in the guidelines include a "grade" and an "evidence level". The grade shows the strength of the recommendation based on findings in published studies, and the evidence level indicates the level of the study. Expert opinions are included in the guidelines if there are no findings in studies or if the opinions are considered appropriate.

Grade level

1. Major recommendation: Most patients receive benefits.
2. Minor recommendation: Many patients receive benefits. Requires consideration and selection based on the patient's conditions.

Evidence level

●○○ Low: Evaluation of case reports without controls
●●○ Medium: Cohort study without controls
●●● Cohort study with controls, nonrandomized comparative study
Consensus: Widely recognized ideas, even if a study has not been performed

1. Definition of CH

Recommendation

1-1. "Primary CH" should be used as a generic term for congenital thyroid hormone deficiency due to a morphological abnormality or dysfunction of the thyroid gland that develops in the fetal or perinatal period. 1 (Consensus)
1-2. CH may occur due to thyroid hormone insufficiency. (Consensus)
1-3. Most cases of CH are permanent, but transient CH also occurs. Treatment should be the priority for hypothyroid patients. 1 (●●●)
1-4. CH includes subclinical CH. However, there is a lack of consensus on the definition of subclinical CH. It is difficult to define subclinical CH, particularly in the neonatal period, because hypothyroidism may then suddenly become apparent. 2 (●○○)

Explanation

1) CH

CH is a generic term for congenital thyroid hormone deficiency due to a morphological abnormality or dysfunction of the thyroid gland that develops in the fetal or perinatal period. Thyroid hormones are essential for nerve myelination in the fetal, neonatal, and infant periods. An insufficient thyroid hormone level causes irreversible intellectual disability. In addition to direct involvement in bone maturation, thyroid hormones stimulate growth hormone secretion and enhance production of IGFI. Therefore, thyroid 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 insufficiency have been determined as the pathogenesis 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 hormones (selenocysteine insertion sequence-binding protein 2 [SBP2]).

Diseases and conditions associated 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 (13–20).

2) Transient CH

Patients with transient CH exhibit continuous, normal thyroid function after a transient increase in TSH and decreased in FT4 concentrations (1, 6). In North

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Table 1. Pathology and diseases associated with elevated TSH levels in newborns screening

1. Congenital hypothyroidism
1.1. Permanent hypothyroidism
• Primary hypothyroidism (thyroid origin) Dysgenesis (agenesis, hypoplastic, hemiagenesis, ectopic gland, etc.) Dyshormonogenesis
• Peripheral thyroid hormone insufficiency Thyroid hormone resistance, thyroid hormone transporter abnormality (MCT8 deficiency), etc.
1.2. Transient hypothyroidism
• Severe iodine deficiency
• Iodine excess
• Administration of anti-thyroid drugs to mother
• Transplacental transfer of TSH stimulation-blocking antibodies
• Loss of function variants of DUOX2 gene and DUOXA2 gene
• Transient infantile hyperthyrotropinemia
• Low birth weight infants
2. Others
• Pseudohypoparathyroidism
• Acrodysostosis with hormonal resistance
• Infantile hepatic hemangioma
• Interference for TSH measurements (Anti-TSH antibody, anti-mouse IgG antibody, etc.)

America, 5% to 10% of children are positive for CH in NBS, or 1/50,000 births (1). However, a study in Israel (2002–2012) reported that among patients diagnosed with CH and treated before the age of 2, 41% exhibited an ectopic thyroid or agenesis, and 59% presented with a eutopic thyroid (47% permanent, 12% transient) (21). A study from France from 2002–2012 also reported that 54% of the children with a eutopic thyroid who tested positive by NBS had a transient form of CH (22). 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.

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 two weeks after birth. Neonates delivered by mothers with Graves' disease may have transient CH due to inhibition of the hypothalamic-pituitary axis caused by exposure to excessive thyroid hormone in the fetal phase (23).

③ Transfer of inhibiting antibodies from the mother TSH may be inhibited due to transfer of TSH stimulation-blocking antibody (TSBAb) from mothers with thyroid disease (9, 16, 24, 25). The action of TSBAb continues for three to six mo after birth. In approximately 570,000 newborns who underwent NBS in Hokkaido from 1981 to 1994, Harada *et al.* found one case of transient CH due to the transfer of maternal TSBAb (16). In a study in Niigata from 2002 to March 2010, four subjects exhibited transient CH due to maternal TSBAb and the incidence was 1/40,000 (25).

④ Low birth weight infant: Low-birth weight infants frequently exhibit transient CH (1, 6,10, 26–28). More details on low-birth weight infants are provided in other sections (see 2-3).

⑤ Iodine excess: Iodine deficiency is extremely rare in Japan, the leading iodine-consuming country in the world. Transient CH due to iodine excess is often found in Japan, with many case reports (6, 29, 30). Fetuses under 36 weeks of gestational age cannot suppress iodine uptake by the thyroid gland when exposed to iodine and exhibit low excretion of iodine from the kidney; consequently, they are likely to be affected by excess iodine. Iodine excess may be induced by disinfection with an iodine preparation, oily contrast media used for hysterosalpingography, food containing a high level of iodine, and povidone-iodine rinses. The effects of potassium iodide (approximately 50 mg) taken by a mother with Graves' disease on fetal thyroid suppression is reportedly weaker than that of antithyroid drugs (31). The Guidelines for the Treatment of Graves' Disease (2109 revision), edited by the Japanese Thyroid Association, recommends the use of potassium iodide as a pharmacotherapy in early pregnancy. Additionally, it is used frequently in Japan as treatment for Graves' disease in pregnant women (32, 33). Women who undergo hysterosalpingography with oil-soluble contrast media containing iodine exhibit an excess of iodine lasting six or more mo after the test; however, transient CH is not observed in all pregnant women who undergo hysteosalpinography. Notably, the incidence of CH is low in women receiving hysterosalpingography (34, 35). 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

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enzyme that produces H_2O_2, which is required for iodide organification in the thyroid gland. DUOXA2 is required to stimulate DUOX2 action. Some transient CH develops due to loss-of-function mutations in both alleles of the DUOX2 gene (18, 19) and mutation in both alleles of the DUOXA2 gene (36).

The importance lies in that transient CH, like permanent CH, is a form of hypothyroidism, and accordingly requires thyroid hormone replacement therapy. The intellectual quotient (IQ) of subjects with transient CH is low in areas with iodine deficiency (37, 38). A case of transient CH in which the cause is uncertain is difficult to differentiate from subclinical CH (defined below). Such a case is followed up carefully by a CH specialist when possible.

3) Subclinical CH

Subclinical CH is also referred to as compensated hypothyroidism. The pathogenesis has been identified in NBS with TSH as an indicator. Subclinical CH has no symptoms, i.e., it is a subclinical disease, but some patients may exhibit low thyroid hormone levels and are diagnosed with mild CH (1, 5, 6, 10, 39). Because these cases are called subclinical CH in some countries, the present guidelines also refer to mild CH as subclinical CH. However, it is difficult to diagnose subclinical CH in the neonatal period, as hypothyroidism becomes evident only after infancy in some cases. Therefore, infants in such cases should be very carefully followed up from birth until three mo of age.

Some infants with subclinical CH exhibit morphological abnormalities (hemiagenesis, enlargement, hypoplasia) of the thyroid gland and mutations of thyroperoxidase (TPO) and thyroid-stimulating hormone receptor (TSHR) genes (17). Patients with slightly high TSH levels may subsequently be diagnosed with permanent CH (40–42). However, there are no global consensus for the range of TSH considered abnormal, and diagnosis depends on clinician discretion. In a survey of pediatric endocrinologists, infants with TSH ≥ 10 mIU/L within six mo of birth (excluding neonates) and those with TSH ≥ 5 mIU/L at 12 mo after birth were considered to have abnormalities requiring treatment (43, 44). 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 (45).

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 (46). 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 within six mo of age and those with TSH ≥ 5 mIU/L at 12 mo of age were considered to have abnormalities and were diagnosed with subclinical CH. Because the survey did not cover the information on children of aged 6–12 mo, the patients of this age group are not represented in the definition. 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.

