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Complete List of Authors:	Cassio, Alessandra; University of Bologna, Department of Pediatrics Corbetta, Carlo; V.Buzzi Children Hospital, Regional Screening Center of Lombardia Region Antonozzi, Italo; University "La Sapienza", Department of Experimental Medicine and Pathology Calaciura, Francesca; University of Catania, Department of Clinical and Molecular Biomedicine Caruso, Ubaldo; G. Gaslini Institute, Departement of Pediatric Sciences "Giovanni de Toni" Cesaretti, Graziano; University of Pisa, Department of Pediatrics Gastaldi, Roberto; G.Gaslini Institute, Pediatric Clinic Medda, Emanuela; Italian National Institute for Health, National Centre for Epidemiology Surveillance and Health Promotion Mosca, Fabio; University of Milan, Department of Clinical Sciences and Community Health Pasquini, Elisabetta; Meyer Children Hospital, Clinic of Pediatric Neurology Salerno, Mariacarolina; Università di Napoli Federico II , Dipartimento di Pediatria Stoppioni, Vera; S.Croce Hospital, Department of Pediatric Neuropsychiatry Tonacchera, Massimo; University of Pisa, Endocrinology Giovanna, Weber; Vita-Salute San Raffaele University, Departmento of Pediatrics Olivieri, Antonella; Italian National Institute of Health, Deparment of Cell Biology and Neurosciences
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The Italian screening program for primary congenital hypothyroidism: actions to improve screening, diagnosis, follow up, and surveillance

*A.Cassio[1], *C. Corbetta[2], I. Antonozzi[3], F. Calaciura[4], U. Caruso[5], G. Cesaretti[6], R. Gastaldi[7], E.Medda[8], F. Mosca[9], E. Pasquini[10], MC. Salerno[11], V. Stoppioni[12], M. Tonacchera[13], G. Weber[14] and A.Olivieri[15]

*equally contributed to the article

[1]Department of Pediatrics, University of Bologna, Bologna; [2]Regional Screening Center of Lombardia Region, V.Buzzi Children Hospital, Milan; [3]Department of Experimental Medicine and Pathology, University "La Sapienza", Rome; [4]Departement of Endocrinology, University of Catania; [5]Departement of Pediatric Sciences "Giovanni de Toni", G. Gaslini Institute, Genova; [6]Department of Pediatrics, University of Pisa, Pisa; [7]Pediatric Clinic, G. Gaslini Institute, Genova; [8]National Centre for Epidemiology Surveillance and Health Promotion, Italian National Institute for Health, Rome; [9]Department of Clinical Sciences and Community Health, University of Milan, Milan; [10]Clinic of Pediatric Neurology, Meyer Children Hospital, Florence; [11]Department of Pediatrics, University of Naples Federico II, Naples; [12]Department of Pediatric Neuropsychiatry, S.Croce Hospital, Fano; [13]Department of Endocrinology and Metabolism, University of Pisa, Pisa; [14]Department of Pediatrics, Vita-Salute S. Raffaele University, Milan; [15]Department of Cell Biology and Neurosciences, Italian National Institute of Health, Rome, Italy.

On behalf of the Italian Society for Pediatric Endocrinology and Diabetology, Italian Society for the Study of Metabolic Diseases and Neonatal Screening, Italian National Institute of Health.

With the consensus of the Italian National Coordinating Group for Congenital Hypothyroidism**, Italian Thyroid Association, Italian Society of Pediatrics, Italian Society of Neonatology, Italian Society of Endocrinology, Associazione Medici Endocrinologi.

