

Congenital hypothyroidism in Calabria: epidemiological and clinical aspects

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Summary. Neonatal screening of congenital hypothyroidism (CH), carried out on all newborns 3rd-5th day of life, has a very important priority because the incidence of this disease is the highest of all congenital diseases involving brain damage which can be preventable with early specific treatment. In recent years, the values of TSH that were considered pathological were modified and the TSH cut-off, the title of hormone to be taken as the limit of significance for determining a subject suffering from CH, has been progressively lowered. In Calabria the introduction of the new value of TSH cut-off on blood spot, has led to a considerable increase in the frequency of CH, particularly in the case of the thyroid *in situ* normal ultrasound and of the diagnosis of transitional forms of CH.

Key words: congenital hypothyroidism, TSH cut-off, neonatal screening, thyroid *in situ*, transient congenital hypothyroidism.

Riassunto (*L'ipotiroidismo congenito in Calabria: aspetti epidemiologici e clinici*). Lo screening neonatale dell'ipotiroidismo congenito (IC), eseguito su tutti i nati in 3^o-5^o giornata di vita, ha un'importanza prioritaria perché l'incidenza di questa patologia è sicuramente la più alta di tutte le malattie congenite che comportano un danno cerebrale, prevenibile con specifico precoce trattamento. Negli ultimi anni i valori di TSH ritenuti patologici si sono modificati, il cut-off del TSH, ovvero il titolo di ormone da assumere come limite di significatività per definire un soggetto affetto da IC, è stato progressivamente abbassato. In Calabria l'introduzione del nuovo valore di cut-off del TSH ematico su spot ha portato ad un aumento considerevole della frequenza di IC, soprattutto delle tiroidi in sede ecograficamente normali, ed alla diagnosi di forme di IC transitorio.

Parole chiave: ipotiroidismo congenito, cut-off del TSH, screening neonatale, tiroide in sede, ipotiroidismo congenito transitorio.

INTRODUCTION

Congenital hypothyroidism (CH) is the most frequent endocrine disease in children caused in most cases by alterations in the embryogenesis of the thyroid gland: absence of the gland (agenesis), reduced volume (hypoplasia) or presence of blanks in ectopic thyroid (ectopic) [1]. Secondary (pituitary origin) and tertiary (hypothalamic origin) hypothyroidism are uncommon.

Transient hypothyroidisms are defined as a condition characterized by abnormal levels of T4 and TSH screening, confirmed in a subsequent control of serum with or without clinical signs of hypothyroidism with spontaneous normalization of thyroid function, in the absence or after a variable period of replacement hormonal therapy [2].

Transitional forms of congenital hypothyroidism have been described due to maternal therapy during pregnancy, to excess iodine in the perinatal period, a maternal autoimmune thyroid disease and iodine endemic deficiency in the territory [3]. The damage due to prolonged lack of thyroid hormone is varied

and spread to all organs and systems, in particular, the dwarfism disharmonious and above all the lesions of the central nervous system, leading to severe mental retardation, or *cretinism*.

Hormone deficiency is reflected electively on the nervous system and on the skeleton, which in the critical phase of development, requires a quantity of hormones iodates greater than those required for other tissues [4]. Good timing and adequate replacement hormonal therapy with levothyroxine, inexpensive and simple administration, makes it possible to prevent such damages, provided it is implemented early.

For this purpose, because in the neonatal period, the symptoms are aspecific, often blurred or completely absent, we use neonatal screening of CH, performed on all newborns born between 3rd-5th day of life [2]. The 3rd-5th day of life are an excellent result in which the physiologic phase of hyperfunctioning thyroid. In fact, in the 1st week of life the thyroid hormone values and TSH are physiologically higher than the typical newborn [4]. The systematic dosage

of tiroxina and TSH represents the optimal method for screening of all the forms of hypothyroidism in primary and secondary situations, a deficit hypothalamic or hypophysical.

In Calabria the dosage of both analytes (TSH and T_4) thanks to this method can detect cases of secondary CH or forms of CH in which the TSH rises belatedly.

In Italy neonatal screening of CH began in 1977 gradually extended to the whole national territory and quickly reaching excellent levels of coverage of the neonatal population. In Calabria neonatal screening has been running since 1 January 1991 pursuant to Regional Law number 26 on 20/04/1990 and all newborns positive to neonatal screening are sent to the Regional Center for diagnostics confirmation and follow-up of the CH.

Since 1995, all newborns in Italy are subjected to screening through the existence of 26 Regional Centers of screening or interregional spread throughout the country [5]. In Calabria the infant who results positive of neonatal screening (TSH higher than normal and/or T_4 values below the normal standards) must be immediately submitted for assay of hormones, TSH and FT_4 , on serum for the confirmation of diagnosis.