4) Transient infantile hyperthyrotropinemia

Transient infantile hyperthyrotropinemia is defined by the following criteria: 1) The patient has high serum TSH (determined in a specialized medical institution), excluding a high concentration in only dried blood specimen [DBS], and blood thyroid hormones are always within the normal range corresponding to age. 2) TSH levels returns to the normal range in the infant period (excluding an excessive response in a TRH stimulation test). 3) No cause of hypothyroidism (maternal administration of antithyroid drugs, inhibiting TBII, fetal imaging, maternal/neonatal exposure to excess 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 it is difficult to differentiate subclinical CH from resistance to pituitary thyroid hormone in the initial stage in infants with thyroid hormone within the normal range and elevated TSH (47). A patient diagnosed with transient infantile hyperthyrotropinemia should be followed up on because a subsequent increase in TSH may occur and result in hypothyroidism (6).

2. NBS

2-1. Effectiveness of NBS

Recommendation

2-1-1. CH screening should be conducted as part of a series of NBS. 1 (Consensus)

2-1-2. Prefectures and major city governments that conduct NBS should establish procedures for screening of inborn errors in metabolism and should develop a protocol to provide rapid and appropriate treatment for neonates who test positive by NBS. 1 (Consensus)

Explanation

Before the development of NBS, 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 exhibited delayed psychomotor development (48, 49). Nakajima *et al.* surveyed 497 patients with cretinism who were treated for five yr from January 1973 to December 1977

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(49). The age at the start of treatment was under one mo in 6.8% of patients and under three mo after birth in 19.8%. Intellectual disability with an IQ < 75 was present in 43% of patients, while 33.3% of patients exhibited an IQ ≥ 90; that is, about two-thirds of the patients exhibited intellectual disability or borderline intellectual disability after treatment. An IQ ≥ 90 was found in 28.2% of children who were aged one yr or older at the initial visit, but in 59.3% of children aged under three mo at the initial visit, showing a significant advantage of early treatment. Regarding body growth and development, the incidence of severe short stature (< –3 SD) decreased from 45% to 11.8% as a result of treatment, but about 30% of patients exhibited non-severe short stature (< –2 SD). These results indicate the importance of early diagnosis and treatment based on NBS.

Naruse *et al*. developed a radioimmunoassay for TSH measurement in DBS in 1975 and started NBS for CH using this method, which is more effective than T4 measurement (48). CH was added to the public health program of NBS for phenylketonuria and screening was conducted at public expenditure (4, 48). In the late 1980s, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed and widely utilized for NBS (50). At present, almost 100% of neonates undergo NBS. The intelligence prognosis of patients with CH has been significantly improved by NBS and few patients now have irreversible intellectual disability or growth failure (3, 5, 51–53).

Recent studies have suggested an increased incidence of CH detected by NBS (54–56). There are some possible reasons for this issue, such as a lower cut-off value, changes to the ethno-racial composition of the populations tested, and increased rates of preterm and low birth weight infants. There are no recent Japanese nationwide data on the incidence of CH. The incidence of CH before the start of the NBS was approximately 1/4,000–5,000 individuals (3, 48); however, according to the data of Hokkaido, Sapporo, Miyagi, Chiba, Hiroshima, Nagasaki, and Kagoshima in 1991–2000, the incidence of permanent CH is 1/2,631 individuals and that of transient CH is 1/2,183 individuals (57). According to foreign reports, the incidence of hypoplastic or ectopic CH remains unchanged from that in previous reports (54–56). In contrast, the incidence of eutopic CH, which is characterized by a normally developed and located thyroid gland, is increasing (54–56). Interestingly, the frequency of CH has increased during the 38 yr of NBS in Ireland, despite never changing the cutoff value for TSH (58). According to the same report, the incidence of CH has increased from 1/3,703 (1979–1991) and 1/2,439 (1992–2004) to 1/1,538 during the yr of 2005–2016; moreover, eutopic CH accounted for 47% of all cases during this recent period. The authors of the Irish study hypothesized that such an increase may be associated with an increase in low-birth-weight infants; the increase in the incidence of CH in Japan remains to be investigated in detail.

2-2. Current status of NBS

Recommendation

2-2-1. CH NBS is performed using TSH measurement. DBS drawn from the external marginal part of the foot pad at four to six days of age should be used as a sample. DBS TSH should be presented as a whole blood concentration. However, if TSH is presented as a serum concentration, the whole blood TSH concentration should also be added.
A neonate with TSH levels exceeding 15-30 mIU/L blood in the first DBS should immediately be referred to a specialized medical institution designated by the Regional Council for NBS for diagnostic confirmation. (Note 1-1) 1(●●●)

2-2-2. If TSH levels are 7.5-15 mIU/L blood in the first DBS, a recalled DBS should be tested at the same facility that performed the first blood test. If TSH in the second DBS is higher than the cutoff level of the screening laboratory, the neonate should be referred for diagnostic confirmation. (Note 1-2) 1(●●○)

(Note 1-1) The incidences of CH, transient CH and false-positive findings change with cut-off levels. Therefore, an appropriate cut-off level for each area should be determined based on their previous results. In order to prevent delay of treatment due to the necessity of secondary DBS sampling, it is important that the appropriate cut-off level for first DBS is set for immediate referral for diagnostic confirmation.

(Note 1-2) The second DBS sampling should be conducted at 14 days of age to obtain the final NBS result.

Additional notes: Precautions in NBS:

1) The blood sampling age of 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 four to six days if possible because CH NBS is not affected by feeding. For precautions for low-birth weight infants, see other items.
2) Early detection requires routine validation of transport of DBS, measurement in test facilities, information on abnormal results, a second DBS test for subjects who are positive in NBS, 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 of CH in NBS. Countermeasures are difficult, but the situation should be recognized. If there is no difference in performance between disinfectants, iodine-containing disinfectants should be avoided.

2-2-3. Some cases of CH are not detected in NBS. 1 (●○○)

Explanation

The previous guidelines recommended that a subject with TSH >30 mIU/L (whole blood) in the first DBS should immediately undergo detailed examination (6). In the United States, TSH ≥ 30 mIU/L is also generally used as the threshold for a detailed examination (1, 10,

59). Based on the 1998 guidelines, > 30 mIU/L in the first DBS indicate the need for a diagnostic confirmation in many regions in Japan, but this is not followed nationwide (60–63).

There are several reports in which the TSH cut-off in the NBS was lowered. The benefits of lowing cut-off value lies in that we can better detect permanent CH that requires treatment (54–56). There are cases in which permanent CH due to morphological defects or dyshormonogenesis was detected after NBS even when the TSH was below the cut-off for NBS (1, 4–6, 54, 64). However, lowering the cut-off value also has some disadvantages; namely, a higher likelihood of requiring a second DBS test for NBS, an associated increase in the cost of NBS, and anxiety in parents by necessitating a second DBS test (56). It is thus important to continue discussing the optimal TSH cut-off value in Japan.

One of the problems regarding NBS for CH is that individuals with CH may present with TSH levels below the cut-off value in the first DBS, leading to a lack of detection by NBS. In a national survey in 1999, Inomata *et al.* identified 35 patients with CH who were not found in NBS, with an incidence of about 1/750,000 (65). The causes included delayed TSH elevation, measurement-related problems, and paperwork errors. Nagasaki *et al.* performed a thyroid function test on siblings of patients diagnosed with CH and found that siblings in several families also had CH (66). Therefore, siblings of CH patients with high TSH in the first DBS test and normal TSH in the second DBS test should be carefully followed up on 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 the second DBS test [1] one mo after birth, [2] when their body weight reaches 2,500 g, or [3] upon hospital discharge, even if data from the first DBS test at four to six days of age are within the normal range. 1 (●●●)

2-3-2. Infants with delayed TSH elevation in the second DBS test should undergo diagnostic confirmation. 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 (67). Hypothyroxinemia without increased TSH is sometimes caused by administration of dopamine, high-dose steroid therapy, undernutrition, or exchange transfusion (68). CH with delayed TSH elevation, which is diagnosed as CH at a later stage due to TSH values below the cut-off level in the first DBS, is common in premature and low birth weight infants (40, 69, 70). Therefore, neonates with a birth weight < 2,000 g should undergo a second DBS test at one mo after birth, when body weight reaches 2,500 g, or upon discharge from the hospital (71).

A survey by Kamitaki *et al.* showed that 150 of 391 infants who underwent a second DBS test underwent a detailed examination, and 51 were diagnosed with CH (72). Other studies report incidences of delayed TSH elevation in the second DBS test as 1/58 in extremely low birth weight infants and 1/95 in low-birth-weight infants, with three of these patients were treated with thyroid hormone (73). A report from Tokyo (74) found that analysis of the second DBS obtained from low-birth weight infants (TSH cutoff value set at < 5 mIU/L) resulted in a similar frequency of infants requiring diagnostic confirmation (0.68%) to that of infants requiring diagnostic confirmation (0.53%) after the first DBS test. In particular, the rate of requiring diagnostic confirmation for extremely very low birth weight infants based on the first DBS was 1.12%, but that after the second DBS rose to 2.19%. The positive cases in the second DBS are not always representative of CH requiring treatment. However, patients with positive results in their second DBS test should undergo a third DBS test at an NBS laboratory or receive diagnostic confirmation at specialized medical institution in accordance with the guidelines of the regional council for NBS.