** **THE ITALIAN NATIONAL COORDINATING GROUP FOR CONGENITAL HYPOTHYROIDISM**
P. Beck-Peccoz, S. Bernasconi, A. Cassio, L. Cavallo, R. Cerone, C. Corbetta, R.Di Lauro, A. Olivieri, A. Pinchera, L. Tatò, H. Valensise, R. Vigneri

Key words: congenital hypothyroidism, neonatal screening, diagnosis, follow-up, surveillance,

Antonella Olivieri, Dr
Metabolism and Endocrinology Unit
Department of Cell Biology and Neurosciences
Istituto Superiore di Sanità
Viale Regina Elena, 299 - 00161 Roma
tel.: +39.06.4990.6150
fax: +39.06.4990.2619
e-mail: antonella.olivieri@iss.it

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List of abbreviations

CH, Congenital Hypothyroidism
INRICH, Italian National Registry of Infants with Congenital Hypothyroidism
b-TSH, blood Thyroid Stimulating Hormone
FIA, fluoroimmunoassay
RIA, radioimmunoassay
b-T4, blood T4
LBW, low birth weight
VLBW, very low birth weight
NICU, Neonatal Intensive Care Unit
IQC, Internal Quality Control
EQC, External Quality Control
ThyAb, thyroid antibodies
Tg , thyroglobulin
US, ultrasound
^{99}mTc, ^{99}m pertechnetate
DR, diagnostic re-evaluation
IOD, iodide organification defects

INTRODUCTION

The Italian screening program for primary congenital hypothyroidism (CH) is an integrated system including neonatal screening, diagnosis, treatment, follow-up and nationwide surveillance of the disease. In Italy the nationwide newborn screening program for CH began in 1977 and 100% coverage of neonatal population was virtually achieved in the '90s thanks to an efficient network of regional and inter-regional screening and clinical reference centers. The surveillance of the disease is performed by the Italian National Registry of Infants with Congenital Hypothyroidism (INRICH) which has been active since 1987 (1).

Despite the important results obtained in terms of standardization of screening and follow-up procedures, in the last years it has become clear that a process of optimization of the Italian screening program for CH is needed to harmonize and improve the screening strategy and diagnostic and therapeutic approach in all affected infants, and to guarantee an optimal quality of life to all CH babies. To this end the Italian Society for Pediatric Endocrinology and Diabetology, the Italian Society for the Study of Metabolic Diseases and Neonatal Screening, and the Italian National Institute of Health promoted national recommendations to realize actions aimed at improving diagnosis, treatment, follow-up and surveillance of CH in our country. These recommendations result from the integration of available guidelines (2-3), the experience of the Italian screening and clinical reference centers, and the knowledge derived from the INRICH surveillance activity.

1. NEONATAL SCREENING

All the Italian screening centers for CH use whole blood Thyroid Stimulating Hormone (b-TSH) as primary screening test, although a screening strategy employing simultaneous TSH+T4 testing is performed in 8 screening laboratories accounting for about 40% of all screened babies every year.

Twenty-three out of the 25 Italian screening centers use fluoroimmunoassay (FIA) methods to detect b-TSH, the others use radioimmunoassay (RIA) methods. For blood T4 (b-T4) FIA methods are used in 7 screening centers, while RIA methods are used in the others. Although secondary CH is not the target disease in the current Italian screening program for CH, babies with this disease may be identified in the screening centers which use simultaneous TSH+T4 testing as screening strategy. It would be helpful in the future to carry out a cost/benefit evaluation of this screening strategy at national level to verify the relevance of this procedure in our country.

The number of newborns screened yearly by each screening center varies among centers (range 5,000-100,000-newborns; median= 20,000). The minimum number of newborns that should be screened per year is debatable and relies on the fact that analytical proficiency is best accomplished when reasonable number of positive cases are encountered and cost efficiency is realized with higher volumes of testing (4). For this reason the Italian regulation on mandatory screening programs (DPCM 9th July, 1999) indicates 60,000 babies as the correct number of newborns to screen per center. This number is similar to that (30,000-50,000) suggested at the European level (http://ec.europa.eu). Therefore, it is recommended that in each region local authorities establish the adequate number of babies to screen, and hence the number of screening centers per region, on the basis of a correct cost efficiency evaluation and according to the Italian law and European indications.