The determination of basal TSH, together with the determination of FT_3 , FT_4 , TBG (thyroxine binding globulin) and TG (tiroglobulin) allows a complete assessment of thyroid function [6].

Further investigations are performed to identify the etiology, to check the persistence or transience and to assume part of the prenatal onset of the disease or not. They consist of the thyroid ultrasound and/or thyroid scintigraphy (with I^{123} or Tc^{99m}) in the radiography of the knee (Beclard's nucleus) and possibly in the determination of iodide, maternal antibodies blocking the TSH receptor, anti-TPO, anti-TG or genetic studies [7].

The dosage of TG and iodate particles to low molecular weight, as well as the measurement of iodide, contribute to define differentiation of different types of defects, providing evidence to allow discrimination of congenital errors in addition to those acquired, and transient forms of hypothyroidism,

due to environmental iodine deficiency or excess of iodine in the perinatal period [8]. In Calabria a clinical-laboratory control is carried out after 2-3 weeks of therapy and future laboratory controls, clinical and auxological, should be done regularly, with varying frequency depending on age of the child (Table 1).

Children will also have to be all screened for hearing deficits and followed closely in their neuropsychiatric development [9].

The implementation on a national prevention has involved close liaison between neonatal units, centers of screening and reference structures for the care and follow-up of children with CH and was made a national coordination of thyroid screening and other activities related to this disease through the National Registry of Congenital Hypothyroidism established in 1987 [5]. In recent years, the values of TSH, that were considered pathological, were changed and the limit value of cut-off was gradually lowered [10]. The point of cut-off depends on the parameter distributions of TSH observed in a population and by sensitivity and specificity of the screening programme [11]. In this study, we wanted to assess in the Calabria Region the impact of the introduction of the new value of TSH cut-off of blood spot on, which is considered today a pathological value of TSH > 7 mU/L, contrary to what happened a few years ago when it was assumed a value of pathological TSH > 20 mU/L.

MATERIALS AND METHODS

296 infants (150 females-146 male) with suspected CH, arrived from 1987 to 2008 at the "Regional Center of diagnostics confirmation and follow-up of Congenital Hypothyroidism" of Calabria Region, to the Department of Paediatrics of the University "Magna Græcia" of Catanzaro.

Of these: 12 (4 females-8 males) were diagnosed and treated before 1991 (when there were not the newborn screenings); 156 (90 females-66 males) are currently in substitution treatment with levothyroxine and were diagnosed from 1 January 1991, when the "Regional Center for Neonatal Screening" start-

Table 1 | Follow-up of newborn with congenital hypothyroidism in Calabria

	3 rd month	6 th month	9 th month	12 th month	15 th month	18 th month	24 th month	30 th month	36 th month	36 th month once a year
Objective examination	*	*	*	*	*	*	*	*	*	*
Biochemical valuation	*	*	*	*	*	*	*	*	*	*
Neuropsychomotor development	*			*		*	*		*	*
Bony tissue age		*		*			*		*	
Audiological control		*		*			*		*	*
Ophthalmologic control		*					*			
Cardiological control		*		*			*		*	*

ed operating; 128 (56 females-72 males) were affected by transient congenital hypothyroidism; of these 106 (49 females-57 males) have never made replacement therapy and 22 (7 females-15 males) stopped therapy for the gradual normalization of hormonal values, all with thyroid *in situ*.

Of these 22 children: 19 (6 females-3 males) have interrupted therapy with gradual decrease of the same without reevaluation with thyroid scintigraphy, 3 (1 female-2 males) suspended therapy after reevaluation with thyroid scintigraphy without relapse.

The parameters evaluated for the suspension of substitution therapy were: age > 1 year and reassessment of thyroid function after at least 2 months of suspension.

The average duration of therapy before the stop in these 22 patients were: females 42 months (range 36-48 months); males 44 months (range 13-96 months).

Our data shows that this phenomenon has increased in recent years, particularly from January 2000 to December 2008, during which it was diagnosed with almost all patients with Transient congenital hypothyroidism of the Center.

The peak of the diagnosis of this condition was in 2004, when there was further lowering of cut-off value of TSH from 10mU/L to 8 mU/L.

Each year, about 18 500 newborns are screened at the Regional Center for Neonatal Screening [12]. In Calabria the TSH cut-off, which until the early months of 2002 was 20 mU/L, was gradually changed in recent years on the basis of experimental evidence; became 15 mU/L in May 2002, 10 mU/L in April 2003, 8 mU/L in May 2004 has reached the threshold value of 7 mU/L in March 2007.

In the cohort of patients with congenital hypothyroidism of our Center, we assessed the following data:

1. sex;
2. values of TSH and T4 in the I and II *spot* (if performed);
3. the dosage of spheric hormones;
4. the presence of a possible family history of thyroid disease;
5. enforcement of thyroid echography to determine of etiology and / or thyroid scintigraphy with Tc⁹⁹ or I¹²³ to evaluate the morphology and function of thyroid gland;
6. the performance of radiography of the knee, to see the presence or absence of nucleus of ossification in the cases indicated;
7. the age of diagnosis;
8. the date of onset of therapy, the dosage and its possible variations.