Hypothyroxinemia requires differentiation from CH with delayed TSH elevation. More than 50% of low-birth weight infants under 30 weeks of gestational age exhibit hypothyroxinemia, with greater prematurity associated with more severer thyroxine decrease. In comparison with decreased total thyroxine levels (T4), FT4 levels are 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 six to ten weeks of birth and develop normally without treatment. Many studies show that 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 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 NBS, clinical symptoms, imaging and thyroid function tests in a detailed examination. 1 (Consensus)

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3-2. Assessing the severity of CH

1) Clinical symptoms
Clinical evaluation of CH, where two or more items in the following checklist indicate a severe condition. (a) prolonged jaundice, (b) constipation, (c) umbilical hernia, (d) poor body weight gain, (e) dry skin, (f) sluggishness, (g) macroglossia, (h) hoarseness, (i) cold extremity, (j) edema, (k) wide posterior fontanelle, and (l) goiter.

2) Serum FT4 levels
The approximate standards for serum FT4 levels are as follows: most severe: <0.4 ng/dL; severe, 0.4 to 0.8 ng/dL; and moderate, 0.8 to 1.2 ng/dL. The normal range for FT4 differs among test facilities (see Explanation below).

3) Serum thyroglobulin (Tg) level
If serum Tg is low (< 10 ng/mL), thyroid agenesis or Tg deficiency are suspected as indicators for severe CH.

4) Thyroid ultrasonography.

5) Distal femoral nucleus.
Evaluation is conducted comprehensively based on the above items 1) to 5). 1 (●●●)

Explanation

1) Diagnosis for CH

(1) Key points for the first medical examination

① Family history: Confirm the presence or absence of thyroid disease.

② Maternal condition: a) Current or history of thyroid disease. If positive, the details of the diagnosis and treatment (e.g., thyroid surgery, history of oral ^{131}I and other medications) should be noted. b) Conditions other than thyroid gland disease and information about treatments. It is important to check whether amiodarone, lithium preparations, and other drugs that can impact thyroid function of the child via the placenta or breast milk were taken. c) Effects of hysterosalpingography using an oil-soluble, iodinated contrast medium in reproductive assistance care. This procedure can leave effects for up to six mo and can even affect thyroid function of the child; thus, it is important to check this as well. d) Excessive intake of iodine-containing foods during pregnancy and/or regular use of disinfectants containing iodine. e) As needed, testing of the maternal thyroid function, thyroid autoantibodies, total urinary iodine concentration, and thyroid ultrasound should also be considered.

③ History of the present illness in the child: It must be determined whether contrast-enhanced fetal imaging was performed and if neonates were exposure to high levels of iodine disinfectants at birth. Additionally, the mode of nutrition should be determined to evaluate whether iodine was transferred via breast milk.

(2) Twins*

Twins may test false-negative in NBS; thus, the second screening is mandatory. In the case of one twin with CH, it is possible that the other who tests negative at NBS is later diagnosed as CH as their TSH levels elevate, thus warranting cautious follow-up (81–83).

*There is additional information in the Supplementary Material regarding the handling of twins.

2) Assessing the severity of CH

① Clinical symptoms

The checklist of clinical symptoms includes the following 12 items: (a) prolonged jaundice, (b) constipation, (c) umbilical hernia, (d) poor body weight gain, (e) dry skin, (f) sluggishness, (g) macroglossia, (h) hoarseness, (i) cold extremity, (j) edema, (k) wide posterior fontanelle, and (l) goiter.

Patients who correspond to two or more items on the checklist of clinical symptoms are classified as severe CH (6, 7, 84). The inspection should examine for the presence of any of these symptoms; however, they are often unobserved at the first detailed examination. Therefore, regardless of the severity as classified by clinical symptoms, treatment should be introduced promptly according to TSH and FT4 levels to avoid the onset of the above symptoms.

② Severity assessment by thyroid hormone level

The European Society for Paediatric Endocrinology recently proposed a consensus of FT4 < 5 pmol/L (< 0.4 ng/dL), 5–10 pmol/L (0.4 to 0.8 ng/dL), and 10–15 pmol/L (0.8 to 1.2 ng/dL) as cut-off values for severe, moderate and mild cases, respectively (14). Traditionally, the Japan Pediatric Endocrine Society has used the terms “most severe”, “severe”, and “moderate”, according to FT4 levels. However, FT4 values vary depending on the measurement kit used and are not standardized. Therefore, the range for classification of severity should be considered as merely referential values. Moreover, it is important to collect information on which kit was used to evaluate the FT4 levels. Furthermore, most institutions do not publish standard ranges for neonates and infants. Therefore, diagnosis of moderate to most severe hypothyroidism using FT4 is based on physician experience.

③ Severity assessment by serum Tg level

Serum Tg levels are low in patients with thyroid agenesis and abnormal synthesis of Tg (12, 14). Abnormal Tg levels can occur in hypothyroidism caused by some types of thyroid dyshormonogenesis or an excessive intake of iodine (12, 14). The levels can be relatively high in ectopic thyroid as well.

④ Severity assessment by thyroid ultrasonography

A thyroid gland that cannot be identified on ultrasound or with thyroid adenoma corresponds to a severe CH (see 7. Diagnostic Imaging of the Thyroid Gland for details) (1, 6, 7, 12–14).

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⑤ Severity assessment by radiography of the femoral epiphysis

In the case that the femoral epiphysis is either unilaterally or bilaterally not visible, a lack of thyroid hormone in the fetal period is indicated, and T4 concentration at diagnosis is thought to correlate with future IQ (84–87). The delayed appearance of the femoral epiphysis in a full-term infant (38 weeks and later) is considered to indicate severe CH; thus, a radiograph of the femoral epiphysis is taken. Several studies, such as Tamaru *et al.* and several foreign studies report on the normal size of the femoral epiphysis (85–87).

4. Criteria for Initiation of CH Treatment

Recommendation

4-1. Children who are positive for CH by NBS with a high TSH value should consult a pediatric endocrinologist. 1 (expert opinion)

4-2. Criteria for starting treatment immediately

1) If a patient exhibits two or more 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 levels are ≥ 30 mIU/L or are at 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) As a general rule, commencement of treatment should be evaluated based on serum TSH and FT4 levels at the time of the detailed examination. However, DBS testing should be used when thyroid functions cannot be tested adequately. 2 (●○○)

4-3. Management of subclinical CH

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 one to two weeks later. If TSH is > 10 mIU/L at three to four weeks after birth, initiation of treatment should be considered. Even if treatment is started, administration of L-T4 may be discontinued at three yr of age and not restarted, and a thyroid function test should 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, and the patient should be followed up on. 2 (●○○)

Explanation

1) Children who are positive for CH by NBS with a high TSH value should consult a pediatric endocrinologist.
2) Criteria for starting treatment

If a patient presents with two or more 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. Presently, most institutions that conduct detailed examinations should be able to provide the results of thyroid function tests immediately. Therefore, as a general rule, the commencement of treatment should be determined based on serum TSH and FT4 levels at the time of detailed examinations. However, some institutions conducting detailed examinations may not be able to provide thyroid function testing due to long-term closure of the facilities, natural disasters, or other causes, in which case the commencement of treatment should be evaluated by TSH in the eluate of the DBS. Niimi *et al.* evaluated findings and thyroid function of subjects who were positive in NBS at the first medical examination (84). Among patients who undergo an immediate detailed examination, those who meet the following criteria likely have hypothyroidism and should receive immediate treatment: 1) TSH ≥ 30 mIU/L in the DBS test; 2) one or more item on the checklist or no appearance of the distal femoral nucleus, even if TSH < 30 mIU/L in the DBS test; TSH ≥ 20 mIU/L in the second DBS test; or TSH levels in the second DBS test ≥ 15 and < 20 mIU/L higher than those in the first DBS test. If no symptoms in the checklist or a distal femoral nucleus is found, but serum TSH levels are ≥ 30 mIU/L, TSH is 15–30 mIU/L and FT4 is < 1.5 ng/dL despite a lack thyroid ultrasonography, or if a test facility determined that FT4 was lower than that in normal infants, the patient should be treated (6, 10, 12).