1.1 The aim of the screening program

According to WHO criteria on newborn screening (5) the initial priority of newborn screening for CH is to detect primary CH and expedite thyroid hormone replacement therapy as early as possible. In 2006, the USA Health Resources and Services Administration - Maternal and Child Bureau and

the American College of Medical Genetics document "Newborn Screening: Toward a Uniform Screening Panel and System" (6) recommended:

- Mandate reporting of all secondary target conditions and reporting of any abnormal results that may be associated with clinically significant conditions, including the definitive identification of carrier status
- Consider that the range of benefits realized by newborn screening includes treatments that go beyond an infant's mortality and morbidity

These statements and recommendations are relevant also for CH newborn screening which is a part of a screening system addressed to select – by means of new technologies - many rare diseases. On the basis of this broader concept of newborn screening, the screening's target for CH is not only severe permanent CH (*core target*), but also mild persistent and transient forms that could have a benefit from an early replacement therapy (*secondary target*), as recommended by the American Academy of Pediatrics (2) and confirmed by recent studies (7-8)**.**

1.2 Primary TSH measurement: laboratory methodologies and cutoff values

The purpose of tests used for the newborn screening is to identify all infants that are at risk or presumptive positive for a given disorder in a population of apparently healthy newborns. The most sensitive test to detect primary CH is the measurement of TSH. It has been demonstrated that serum TSH levels as well as the log TSH are inversely proportional to the FT4 concentration. This implies that small changes in FT4 are reflected in large changes in serum TSH (9). At present, highly sensitive non-isotopic immunometric assays are available on a variety of automated immunoassay analyzer platforms. Furthermore methods for blood TSH (b-TSH) measurement can achieve a functional sensitivity of 1.0 mU/L and an interassay coefficient of variation ideally < 10% and not >

20%. As for RIA methods, these have similar sensitivity to that of FIA methods but are not amenable to high throughput automation.

Cutoff values for TSH used in the Italian screening centers varies between 7 and 15 mU/L whole blood (3 centers use a cutoff of 7 mUI/L, 20 use 10 mUI/L, 2 use 15 mUI/L). In 2002, the USA National Academy of Clinical Biochemistry promoted guidelines to support diagnosis and monitoring of thyroid diseases. The statement I.6 *"Cutoff TSH for screening of Neonates > 48 hours of age"* identifies a value of 10 mU/L whole blood as correct cutoff (4). This statement was subsequently confirmed by the American Academy of Pediatrics (2). However, each screening laboratory should calculate their b-TSH cutoff level and verify the congruence with international recommendations. The calculation of the cutoff value is performed on the basis of the evaluation of b-TSH Reference Interval which is generally the non parametric central 95%. Is worth to note that Reference Intervals are method- and age-specific. In a screening program the cutoff value represents the "*decision value*" at which a result is considered positive and determines the recall rate in the examined population. Therefore, each screening laboratory to correctly determine its test cutoff should calculate the test's sensitivity and specificity and weigh increased detection of mild cases *vs* harm from recall of normal infants.

1.3 Screening procedures for special categories of newborns

There is a subgroup of neonates in which primary CH may be masked by reduced levels of TSH at screening. These can be due to: hypothalamic-pituitary immaturity (10), foetal blood mixing in multiple birth (11), serious neonatal illnesses (12), some medications such as dopamine and glucocorticoids (13-14).

On the basis of these evidences a multiple sampling strategy is recommended for preterm newborns, babies with low birth weight (LBW) or very low birth weight (VLBW), neonates from multiple

birth, and sick newborns admitted to Neonatal Intensive Care Unit (NICU) (15-17). This implies that screening procedures for these special categories of neonates should routinely include a repeat b-TSH test at 2 and/or 4 weeks of life. Therefore, a close interaction among neonatologists, laboratorians and pediatric endocrinologists should be carried out in order to ensure a prompt diagnosis and an early treatment also in these special categories of neonates.

1.4 Neonatal TSH detection and iodine deficiency monitoring

The measurement of TSH as primary screening test has advantages in areas characterized by iodine deficiency as neonatal TSH has been demonstrated to be a sensitive indicator of neonatal and maternal iodine nutritional status (18). In facts, neonates are more susceptible to the effects of iodine deficiency than adults because of their limited iodine stores. Therefore, even mild iodine deficiency during pregnancy can compromise neonatal thyroidal secretion of T4 with a consequent increase in pituitary TSH secretion, which reflects an inadequate supply of thyroid hormone to the developing brain. This implies that the number of neonates with moderately elevated TSH concentrations (above 5 mlU/L whole blood) is proportional to the degree of iodine deficiency during pregnancy.