RESULTS

An increase was noted in the percentage of calls or an increase in the incidence of positive neonatal screening after confirmation of the value of TSH and FT₄ hormones on serum: the impact of

CH in Calabria was 1/2680 in the period 1987-2000 and was increased to 1/830 in the period 2001-2005 [13]. The Calabria region, historically known as an area with iodine deficiency shows values of incidence above the national average [12]. Several factors probably contribute to this significant increase in the incidence of CH in recent years, it is possible that a few cases of these may be due to forms of transient congenital hypothyroidism.

All our data also indicates that a great part of cases with CH with the thyroid *in situ* when it had not been diagnosed with the previous value of cut-off and that the prevalence of congenital hypothyroidism in our region was higher than previously considered [14].

Of the 168 patients (94 females-74 males) of our Center, still in substitution therapy with levothyroxine, the etiology of thyroid failure was 9.5% ectopy, 17.0% agenesis, 19.0% hypoplasia, 54.5% thyroid *in situ*.

29 children with agenesis, 16 with ectopy, 32 with hypoplasia and 91 with thyroid *in situ* were diagnosed between 1987 and 2008.

6 children with thyroid *in situ* were diagnosed between 1991 and 2001, 85 between 2002 and 2008 with a peak of 21 in 2004.

Of these 91 thyroid *in situ*, 9 (6 females-3 males) are still down scaling the therapy, 3 (2 females-1 males) had discontinued therapy and have again due to resumption after a further increase of TSH (in these patients the average duration of the suspension was about 3 months), 82 continued the therapy. These children will be monitored in follow-up until the age of 18.

The follow-up after discontinuation of therapy is important in order to avoid any future deficits related to temporary malfunction of the thyroid. 61% of females and 42% of males with CH have familiarity for thyroid disease.

In the period 1987-2001, in 57 patients, the mean value of TSH in the first paper (*spot*) was 386.2 mU/L (range 21.5-1520 mU/L) and the TSH cut-off was 20 mU/L, the average the values of T4 was 2.45 µg/dl (range 0-5.7 µg/dl).

In the period 2002-2008, in 111 patients, the mean value of TSH in the first paper (*spot*) was 128.7 mU/L (range 8-780 mU/L), the mean value of T4 was 4.4 (range 0-12.7 µg/dl).

It should be emphasized as in the second period, the prevalence of agenesis has been drastically reduced, although in early 2006 it was possible to observe a new increase in cases of agenesis more frequently in females (0 M- 4 F).

These contrasts with the data for the triennium 2003-2005 in which there was no diagnosed agenesis but there has been a marked and significant increase of patients with normal thyroid *in situ*.

The values of TSH and T4, also have proportionately adjusted by a decrease of the average values of elevation of TSH and T4 values from I to II period [15]. Average age at diagnosis was 23 days

(range 10-57 days); average age of starting therapy was 24 days (range 11-58 days); average dose of levothyroxine was 37.5 µg/days (range 25-50 µg/days).

In the period 1987-2001 the average age at which children with CH, diagnosed at neonatal screening, that undertook replacement therapy was 26 days (range 10-57 days).

In the period 2002-2008 the average age of starting therapy was 21 days (range 9-39 days).

In the period 2002-2008, children with CH have started replacement therapy before the 21st day of life with an advance of 5 days to the period 1987-2001.

DISCUSSION AND CONCLUSIONS

The natural history of congenital hypothyroidism changed dramatically since neonatal screening was introduced.

Before screening tests were available many newborns with this disease showed a mental retardation moderate to severe and a considerable physical delay which translated respectively in cretinism and dwarfism disharmonious; these results are now very uncommon, if not completely disappeared.

Even today, however, despite early treatment appears to preserve these patients from a significant mental retardation, there are some specific difficulties such as hinder mobility, attentive deficits, changes in selective memory and visual-spatial skills.

The dissemination of multidisciplinary programs of follow-up, with the participation of child neu-

ropsychiatrist, ophthalmologist, audiologist, coordinated by endocrinologist pediatrician, has minimized the incidence of neurological complications: the psychological and neuromotor development of children with CH early treated, is comparable to that of normal children, as well as the growing stature-weight (*Table 1*).

We can therefore say that the prognosis of CH, once among the most severe in the brain and somatic development, is now considered optimal for all functions of the individual [10].

Final data, on the height of patients with CH treated within the first month of life shows the average values perfectly normal and sometimes even higher than the genetic potential.

Therefore, the early start of pharmacological treatment of CH determines not only a normal increasing stature, but also a normal maintenance of correct body proportions between the upper and lower decks.

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