3) Management of subclinical CH

No evidence-based study exists regarding a treatment policy for patients with no clinical symptoms, serum FT4 within the normal range, and serum TSH higher than the normal range (≥ 5 to < 15 mIU/L). If TSH does not return to normal within three to four weeks of 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 between subclinical CH, transient increased blood TSH, and permanent CH. As described in the section on subclinical CH, it has been suggested that infants with TSH ≥ 10 mIU/L before six mo of age and TSH ≥ 5 mIU/L at 12 mo of age should be followed up on carefully and treated. However, it is unclear if 12-mo-old infants with TSH ≥ 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 exhibit hyperthyroidism. If treatment continues, it should be discontinued at the age of three yr, at which time the thyroid system should be reevaluated and a formal diagnosis, including a disease type diagnosis, should be considered.

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5. CH Treatment and Monitoring

Recommendation

5-1. Treatment should be started with levothyroxine sodium (L-T4) at a dose of 10–15 μg/kg once a day, or at 15 μg/kg/d for the most severe patients. 1 (●●●)

5-2. A patient with subclinical CH can be treated with L-T4 at 3–5 μg/kg/d. (Expert opinion)

5-3. Oral administration of L-T4 is possible in the morning or evening, before or after a meal. L-T4 should be taken at the same time every day. For neonates and infants, LT-4 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. 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. If TSH levels are maintained at a normal level for the age group, decreasing the dose is not necessarily required even if the FT4 level exceeds the upper limit of the reference range for patient age. 1 (●○○)

5-6. Follow up is required at one, two, and four weeks after initial administration; at one-mo intervals until one yr of age; and age 1 yr, and then at three- to four-mo intervals until the adult. 1 (●○○)

Explanation

Treatment with L-T4 (Thyradin S®) should be started at a dose of 10 μg/kg/d, or at 15 μg/kg/d for the most severe CH cases (6, 10, 12–14, 86, 88). Subclinical CH should be treated with 3–5 μg/kg/d because these patients often become hyperthyroid after receiving L-T4 at 10 μg/kg/d (expert opinion). The newest consensus guidelines of the European Society for Paediatric Endocrinology (2020) recommend L-T4 at 10–15 μg/kg/d for severe cases (FT4 < 0.4 ng/dL), 10 μg/kg/d for moderate cases (FT4 > 0.8 ng/dL) and 5–10 μg/kg/d for case with FT4 values within the normal range (14).

Whatever the dosage, it is important to pay attention to the thyroid function test and clinical symptoms and to prevent underdose and overdose, regardless of the dose. L-T4 at a dose of 15 μg/kg/d can still cause overdose in severe patients with eutopic CH including DUOX2 abnormality, in which cases a dose of 10 μg/kg/d is sufficient (expert opinion). Many severe patients return to normal range of FT4 within 3 days, and within two to four weeks of TSH at 10–15 μg/kg/d with L-T4 administration (53, 88). Early normalization of thyroid hormone is important for the intelligence prognosis (5, 51–53, 88–90).

In a meta-analysis comparing the initial L-T4 doses of < 8.8, 8.8–10 and > 10 μg/kg/d, IQ was the highest in patients receiving > 10 μg/kg/d L-T4, suggesting that an early, high-dose L-T4 therapy is necessary (91). However, L-T4 therapy may be started at dose of 12.5 μg/kg/d or higher, in which case the dose will need to be decreased in a significantly higher number of patients (92). Therefore, as per the previous guidelines, we consider it essential to start L-T4 therapy at a high dose (10–15 μg/kg/d) for adequate psychomotor development as per the previous guidelines; however, subsequent monitoring requires particularly close attention.

For treatment monitoring, it is recommended that serum TSH levels be targeted to the age-specific normal range and FT4 or T4 levels from 50% to the upper limit of the normal range. There are no clear data indicating whether TSH or FT4 level is the most important parameter to be monitored in primary CH. However, in L-T4 therapy for severe CH, aiming to keep TSH levels in the normal range for the age will result in normal FT3 levels, though FT4 can exceed the normal range for the age. In one study, IQ at 11 yr of age was significantly lower in patients with high FT4 by the age of two yr due to the excessive administration of L-T4 (93). Additionally, the rate of attention deficit hyperactivity disorder has been reported to increase in children with high FT4 at one to three mo of age (94). Therefore, the effects of high FT4 until the age of two yr should be closely examined. A comparison of 76 CH patients treated with high dose L-T4 (13.5 μg/kg/d) and 40 siblings found that their IQ at age 15 yr and older was not different between siblings despite a higher FT4 level up to two yr of age in more than half of the patients. Additionally, no correlation was observed between the frequency or duration of high FT4 levels and IQ (91). Therefore, we recommend that FT4 levels above the upper limit of the normal range corresponding to age does not necessarily indicate the need for a dose reduction if the TSH level is maintained within the normal range corresponding to age. However, an appropriate dose reduction is recommended when the TSH levels are suppressed or thyrotoxic symptoms, such as tachycardia and hyper-sweating, are observed.

The appropriate maintenance dose after the start of treatment will taper off per body weight with advancing age if the dose is not changed. A study that investigated the L-T4 dose by disease type showed that normal thyroid function was maintained in preschool and school-aged children at doses of 3–4 μg/kg/d and 2–3 μg/kg/d, respectively. Furthermore, the L-T4 dose was reported to be lower in children with eutopic CH than in their ectopic or agenesis CH counterparts (95).

Regarding monitoring intervals in Japan, thyroid function is usually evaluated by blood sampling conducted one, two and four weeks after starting treatment. Patients are then followed up at one-mo intervals until one yr of age, and at three- to four-mo intervals from the age of three yr until adolescence (6, 13). Results at one facility showed that patients were monitored once a mo from six mo to one yr of age, but that 35% of patients did not target the TSH and FT4 levels with CH treatment. Therefore, it was proposed that patients receive more frequent follow-up until one

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yr of age and that the dose be adjusted (96). Additionally, in severe CH, the L-T4 doses should be adjusted frequently before one yr of age; however, difficulties regarding individualized treatment have been reported (97). Monthly follow-up is recommended if the L-T4 dose is revised, thyroid hormone levels are abnormal, and poor compliance is observed (6, 10, 12, 13). Adult patients usually receive follow-up at an interval of six mo to one yr in Japan, and follow-up at this interval is considered reasonable (98).

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® tablets are manufactured at five doses (12.5, 25, 50, 75 and 100 μg), making it easy to adjust the dose. However, 12.5- and 75-μg tablets have no score line, and therefore cannot be divided. As a different formulation, 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.

For neonates and infants, drugs can be dissolved in a small amount of water, breast milk, or formula. Substances inhibiting L-T4 absorption include soy milk, iron preparations, calcium, stomachics, ion exchange resins, and new quinolone antibiotic drugs (10, 99). 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 (100). The Lawson Wilkins Pediatric Endocrine Society suggested that the dose can be set based on a thyroid hormone test if the administration time is constant (101). No study has definitively shown that fasting administration causes poor compliance after the neonate age, but it is empirically assumed that fasting administration may affect patients. Therefore, it is recommended that drugs be taken after a meal at constant intervals (100). A clinical study in adults showed the efficacy of administration before sleep (101), but there is no similar study in children. According to one report, the thyroid function was similar between patients receiving daily L-T4 in childhood versus those administered twice the daily dose every two days (102). The European Society for Paediatric Endocrinology recently proposed the consensus that each L-T4 dose should be taken at the same time, whether while fasting, after a meal, or in the morning or evening (12, 14). Therefore, the guidelines recommend that neonates and infants need not take L-T4 while fasting, but older infants and adults should always take L-T4 at a specific time, with the administration 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 exhibit congenital anomalies, particularly congenital heart disease including atrial septal defect, and other diseases with delayed psychomotor development, than the general population (103, 104). A study in Japan showed that 14.6% of patients with primary CH exhibited complication of congenital heart disease and congenital anomalies in the nervous and muscular systems (105). This study also showed that female patients frequently exhibited congenital heart disease and congenital anomalies in the nervous and muscular system, whereas male patients exhibited significantly more congenital anomalies in the gastrointestinal and urinary system. 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 period and thereafter (106, 107), and increased blood TSH cannot always be identified in neonatal NBS. A characteristic feature of thyroid function tests in Down's syndrome is high TSH levels that deviates from FT4 levels. TSH, which stimulates the secretion of thyroid hormones, is controlled by the hypothalamus-pituitary-thyroid axis, which does not seem to be modulated adequately in Down's syndrome (108). Subclinical CH as a complication of Down's syndrome often enters spontaneous remission, but worsens in some cases. Therefore, hyperthyrotropinemia in Down's syndrome should be carefully examined to determine whether it is caused by true CH (109). The prevalence of CH in Down's syndrome is estimated to be 28–40 times that of the general population (110, 111). Furthermore, CH in Down's syndrome often consists of thyroid hypoplasia; ectopic thyroid, hemiagenesis and enlargement of the thyroid are rare (110, 111).