1.5 **Quality assurance**

Quality assurance (QA) is mandatory for all clinical pathology and biochemical genetics activities and newborn screening does not escape from this rule (19). Three levels should be defined:

- *Internal Quality Control (IQC)* – It allows monitoring of test performance by the routinely (daily) measure of QC material of known concentration (high and low). This procedure allows to verify the test performance in terms of precision and accuracy, and to early identify any trend of systematic errors before the analytical process is out of control. Usually IQC material is provided by the analytical kit manufacturer. However, the participation to other QC programs managed by

national/international organizations is strongly recommended. QC material can also be produced in-house with special regard to the stability. It is worth to note that calibrators must not be used as QC material. IQC results should be evaluated by means of appropriate statistical tools (Levey-Jennings control charts, regression, Youden plot, etc…) supported by specific computer programs.

- *External Quality Control (EQC)* – It implies the measure at scheduled times of unknown QC material provided by an external organization which also manages the results and provides a report. This procedure assesses systematic errors and performs inter-laboratory comparison (accuracy). A deep and accurate inquiry of the causes as well as corrective actions are required when a substantial and/or a systematic error is evidenced.

- *Proficiency testing* – It is similar to EQC, although it also evaluates the classification of a screening test. Therefore it assesses the whole screening laboratory performance.

Audit of the whole screening procedure should be performed at scheduled times, looking for: specimen quality, cutoff variations, false negative rate, false positive rate, positive predictive value, newborn's age at sampling and at diagnosis.

2. CONFIRMATION OF DIAGNOSIS AND SHORT TERM FOLLOW-UP

The screening laboratory is responsible for the quick communication of positive screening results to the clinical reference center. A close relationship between the screening center and the clinical reference center is strongly recommended to facilitate diagnostic evaluation and optimal management of affected babies. A positive screening result is only the first "step" of the management of an infant with a suspected congenital disease. As for CH, it may be different according to the screening strategy and to the expanded spectrum of neonatal thyroid disorders now detectable by neonatal screening (table 1) (20).

The reference clinical center should be characterized by a multidisciplinary experienced team (pediatric endocrinology, imaging studies support, neurocognitive evaluation, genetic counseling) that should be responsible for: i) the confirmation of diagnosis and follow-up, ii) the relationship with maternity/neonatologic units and paediatricians, iii) consultant activity in "at risk" infants. The goal of the confirmation of diagnosis is to confirm or to rule out CH by means of mandatory evaluations, and to start the replacement therapy as soon as possible (by 7-14 days of life). Optional diagnostic studies may be performed to specify the causes and the prenatal severity of CH (Table 2). If these studies are not readily available, treatment of children with confirmed CH should never be delayed.

2.1 Mandatory evaluations

1. Complete history: family history, prenatal thyroid status (maternal thyroid diseases, drugs and medications, iodine supply), pregnancy and labour features, personal history (birth weight, gestational age, perinatal features, chromosome disorders, drugs/substances interfering with thyroid function);

2. Physical examination with careful evaluation of possible extra thyroidal congenital malformations (21);

3. Serum should be obtained immediately for confirmatory measurements of TSH and freeT4 (FT4) in all newborns with b-TSH >20 mU/L at screening. In cases with b-TSH at screening ranging 10-20 mU/L a second filter-paper specimen should be obtained (according to local protocols) between 1-2 weeks of age in order to confirm or rule out the hypothyroid status. The result should be interpreted according to age- and method-related reference data (2).

2.2 Optional diagnostic studies

1. Serum for thyroid antibodies (ThyAb) and thyroglobulin (Tg) can be drawn. ThyAb positivity may be suggestive for a transient form of neonatal hypothyroidism when there is a history of maternal autoimmune thyroid disorder. Detection of serum Tg, especially if associated with imaging studies, may be useful to confirm the presence of thyroid tissue and to distinguish between Tg synthetic defects and other causes of hypothyroidism with in situ gland (22).