Pendred syndrome (with or without goiter) and pseudohypoparathyroidism also cause mild or moderate TSH elevation at the neonatal period, and these conditions may be found in NBS (112, 113). Primary CH may also be present in Alagille syndrome, Williams syndrome, 22q11.2 deletion syndrome, Prader-Willi syndrome (more often with central hypothyroidism), and Young-Simpson syndrome (114–117). (See 10 Genetic Counseling and Diagnosis of CH for genetic abnormalities with complications that do not involve the thyroid gland.)

*The term "malformation" is inappropriate, and

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the Japanese Association of Medical Sciences is now considering a way to replace it. The Japanese Society of Pediatric Cardiology and Cardiac Surgery recommends replacing the term "congenital malformation of the heart" with "congenital heart disease". Thus, the term "congenital heart disease" is in use from this edition onwards.

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 is not mandatory in the neonatal period, during which treatment is given priority, and can be performed only when feasible. When the disease-type is determined, L-T4 treatment is withdrawn and thyroid scintigraphy should be considered. 2 (●○○)

Explanation

Imaging using thyroid ultrasonography and scintigraphy is useful to determine the causes of CH. Ultrasonography can be used in the neonatal period. 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 dyshormonogenesis, and should be performed during the first detailed examination when possible (1, 6, 10, 12–14, 118). However, there may be a delay in performing ultrasonography at some test facilities. If ultrasonography is difficult to implement, treatment should not be delayed (6, 13). Diagnosis should be determined based on NBS results, clinical symptoms, and endocrine tests in a detailed examination.

Onishi *et al.* showed that ultrasonography can be used to differentiate between eutopic CH and thyroid dysgenesis (118). Of 23 patients who were not confirmed to present with eutopic thyroid, 6 and 16 were diagnosed with thyroid agenesis and ectopic thyroid, respectively, and one patient who was diagnosed with ectopic thyroid was found to be normal using scintigraphy. An ectopic thyroid gland can also be diagnosed by color Doppler ultrasonography with 90% accuracy (119). However, the specificity of an ectopic diagnosis by ultrasonography differs among studies and ranges from 0% to 21% (120–122). Therefore, it may be difficult to diagnose a neonate as ectopic using ultrasonography. Residuals of the ultimobranchial body, which develop into parafollicular cells of the thyroid are visualized as hypoplastic, bright tissues and cysts and can be mistaken for a eutopic thyroid gland (123–125). Additionally, in ultrasonography, hypoplasia is suspected when the ratio of the total transverse diameters of the thyroid lobes (Th) to the width of the trachea (Tr) (Th/Tr ratio or Yasumoto ratio) is 1.7 or lower (126–128).

Thyroid scintigraphy is reliable for definitive diagnosis of dysgenesis (ectopia, hypoplasia and agenesis); ^{99m}Tc or ^{123}I may be used (129–131). Thyroid scintigraphy using ^{123}I can allow the evaluation for thyroid formation abnormalities, iodine uptake deficiency, and organification defects; however, it requires the restriction iodine intake for one to two weeks prior to the test. Scintigraphy with ^{99m}Tc does not require the restriction of iodine intake before the test; however, it is only effective for evaluating dysgenesis (128). In dyshormonogenesis, isotope uptake is 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 and a perchlorate discharge test. However, if a patient possesses an abnormal iodide symporter as a type of dyshormonogenesis, uptake is not recognized by thyroid scintigraphy. In such a case, thyroid morphology should be examined by ultrasonography because uptake deficiency also may occur due to a TSHβ genetic abnormality, a TSH receptor inactivated mutation, or an abnormal iodine symporter (131, 132).

Regarding the implementation and timing of thyroid scintigraphy, European and US guidelines recommends that scintigraphy be performed in the neonatal period prior to treatment because thyroid dysgenesis can be definitively diagnosed and an eutopic thyroid with normal uptake can suggest transient CH (10, 12). However, scintigraphy is not generally used for CH diagnosis in the neonatal period in Japan. The 1998 Guidelines for Mass Screening of Congenital Hypothyroidism in Japan recommended scintigraphy to confirm the disease type at an age of three yr or older (6). Therefore, the current guidelines conform to this policy.

8. Reevaluation of Thyroid Function for Differentiation of Transient and Permanent CH and Disease Type Diagnosis

Recommendation

8-1. The thyroid system should be re-evaluated after L-T4 withdrawal and the disease type should be diagnosed at three ys of age or older. However, the likelihood of transient CH is high in the case of children with stable thyroid function at the following dosages; thus, an early discontinuation of treatment can be considered. 1 (●●●)

Age (Mo)	Dosage of L-T4 replacement (μg/kg/d)
12	< 1.7
24	< 1.45
36	< 1.25

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8-2. Re-evaluation 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 dyshormonogenesis, agenesis, or hypoplasia are not determined by genetic tests. 2 (●○○)

8-4. Children who do not require an increased dose of L-T4 after three ys of age are likely to represent cases of transient CH. 2 (●○○)

Explanation

Re-evaluation or disease type diagnosis is required after L-T4 withdrawal, including differentiation of transient from permanent CH if definite causes of CH have not been identified, particularly for patients diagnosed with eutopic CH by ultrasonography (6, 10, 12–14). It has been shown that 12% to 54% of patients diagnosed with eutopic CH during the neonatal period and treated with L-T4 have transient CH (133, 134). Low birth weight infants diagnosed with CH and treated with L-T4 may also have transient CH, and thus re-evaluation and disease type diagnosis are required. These should be conducted upon completion of neuronal development, at or after three ys of age (135). However, the likelihood of transient CH is high in the case of stable thyroid function at an L-T4 dosage below the therapeutic dose for age (in mo); thus, an early discontinuation of treatment can be considered before the age of three yr with informed consent. The present guidelines reflect studies investigating an early discontinuation of therapy with the lowest L-T4 doses at three yr of age or younger (133, 136–145) to avoid false negatives for reference. Furthermore, another study reported a high likelihood of transient CH among children who do not require a L-T4 dose increase between the ages of three yr and five yr three mo (146).

Even if the diagnosis is agenesis, hypoplasia or ectopic thyroid by ultrasonography at the neonatal period, images should be examined again by ultrasonography. Diagnosis of 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, dyshormonogenesis, family history, or other characteristic symptoms before the age of three yr and confirmed by genetic diagnosis, re-evaluation and disease type diagnosis may not be necessary. However, it is preferable to determine the diagnosis independently. In the case of a DUOX2 gene abnormality, it is possible that thyroid function normalizes; thus, re-evaluation is important.

The procedures for disease type diagnosis are as follows: replace L-T4 with one-fourth the dose of liothyronine sodium for four weeks (t.i.d.), measure ^{123}I thyroid uptake after withdrawal for 7–10 days, 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 agenesis, hypoplasia, ectopic thyroid gland, iodine organification defect, and iodine transport defect can be performed. In the case of re-evaluation without a disease type diagnosis, an ultrasonography after withdrawal and serum TSH, FT3, FT4, and Tg measurements are recommended. The TRH stimulation test is not necessary in the diagnosis of primary CH for the disease type diagnosis and re-evaluation (expert opinion).

A patient who is normal in re-evaluation or disease type diagnosis is considered to have transient CH; but should be followed up on because hypothyroidism may develop again. A patient diagnosed with transient infantile hyperthyrotropinemia will have increased TSH levels at a later stage that results in hypothyroidism, and such a patient should also receive follow-up (6). The demand for thyroid hormones increases during puberty and pregnancy, and hypothyroidism may become apparent during these periods (147). Therefore, a follow-up before puberty is best if possible. Girls should also be informed at the end of follow-up that thyroid function should be checked again at the time of pregnancy.

Children who do not require an increase in L-T4 dose between the ages of three and five yr likely exhibit transient CH (85% sensitivity and 100% specificity). Therefore, it is acceptable to re-evaluate such children without a disease type diagnosis.

9. Long-term Prognosis

9-1. Psychomotor Development

Recommendation

9-1-1. Assessment of intellectual development should be performed if intellectual disability is found. Careful follow-up is required for patients with mild developmental disorders and learning disabilities. 1 (●●●)

9-1-2. Appropriate interventions are required for patients with developmental disorders and learning disabilities. 1 (●○○)

Explanation

The recommended initial dose of L-T4 was 5–8 μg/kg/d at the beginning of NBS and the start of treatment was often delayed until four to five weeks after birth. CH patients treated in this way exhibited an IQ that was 6–20 points lower than that of controls, and the prognosis was particularly poor in children with severe CH and serum T4 < 5 μg/dL at the initial visit. In Japan, the mean IQ in the first nationwide survey was 97.5 ± 14.8 (n = 81) (51), and that in the second survey was 99.9 ± 13.7 (n = 151) (52).

The change to an initial L-T4 dose of 10–15 μg/kg/d started within two weeks of birth has steadily improved the outcome of intelligence in patients with CH (53). The latest nationwide survey of CH patients in Japan was published in 2003 (5), and reported that children

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diagnosed with CH from 1994 to 1999 were 17.3 days old at the first visit (limited to direct examination) and that the initial L-T4 dose was ≥ 10 μg/kg/d in over half of severe patients. The developmental quotient (DQ)/IQ at one to five yr of age was normal, ranging from 104.1 to 107.3. As shown here, serious intellectual disability due to CH has almost been eradicated; however, patients with severe hypothyroid conditions during pregnancy may still exhibit mildly reduced IQ.

Patients with severe CH tend to exhibit problems with cognitive ability, behavior and attention deficit in adolescence and adulthood (5, 53). Furthermore, cognitive ability and school outcomes of severe patients are related to the starting time and dose of L-T4 (148–151). Problems related to attention deficit may be linked to transient thyroid hormone excess induced by an increased initial L-T4 dose, resulting in adverse effects on the central nervous system (152); however, there is no definitive evidence for this. Asakura *et al.* examined emotion and behavior in 47 Japanese patients with permanent CH and 16 patients with transient CH (based on disease type diagnosis) aged 4–15 yr and found no differences from healthy controls (153). Furthermore, a 2018 meta-analysis examining the relationship between IQ and initial L-T4 dose stratified by CH severity (91) and reported significantly lower IQ in patients with the most severe CH than in those with moderate and severe CH at a starting dose below 10 μg/kg/d (< 8 μg/kg/d: –6.03 95% CI [–9.10, –2.96], 8–10 μg/kg/d: –9.2 95% CI [–15.07, –3.33]). This difference in IQ or quality of life (QOL) was not found when the starting dose was 10 μg/kg/d or higher, indicating that high-dose L-T4 replacement is essential from the early stages of the most severe CH.

9-2. Adult Height, Obesity, Puberty, Gestational Complications, and Fertility

Recommendation

9-2-1. Information is provided to show that a normal adult height can be attained via appropriate treatment and compliance to medication regimes. 1 (●●●)

9-2-2. Information is provided to show that normal pubertal development and fertility can be obtained with appropriate treatment and compliance to medication regimes. 1 (●●●)

Explanation

The adult height of CH patients diagnosed due to NBS has been studied in many countries, including Japan (154–157). Kanagawa Children's Medical Center conducted an analysis of CH patients and found no difference in adolescent growth patterns in terms of age at the start of adolescence, peak growth rate, and age at peak growth rate in comparison with reference data for the general population. Moreover, no significant correlation has been made between adult height and severity of hypothyroidism or the age of starting treatment (155). Sato *et al.* analyzed height and body weight in 2,341 CH patients (1,030 males and 1,311 females) registered in the Medical Aid Program for Chronic Pediatric Disease of Specified Categories in 2002 and found neither short stature nor obesity, with patients showing normal growth and constitution (156). According to a 2015 Italian report, no difference with controls was observed in the adult height or secondary sexual characteristics among 215 patients with CH born between 1980 and 2000. Additionally, no differences were seen regarding obesity, although the frequency of overweight was higher in patients with CH than in controls (158). It has also been reported that inadequate L-T4 replacement may cause obesity (159). A Taiwanese study of 90 patients with CH reported that 32.2% of the study population was overweight or obese children at six to seven yr of age, a rate 21.4% higher than that of the general Taiwanese population. Furthermore, obese CH patients had significant earlier adiposity rebound, significantly higher BMI at adiposity rebound, and significantly lower T4 after treatment than non-obese CH patients (159). Further investigation is needed to characterize obesity due to inadequate L-T4 replacement.

A French study on gestational complications and fertility in CH patients reported significantly higher gestational blood pressure than that in the general population, along with higher rates of emergency Caesarian section, induced labor, and preterm infants among CH primigravida. Risk of bleeding was higher in CH mothers only in the first and second trimesters, although there were no associations observed with the CH type or severity (160). Close monitoring of thyroid function during the second and third trimesters is expected to prevent gestational complications and has been shown to reduce the rate of preterm births (160). Increasing the maternal L-T4 dose by 20–30% is recommended as soon as the pregnancy is confirmed (161). Women with severe CH have previously been reported to exhibit reduced fertility compared to healthy women (162); however, there has been no similar report since 2012, and the topic remains open for further investigation.

9-3. QOL and Other Complications

Recommendation

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

Explanation

A study on the QOL of adult Japanese CH patients found that patients who were diagnosed with CH by NBS and treated adequately lead normal lives without any particular problems (163). Conversely, a survey of QOL for patients born in 1981–1982, after the start of NBS in the Netherlands, showed a slight decline QOL, with a significant decline in QOL was seen in more severe CH patients (164). A French study conducted after the advent of NBS suggested that QOL of CH patients was slightly

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lower than that of healthy individuals (165). It is possible that these subjects were patients when NBS was first developed, and they may have received low L-T4 doses, delayed start of treatment, and suboptimal follow-up. Data from the Netherlands and France showed a slight decrease in QOL, in contrast to the results from Japan. The discrepancy between European and Japanese data may also depend on evaluation methods and differences in healthcare conditions. Further studies are required in Japan to evaluate how early treatments with a high dose of L-T4 affects compared to the beginning after NBS.

A 2013 French study on the mortality in CH reported a standardized mortality rate of 1.24 among 1,202 CH patients born from 1978–1988 (mean age of 24.7 yr) and diagnosed via NBS; however, this value was not significantly different from that in the healthy population (166).

An Italian study on the rate of hearing loss in 32 patients with severe CH detected by NBS who began early treatment reported mild or subclinical sensorineural deafness at an average age of 15.4 yr in 25% of patients. The rate of hearing loss was particularly high among patients with severe CH with thyroid agenesis or without appearance of the distal femoral nucleus (167). According to a French study of 1,158 CH patients, hearing impairment was observed in 107 patients tested at a mean age of 7.0 yr (3.4–19.0 yr), representing a rate triple that of the control; hearing impairment was correlated with the severity of CH (168). Routine hearing tests are therefore recommended for patients with severe CH.

A 2018 US retrospective cohort study reported that the comorbidity rate of inflammatory bowel disease in CH patients was 73% higher than that in controls (0.52% of 42,922 patients versus 0.30% of controls) (169). The comorbidity rates were significantly higher for ulcerative colitis and other inflammatory bowel diseases rather than for Crohn's disease. Inflammatory bowel disease was observed to be more frequent in case of transient CH than in permanent CH, particularly among a subgroup with abnormalities regarding *DUOX2*. Although no studies from Japan have investigated this, the mean age of the patients in the original study was 39.1 (± 25.5) yr, and thus suggesting the importance of long-term follow-up.

10. Genetic Counseling and Diagnosis of CH

Recommendation

10-1. Consider explaining during genetic counseling whether the CH patient has dysgenesis (ectopic, hypoplastic, or agenesis thyroid) or dyshormonogenesis. 2 (●○○)

10-2. It should be explained to patients that the frequency of identification of the responsible genetic abnormalities in Japanese CH patients is approximately 20%. 2 (●●○)

10-3. Genetic counseling that includes information indicating that thyroid dysgenesis is often sporadic and the risks for recurrence are low can be provided. 2 (●●○)

10-4. Consider explaining that approximately 50% of dyshormonogenesis patients are caused by genetic abnormalities of autosomal recessive inheritance, translating to 25% susceptibility in the next child. 2 (●●○)

Explanation

Most thyroid dysgenesis are not hereditary. A French epidemiological study reported that only 2% of patients with thyroid dysgenesis had a family history (170); however, the frequency of family history in Japanese patients with CH is unknown (171, 172). Moreover, unknown genetic factors may exist because the incidence of familial dysgenesis is over 15-fold higher than that of sporadic cases (173). The first relative of a patient with thyroid dysgenesis may have normal thyroid function, but often exhibits anomalies associated with fine thyroid malformation (174).