2. If there is a history of iodine overload, a single urine sample for assessment of urinary iodine excretion can be useful.

3. The evaluation of bone maturation at birth by X-ray or ultrasound (US) of the knee can be an indicator of prenatal CH severity (23-24)

4. Thyroid US studies are now accepted as the first line of imaging diagnostic investigation to verify the presence of thyroid tissue in the neck (25). Moreover, the use of colour doppler may be useful to identify ectopic tissue in sublingual region for its vascular iperafflux. An experienced investigator is strongly recommended as the interpretation of the results may be difficult at the neonatal age. If no thyroid tissue is detectable in the normal position on US, ^{99}m pertechnetate (^{99}mTc) thyroid scan should be performed to distinguish between thyroid agenesis and ectopy. However, this diagnostic procedure must not delay the start of therapy. Although ^{123}I gives a more accurate uptake, it should be used (if necessary in association with perchlorate test) subsequently in children who will be enrolled in the procedure of the re-evaluation of diagnosis (see below).

2.3 Communication of diagnosis

In all infants with confirmed CH the communication of diagnosis to the family should be regarded as a crucial step that needs careful management by trained personnel. Use of booklets and/or visual

aids is highly desirable, and complete information should be provided on: i) benefit of early diagnosis in preventing mental retardation, ii) appropriate manner of treatment administration, iii) adherence to the treatment plan, iv) importance of the compliance and periodic follow-up. To improve the communication process, the presence of cultural mediators can be helpful in the case of non speaking Italian families.

It is very important that CH newborn's parents understand that therapy with L-thyroxine and follow-up care must be continued for life. In the cases in which the definitive diagnosis is not performed at the initial workup, the family should be clearly informed that the treatment must be continued and the infants must undergo a careful follow-up until the assessment of permanence of hypothyroidism.

2.4 Initial treatment

L-thyroxine (L-T4) is the treatment of choice in CH. Although T3 is the biologically active hormone, most brain T3 is derived from local deiodination of T4. Therefore, combined treatment with T4 plus T3 has been shown not to significantly improve the outcome of CH (26). If the results of serum confirmation tests is not available in few hours (< 12hrs), treatment should be instituted immediately in cases with markedly elevated TSH spot concentration (i.e. > 40 mU/L) and/or absence of thyroid tissue in the neck on US examination. An initial L-T4 fast daily dose of 10 to 15 µg/kg in tablet form (according to the prenatal severity of CH, i.e. by using the highest end of the dosage range in more severe forms) has been recommended (2). The full dose, suspended in few ml of water, should be used from the beginning. Care should be taken to avoid concomitant administration of substances that can interfere with L-T4 absorption (soy, iron, calcium, fiber) (20), and to manage carefully the patients with large hemangiomas presenting a high deiodinase activity and an increased degradation of T4 (27). Recently, liquid formulation has been licensed by the

United States Food and Drug Administration and it is now available in Italy (3.75 μg of L-T4/drop). The liquid formula allows an easier administration. However, the bioequivalence between the two formulations and the possible side effects related to the use of ethanol as excipient have not been adequately studied yet (28-30). The safety of a higher starting dose in children with mild forms of CH or isolated hyperthyreotropinemia remains a matter of debate in light of an increased incidence of iatrogenic hyperthyroidism observed in these patients, and the possibility of adverse consequences as increased behavioural problems and attention deficits (31).

2.5 Controversial aspects in the initial workup

Hyperthyreotropinemia

Hyperthyreotropinemia is characterized by normal or low/normal FT4 values and elevated serum TSH concentrations at the recall examination. The aetiology is heterogeneous and due to genetic and/or environmental factors causing transient or persistent high TSH (32). The need for treatment of this condition is still controversial. Serum TSH values persistently higher than 10 mU/L after the first 2 weeks of life are considered abnormal by some authors who suggest L-T4 treatment in these cases. However, if children are not treated a strictly follow-up is needed (33). The management of infants with TSH values between 5 and 10 mU/L at the recall examination is even more controversial as the reference range for TSH between 2 and 6 weeks of age has been reported to be 1.8 to 7.9 mU/L (34). Whether this condition, if persistent, needs to be treated is still a matter of debate. If not treated, these children should be re-evaluated later (betweeen 1 and 2 years of age) to verify the permanence of high TSH. In fact, in many cases neonatal hyperthyreotropinemia has been demonstrated to be the consequence of persistent (although minor) thyroid abnormalities causing mild hypothyroidism later in life (35).

3. LONG-TERM FOLLOW-UP AND TRANSITION TO ADULTHOOD

3.1 Monitoring of treatment

Hormones

Recent studies suggest that an early treatment (by 7-14 days of life) with the above recommended initial doses can rapidly normalize serum TSH and FT4 levels and restore a normal intellectual outcome even in patients with severe CH (36-38). Higher initial doses are related to quicker normalization times of serum FT4 and TSH levels, but phases of biochemical hyperthyroidism during the first months of treatment and long-term behavioural problems have been described in some cases (31). Therefore, the L-T4 treatment must be monitored by FT4 and sensitive TSH measurements, maintaining serum FT4 levels in the upper half of the normal age-related range and TSH levels strictly within the normal range. The titration of L-T4 dose should be adjusted always according to serum FT4 and TSH concentrations (routine increases of the dosage on the basis of infant's age and weight should be avoided). The hormone monitoring should be done 1-2 weeks after the initial treatment (especially in subjects treated with higher doses and/or in subjects with mild forms to avoid phases of overtreatment) and at frequent intervals thereafter during the first 3 years of age (table 2).

Growth

Linear growth, pubertal development and final height are normal in children with CH treated from the first weeks of life, therefore clinical and auxological parameters should be routinely assessed in CH subjects like in healthy children. No relationship has been found between growth pattern and severity of CH at diagnosis or L-T4 starting dose. Similarly to what occurs in general population, the major factor determining height in these children is the familial genetic growth potential (39). Times at growth evaluation are reported in Table 2.

Neuropsychological development

Psychomotor development should be evaluated by pediatricians at the time of diagnosis of CH, at the age of 6 months, and at each visit thereafter. If developmental delay is suspected a neuropsychiatric evaluation should be immediately performed. Moreover, a specialized team is required for neurocognitive evaluation in babies with permanent CH (especially in those with severe forms) or with CH associated to other pathological conditions. In these cases neuropsychological evaluation should be performed as follows:

- at 12, 18, 24 months of age to evaluate intersubjectivity and interaction skills by Griffiths developmental scale and the McArthur's questionnaire;

- at 36 months for evaluation of language and fine motor development by Griffiths developmental scale and TPL test (Test Primo Linguaggio- Axia);

- at 5 years to evaluate intellectual ability and requirements for reading and writing (by WISC III for intellectual ability, PRCR2 for metaphonological abilities);

- at 7 years to evaluate intellectual ability, specific learning disorders (reading and writing), and attention by WISC III for intellectual ability, MT test for reading, Tressoldi Cornoldi test for writing, AC MT for mathematic, barrage test for attention.

A neuropsychological follow-up is essential until the age of 7 years because of the possible occurrence of symptoms and deficits associated with specific disorders or intellectual retardation. In adolescents and young adults neuropsychiatric evaluation can be necessary in subjects with abnormalities in previous checks or in subjects in whom cognitive or behavioral symptoms not previously underlined appear (40).

3.2 Genetic counselling

Primary CH is a disease with a broad range of expressivity going from severe thyroid developmental defects to mild hyperthyrotropinemia. Therefore after an accurate diagnosis, most

cases of permanent CH need to be investigated in collaboration with molecular biologists and/or clinical genetists .