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*, *JAG1, CDCA8, TUBB1*, *TSHR,* and *GNAS* (pseudohypoparathyroidism 1a) (172, 175–178). Dyshormonogenesis, on the other hand, develops due to mutations of *SCL5A5*, *SCL26A4*, *TG*, *TPO*, *DUOX2*, *DUOX2A*, *IYD*/*DEHAL1* and *SLC26A7* (179–182). It has been reported that biallelic mutations in *DUOX2* or *DUOX2A* do not always cause permanent CH; however, they can cause transient CH in the neonatal period (18, 19, 36). Pendred's syndrome is associated with hearing loss (112), and mutations of the *NKX2-1* are characterized by respiratory disorders (newborn respiratory distress syndrome and cycles of recurrent lower airway infection) and neurological symptoms (choreoathetosis, developmental delay) (175). *PAX8* abnormality is complicated by kidney and urinary tract malformations in rare cases (183). *JAG1* is responsible for Alagille syndrome due to deficits in the Notch signaling pathway. Genetic screening of CH without the typical clinical profile of Alagille syndrome identified heterozygous mutations of the JAG1 gene in 4 of 100 patients (176). SLC26A7 and SLC26A4 transport iodine from the parafollicular cells of the thyroid to the follicle, and abnormalities of *SLC26A7* disrupt the transporters, resulting in iodine organification defects and hypothyroidism (180–182). In patients with *TPO* or *TG* mutations, thyroid cancer from goiter has been reported in adulthood, although it is rare. (184, 185). If a *GNAS* mutation is detected, endocrine function should be examined.

A comprehensive genetic analysis of Japanese patients with CH reports that approximately 20% of the patients exhibit genetic abnormalities (186–189),

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Table 2. Genetic causes of congenital hypothyroidism

Classification	Gene	Protein function	Chromosome	Mode of inheritance	Characteristic findings*
Thyroid dysgenesis	*NKX2.1*	Transcription factor	14q13	AD	Respiratory failure, chorea
	FOXE1	Transcription factor	9q22	AD	Cleft palate, spiky hair, choanal atresia
	NKX2.5	Transcription factor	5q35	AD	Persistent foramen ovale
	PAX8	Transcription factor	2q13	AD	Unilateral kidney aplasia (rare)
	TSHR	G-protien coupled receptor	14q31	AR/AD	
	GLIS3	Transcription factor	9q24.3	AR	
	JAG1	Notch receptor ligand	20p12.2	AD	Alagille syndrome type 1
	CDCA8	Component of the chromosomal passenger complex	1p34.3	AD	
	TUBB1	β-tubulin protein family, cytoskeletal structures	20q13.32	AR/AD?	Macroplatelets
Dyshormogenesis	*SLC5A5*	Sodium iodide symporter	19p13	AR	Inability to concentrate iodide in salivary glands, low saliva to plasma ratio
	SLC26A4	Anion transporter	7q31	AR	Sensorineural deafness, goiter
	SLC26A7	Anion transporter	8q21.3	AR	Goiter
	TG	Matrix for hormone synthesis	8q24	AR	Goiter, very low serum Tg
	TPO	Iodide organification	2p24	AR	Complete iodide organification defect
	DUOX2	H_2O_2 generation	15q15	AR/AD	Partial iodide organification defect, permanent or transient
	DUOXA2	H_2O_2 generation	15q15	AR	Partial iodide organification defect
	DEHAL1	Recycling of intrathyroidal iodine	6q25	AR	Goiter
TSH resistance	*TSHR*	TSH receptor	14q31	AR/AD	
	GNAS	Alpha subunit of the stimulatory G protein	20a13.2	AD (maternal inheritance)	Pseudohypoparathyroidism, PTH resistance
Thyroid hormone insufficiency	*THRB*	Thyroid hormone receptor	19p13	AD	Elevated T4 and T3 with no suppression of TSH, goiter, tachycardia
	THRA	Thyroid hormone receptor	3p24	AD	Growth retardation, constipation, delayed bone maturation, psychomotor developmental delay
	SLC16A2	Thyroid hormone transporter	Xq13	X-linked	Nystagmus, low T4 and high T3, severe global developmental delay
	SECISBP2	Incorporation of selenocysteine into selenoproteins	9q22	AR	High T4 and low T3, developmental delay
Central congenital hypothyroidism (Isolated TSH deficiency)	*TSHB*	TSH β-subunit	1p13	AR	Isolated TSH deficiency, hypogenesis of thyroid
	TRHR	TRH receptor	8q23	AR	Reduced TSH and PRL response to TRH stimulation
	IGSF1	Regulation of TRH receptor expression ?	Xq26.1	X-linked	Macrochidism, low PRL level, delayed puberty, ADHD
	TBL1X	Transcriptional regulation of thyroid hormone	Xp22.3	X-linked	Sensorineural deafness, constipation, ADHD, Chiari malformation
	IRS4	Interface between multiple growth factor receptors	Xq22.3	X-linked	
Central congenital hypothyroidism (Combined pituitary hormone deficiency)	*HESX1*	Transcription factor	3p14.3	AD	Septo-optic dysplasia
	PROP1	Transcription factor	5q35.3	AR	
	POU1F1 (PIT1)	Transcription factor	3p11.2	AD/AR	
	LHX3	Transcription factor	9q34.3	AR	Short and rigid cervical spine
	LHX4	Transcription factor	1q25.2	AR	Hypoplasia of the corpus callosum
	SOX3	Transcription factor	Xq27.1	X-linked	Developmental delay
	OTX2	Transcription factor	14q22.3	AD	Microphthalmia/anophthalmia, developmental delay
	GLI2	Transcription factor	2q14.2	AD	Holoprosencephaly, Cleft palate, midfacial hypoplasia

AD, autosomal dominant; AR, autosomal recessive. *Non-thyroid findings are described. These findings may not develop in all patients.

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among which *DUOX2* abnormality is the most common (186–190). The responsible gene is identified in 20% of cases of dyshormonogenesis and 5–10% of cases of thyroid dysgenesis. Epigenetic factors, such as somatic mutations, may be involved; however, the existing data to support this are insufficient at present (191), warranting further investigations on the causes of thyroid dysgenesis. Recent studies have suggested the concept of oligogenicity; i.e., that two or more variants of different genes cause human disease. Such oligogenecity (e.g., *DUOX2* and *DUOXA2*) may be involved in the onset of CH (188, 192). Currently, genetic testing may be considered if there are specific signs of dysgenesis or strong suspicions of dyshormonogenesis; however, genetic testing is not covered by insurance as of April 2021 and is only possible at the research level.

Conflict of interests of the working committee members: None of the committee members have a conflict of interest regarding development of the guidelines, based on the criteria for conflict of interest of the Japan Pediatric Society and in accordance with the rules of the Japanese Society for Pediatric Endocrinology.

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Appendix

Development process

1. Understanding current conditions

Article search and review methods

This is a revised edition of an existing guideline; thus, new articles published since 2014 were collected for each section to make the revisions without creating new clinical questions or modifying other sections.

The keywords for each section were used to manually search for articles published on Pubmed and Ichushi Web since 2014. A list of studies was created and a responsible person and assistant to the responsible person assigned for each section evaluated the strength of recommendation and quality of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) System for clinical guidelines to prepare an abstract form. The articles that best provided evidence for revisions to the manuscript were selected from the list of abstracts.

Publication process for of the revised guidelines

1. Process of revision

The decision to revise the Guidelines for Mass Screening of Congenital Hypothyroidism was made collectively by the Mass Screening Committee and Thyroid Committee of the Japanese Society for Pediatric Endocrinology and by the Japanese Society for Mass Screening, and the above committee was decided in January 2020 to that effect.

- 2020.5.13 First committee meeting (online conference): A responsible person and assistant to the responsible person assigned for each section met to decide on the methods for literature search.
- 2020.7.7 Second committee meeting (online conference): Articles found via keyword search for each section were reviewed.
- 2020.9.30 Third committee meeting (online conference): Abstract forms for the selected articles were reviewed to determine whether the article should be adopted based on the strength of recommendation and quality of evidence.
- 2021.1.15 Fourth committee meeting (online conference): Draft revisions were reviewed by by the responsible person for each section.
- 2021.2 Draft revisions were reviewed by the assistant to the responsible person.
- 2021.2–3 Reviews and revisions to the entire manuscript were performed by the Guideline Committee.
- 2021.4.21 The Guidelines for Mass Screening of Congenital Hypothyroidism (2021 revision) were drafted.