Thyroid dysgenesis is due to disturbances in the gland organogenesis (thyroid agenesis, ectopy, hypoplasia) (41). Due to the low frequency of known mutations in patients with thyroid dysgenesis, genetic testing should be initiated in those patients with either a familial occurrence of thyroid dysgenesis or in patients having additional extra-thyroidal congenital malformations (21, 42). In particular, genetic testing should be done in children with thyroid dysgenesis associated with: cleft palate (FOXE1 mutations), variable pulmonary symptoms as well as neurological alterations (NKX2.1 mutations), unilateral kidney agenesis (PAX8 mutations), cardiac abnormalities (NKX-2.5). Loss-of-function mutations of TSH receptor or PAX8 genes should be investigated in cases with normal sized/hypoplastic gland (43).

In patients with inborn error of thyroid hormone biosynthesis (caused by mutations in one of the genes coding for proteins involved in hormone synthesis such as Tg, TPO, DUOX2), as well as in babies with defects of iodine transport/trapping/recovering (mutations in Pendrin, NIS, DEHAL1), CH is usually associated with normally located and shaped thyroid or goiter. These cases show classical autosomal recessive mode of inheritance and an exact molecular diagnosis allows genetic counselling. Moreover, the identification of asymptomatic mutation carriers at risk of recurrent hypothyroidism has prognostic value in differentiating transient from permanent CH, and provides a rationale for adjunct iodine supplementation (44).

Clinical and biochemical evaluation aids in selecting the most appropriate candidate gene(s). On the basis of family history, serum Tg determination, thyroid US and scintigraphy with perchlorate discharge test, a molecular inherited defect in thyroid hormone synthesis can be diagnosed: defects in iodide trapping (NIS), in the facilitated iodide efflux across the apical membrane (Pendrin), the organification of iodide within the follicular lumen (thyroid peroxidase, DUOX2, DUOXA2), the

substrate for thyroid hormone synthesis (Tg) and the ability to recover and retain intrathyroidal iodine (DEHAL1).

3.3 Transition to adulthood

CH children should be followed by a pediatric endocrinologist at a reference clinical center up to the achievement of puberty and final height. Thereafter young CH adults should be followed in appropriate centers of endocrinology where a clinical evaluation should be performed every 6-12 months or more frequently if monitoring of serum TSH is abnormal or poor adherence/adequacy of treatment is suspected. In view of a long term replacement therapy with L-T4 one must be aware of the fact that frequent episodes of subclinical hyper or hypothyroidism may occur. These should be avoided in order to prevent cardiovascular abnormalities (45), overweight (46), and negative effects on bone mineral density (47). Possible selective attention problems, memory deficit, fine motor and hearing impairment (46,48) may persist through adulthood affecting their social life, self esteem, and emotional functioning (46). It is important for parents and clinicians to encourage young adults with CH to continue peer-related activities as much as possible to stimulate their social performance and self esteem (49). Awareness of patient health related quality of life and possible gaps in the course of life can be useful in clinical practice.

4. RE-EVALUATION OF THE DIAGNOSIS

Diagnostic re-evaluation (DR) is generally performed at 2–3 years of age to distinguish between permanent and transient CH in patients with in situ thyroid in whom no permanent cause of CH was found at diagnosis, and in children in whom the definitive diagnosis was not performed at starting

therapy. DR can be anticipated at the end of the first or second year of life in patients with a high suspicion of transient CH (exposure to excess iodide, maternal anti-thyroid antibodies) and/or in those not requiring L-T4 dose adjustment during the first months of life. DR includes the assessment of serum TSH, FT4, Tg, and thyroid US evaluation. Moreover, ^{123}I scintiscan should be done at this age in all patients in whom it was not performed it in the neonatal period, whereas ^{123}I scintiscan with perchlorate (KClO4) discharge test and/or analysis of genes related to CH should be performed only in selected cases (see below).

In children with in situ thyroid, DR can be performed following two optional strategies. The first option is to reduce the L-T4 replacement dose by half; if serum TSH concentration is above 20mU/L after 30 days, the permanence of hypothyroidism is confirmed (2). However, this approach does not allow to identify the aetiology of permanent cases of CH. It is therefore challenging to establish an accurate prognosis and genetic counselling of affected families. The second approach includes L-T4 withdrawal for a month before DR. In severe forms of CH with high L-T4 dosage requirement, it can be suggested to replace therapy with Liothyronine for two weeks (at a dose equal to 2/3 of the dose of L-T4, divided into three daily doses), followed by a complete withdrawal of therapy for 15 days. The management of DR is reported in Figure 1.