2. External evaluation

The draft guidelines were made openly available on a website for members of the Japanese Society for Pediatric Endocrinology from May 21, 2021 to June 21, 2021 to solicit opinions, and a

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revised draft for external assessment was developed on July 8, 2021, based on the opinions received.

The validity and appropriateness of the content of the revised guidelines was discussed by the Guidelines Committee, including external members, and revisions were made based on the proposal of the Guidelines Committee (July 5, 2021). This revision was approved by the Board of the Society on July 10, 2021 and published online in Japanese (http://jspe.umin.jp/medical/files/CH_gui.pdf)

3. Consultation with relevant societies

The draft guidelines were published on a website for members of the Japanese Society for Mass Screening from June 8, 2021 to July 7, 2021 for the solicitation of opinions from the Japanese Society for Mass Screening. A revised draft was developed on July 8, 2021 with consideration of the received opinions.

Revision schedule

The guidelines are planned to be revised within three yr on 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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Column: Central Hypothyroidism

1. Disease summary and newborn screening (NBS)

Congenital hypothyroidism (CH) is broadly classified into two types: primary CH, which involves an abnormality of the thyroid gland, and central CH (CCH), consisting of hypothalamic or pituitary abnormality. Compared to primary CH, CCH is mild and rare; thus, whether it is suitable for early detection and treatment, determination of which is the main objective of NBS, is under debated. Currently, T4 screening is conducted in some countries, such as the Netherlands, New Zealand, Israel, Italy, and some parts of the USA (1). In contrast, NBS in Japan targets primary CH, and the TSH levels alone are evaluated by dried blood specimen (DBS). However, concurrent FT4 and TSH screening have been performed in some regions (the city of Sapporo and the prefectures of Yamagata, Kanagawa [including the cities of Yokohama, Kawasaki, and Sagamihara], Saitama [including the city of Saitama], Okayama [including the city of Okayama], Kagawa, Yamaguchi, and Okinawa as of the present in 2020), and patients with CCH have been found (2, 3). Because delayed introduction of treatment for severe CCH can result in intellectual and motor developmental delays (4) and the incidence of CCH is about 1/15,000 – 1/30,000 individuals, higher than that previously reported according to the recent studies in Japan and the Netherlands (2, 5, 6), early detection by NBS is desired. A nationwide survey reported that isolated TSH deficiency goes undetected in municipalities that conduct TSH-only NBS (3). Moreover, some patients with CCH who are not detected by FT4 screening and are diagnosed from an examination of jaundice or short stature.

A Dutch study reported that the differences between the average cost of TSH, T4+TSH, and T4+TSH+ thyroxine-binding globulin (TBG) testing per case of detected CH (primary and central) was only marginal, at $6353, $6209, and $6851, respectively (7). In Japan, Adachi *et al.* estimated that the cost-to-benefit ratio would change only from 4.96 to 3.82, which is sufficient to meet the cost-benefit, because the increase in cost is generally limited to reagents kits for FT4 measurement when FT4 is added to the current system. With the addition of FT4, an increase in benefit is expected to due to increased early detection of patients (8). Moreover, the requirement of concurrent DBS testing for FT4 and TSH may also increase the re-test rate from approximately 0.3% for TSH screening alone to 1% (9).

2. Classification and etiology

CCH is broadly classified into that associated with combined pituitary hormone deficiency (CPHD) and isolated TSH deficiency. The former is further classified into three subtypes according to other complications (malformations); 1) Abnormal pituitary morphology only, such as pituitary hypoplasia or pituitary stalk interruption syndrome; 2) septo-optic dysplasia (de Morsier's syndrome) with optic nerve hypoplasia and abnormal formation of midline of the brain, such as absent septum pellucidum, and 3) multiple malformations, such as holoprosencephaly and other syndromes. Comprehensive Japanese studies have only succeeded in identifying pathogenic variants in a small percentage of patients, and their causes remains unknown. Holoprosencephaly that manifests with midline brain malformation and Prader-Willi syndrome, which presents with hypothalamic disorders, can also cause CCH.

Most causes of CCH with isolated TSH deficiency are unknown; however, abnormalities in *TSHβ*, *TRHR*, X-linked *IGSF1* associated with testicular enlargement (2012); X-linked *TBL1X* associated with hearing loss (2016); and X-linked *IRS4* (2018) have been reported to date. Studies in Japan have suggested that *IGSF1* is the main gene responsible for abnormalities in CCH, whereas abnormalities in other genes are extremely rare (10). Because CCH can be confused with other disorders such as transient hypothyroxinemia of prematurity or non-thyroidal illness syndrome (NTIS), which can occur due to undernutrition or poor general conditions, and, genetic analysis is usefull for diagnosis. As of April 2021, genetic screening for CCH is not covered by health insurance.

3. General clinical findings

The general symptoms of CH (dry skin, abdominal distention, jaundice, umbilical hernia, hoarseness, edema, and wide posterior fontanelle) may be observed; however, these symptoms are not notable except in the severe cases. CCH associated with hypopituitarism is diagnosed before NBS during detailed examinations of symptoms such as hypoglycemia or cyanosis in one third of all cases (3). It can also be detected by ocular symptoms, such as a lack of eye-tracking or nystagmus in patients with septo-optic dysplasia. Moreover, delayed motor development and impaired growth rate can indicate CCH in childhood.

4. Definitive diagnosis

Diagnosis of CCH is not easy; therefore, it is best to refer to or consult an experienced pediatric endocrinologist. In NBS, the following is checked in neonates who are referred to detailed examination for low FT4:

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Medical interview: Details regarding the weeks of gestation, birth weight and length, asphyxia, and frequency of defecation are obtained to consider possibilities, such as transient hypothyroxinemia in preterm infants or NTIS. A family history of thyroid disease, particularly Graves' disease in the mother, should be checked. Untreated Graves' disease is occasionally discovered in mother when examining a neonate for CCH.

Clinical findings: Patients are evaluated for general condition, weight gain, nystagmus, and external malformation, as well as the general symptoms of CH.

Testing: Examination at the first hospital visit includes complete blood count, serum chemistry, TSH, FT3, FT4, prolactin, TBG, radiograph of the knee, and thyroid ultrasonography. If TSH is inappropriately low relative to FT4 levels and other factors such as TBG deficiency are negative, then an assessment of anterior pituitary function should be performed including a TRH stimulation test, corticotropin-releasing hormone (CRH) stimulation test, and, if possible, a head MRI to assess pituitary structure should be performed. It should be noted that serum TSH levels can occasionally exceed reference values. The TRH stimulation test is not a strict requirement; however, a prolonged response is typically observed in which TSH levels peak after 90 min. In the case of a long course of disease, the TSH response is low overall. Approximately 75% of patients with CCH are associated with CPHD (3). Thus, hypothalamic, pituitary, and adrenal system functions should be evaluated before levothyroxine Na (L-T4) replacement therapy.

5. Treatment and prognosis

It is important to always replace hydrocortisone first and then L-T4, as L-T4 treatment can lead to adrenal insufficiency if accompanied by ACTH deficiency. There are few data on how early hydrocortisone should be replaced before the L-T4 treatment. Even when there is no clear evidence of ACTH deficiency, the post-therapeutic course should be monitored cautiously for possible adrenal insufficiency after starting L-T4 treatment, especially during the seventh to tenth days of therapy. There is a similar lack of strong evidence regarding the dosage of L-T4 for CCH treatment; nonetheless, the recommended starting dosage in the most severe forms of CCH (FT4 < 0.4 ng/dL) and in moderate to severe CCH (FT4 0.4–1.2 ng/dL) discovered by NBS is L-T4 10–15 μg/kg/d and L-T4 5–10 μg/kg/d, respectively, as in primary CH (11). The dosage is subsequently adjusted as needed, such that the FT4 level is within the average to upper limit of the reference range for the age group (5, 11). Unlike in primary CH, serum TSH level is not an indicator for dosage in CCH; however, studies have reported that the L-T4 dose is insufficient if TSH is 1 μU/mL or higher (5, 11). The L-T4 dose for pediatric CCH patients is approximately 50–100 μg/m^2/d (5). Prognosis of CCH has yet to be elucidated; however, a high rate of patients with septo-optic dysplasia detected with CCH exhibit intellectual disability (3).

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