To identify iodide organification defects (IOD) a ^{123}I scintiscan with KClO4 discharge test should be performed in selected cases with in situ thyroid (thyroid hyperplasia, elevated Tg at diagnosis, positive family history for thyroid disorders). A ^{123}I discharge >90% of the basal uptake measured 2h after ^{123}I administration is typical of total IOD, while discharges ranging 10–90% indicate partial IOD. Defects in Tg synthesis should be suspected in patients with normal thyroid or goiter, TSH elevation and low or undetectable Tg levels. In these selected cases, testing for specific genetic mutations should be considered.

5. NATION-WIDE SURVEILLANCE

Monitoring and evaluation of a national screening program allows for the assessment of the effectiveness and efficacy of the program, as well as improvements according to established objectives. Therefore, in a country where a nation-wide screening program for CH is active the implementation of a population-based registry, collecting information on new cases diagnosed by screening and linking laboratory tests information with clinical evaluation, is recommended. Such a registry represents a useful tool to perform nation-wide surveillance of the disease and to promote scientific research.

According to WHO's definition, a register is a collection of permanent records on individuals with the intention of long-term follow-up (50). More recently the definition of a "registry" has been extended from a simply database to a more complex systematic data collection program (51). The main objectives for a registry are: i) to perform epidemiological surveillance, ii) to assess total needs for care in terms of evaluation of effectiveness of health services, iii) to contribute to clarify the etiology aiming at the prevention of the disease. The high-standard registries can also contribute to develop norms, standards and recommendations. The main reason why a nation-wide, and hence a population-based registry, gives an added value when compared with smaller and local databases for a certain disease is represented by the fact that decentralization reduces standardization and thus comparability. This implies that a population-based registry has invaluable potentials for public health surveillance and scientific research. However, any registry program must collect high quality data to be useful for its stated purpose. As a registry is a tool to either count or characterize the recorded affected subjects, completeness of case ascertainment and accuracy of reported information have important implications for the conclusions and generalizability of the results.

The INRICH performs the nation-wide surveillance of CH in our country (1). It was established in 1987 as a program of the Health Ministry and is coordinated by the Istituto Superiore di Sanità

(Italian National Institute of Health). The 25 Italian screening centres for CH are responsible for collecting information on new cases of infants with diagnosis of CH who started the replacement therapy, and for sending data to the INRICH . Information on re-evaluation of the diagnosis is also collected in the INRICH.

Over the years, the INRICH has contributed to improve procedures for diagnosis, treatment and follow-up of affected babies by identifying critical points in screening program procedures. Moreover, the large amount and the high quality of information collected in the INRICH have provided a unique opportunity for research. This because data collected in the INRICH are referred to the entire Italian population of CH infants. The results derived from epidemiological studies performed by using the INRICH data have contributed to deepen knowledge of CH (21), to start identifying the most important risk factors for the disease (11,52), and to orient molecular biologists towards the identification of new genes involved in the etiology of this disease (53).

6. LEGAL ASPECTS

In 1992 in our country a national law (Law n.104, 5th February1992) introduced mandatory newborn screening for three diseases: CH, Cystic Fibrosis and Phenylketonuria. Aim of the law was the early detection of defects and the mandatory control of all positive newborns to perform a prompt diagnosis and treatment aimed at preventing the severe physical and neuro-psychological sequelae. Given the mandatory nature of the Italian screening program for CH the possibility that parents decline screening for their baby is not permitted. If this eventuality occurs the right authorities should be informed.

In force of the above mentioned law many Italian regions established one or more regional newborn screening centers. It is recommended that all the Italian regions identify one or more (related to the

number of screened babies) regional clinical centers for diagnosis and clinical management of babies with CH.

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