EXPLORING THE UTILITY OF A POPULATION-BASED REGISTRY OF CONGENITAL HYPOTHYROIDISM (CH): THE MODEL OF THE ITALIAN NATIONAL REGISTRY OF INFANTS WITH CH

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ABSTRACT

A population-based Registry of congenital hypothyroidism (CH) has the potential to assess temporal and geographical trends of the disease incidence, to identify possible clusters of the disease, to characterize the affected population, and to promote development of ad hoc investigation of suspected exposures as possible causes of the disease. Moreover, by identifying critical points in screening program procedures it can contribute to develop recommendations to improve diagnosis, treatment, and follow-up of CH babies.

In Italy the neonatal screening program for CH is a complex system including screening, diagnosis, treatment, follow-up and nationwide surveillance of the disease. This is performed by the Italian National Registry of Infants with Congenital Hypothyroidism (INRICH). All the Italian Centres in charge of screening, diagnosis and follow-up of infants with CH take part in the INRICH. The aims of the Registry are to monitor efficiency and effectiveness of neonatal screening, to provide disease surveillance and to allow identification of possible aetiological risk factors for the disease. Therefore, the INRICH represents a useful epidemiological tool for surveillance of the disease and a powerful resource of information on CH babies. In fact, the results derived from epidemiological studies performed by using the INRICH data have contributed to deepen knowledge of CH, to start identifying the most important risk factors for the disease, and to orient molecular biologists towards the identification of new genes involved in the aetiology of CH, which still represents the most frequent endocrine disease in infancy.

Key-words: congenital hypothyroidism, neonatal screening, surveillance, population-based registry.

Introduction

Congenital hypothyroidism (CH) is the most frequent congenital endocrine disorder and the leading cause of preventable mental retardation. This represents the most dramatic long term sequel of the disease. The etiologies include thyroid dysgenesis (agenesia, ectopia, hypoplasia), thyroid dyshormonogenesis, hypothalamic-pituitary deficiency (central hypothyroidism), and transient hypothyroidism. By measuring Thyroid Stimulating Hormone (TSH) or TSH + total thyroxine (T4) in dried blood spots in all babies shortly after birth, newborn screening programs are able to identify biochemically infants who may have CH even before there are any signs or symptoms of hypothyroidism. The eradication of mental retardation, the main objective of neonatal screening, has been achieved in industrialized countries where nationwide screening programmes have been established [1-3].

In Italy the nationwide newborn screening programme for CH began in 1977 and 100% coverage of neonatal population has been achieved since the 90’s thanks to an efficient network of 26 regional and inter-regional Screening and Follow-up Centres. At present blood spot detection of TSH is used as primary screening test in 15 of the 26 Italian Screening Centers, while in the remaining Centers TSH+T4 screening strategy is used. In all the Centers positive results of screening are confirmed by definitive tests of thyroid function on serum (TSH, free T4 and/or T4). Thyroid ultrasound and/or scintigraphy are generally performed to complete the CH diagnosis. Infants with confirmed primary CH are then referred to the Follow-up Center of their own region for starting replacement therapy.

According to available guidelines [1, 4], when the definitive diagnosis is not established in the neonatal period and a suspicion of transient primary hypothyroidism is present, a reevaluation of diagnosis is performed at the age of 3 years after a withdrawal of the replacement therapy to ascertain the persistence of CH.

The Italian National Registry of Infants with CH (INRICH)

In Italy the neonatal screening program for CH is a complex system including screening, diagnosis, treatment, follow-up and nationwide surveillance of the disease. This is performed by the Italian National Registry of Infants with Congenital Hypothyroidism (INRICH) in which all the Italian Centres
in charge of screening, diagnosis and follow-up of infants with CH take part (www.iss.it/rnic/). The Registry 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) [5-6]. The INRICH is a population-based Registry. This implies that results obtained in the analyses conducted on the data collected in the INRICH are highly representative, can be easily used to improve the health of CH children, and provide information critical to understanding the etiology of the disease. The aims of the Registry are: 1) to monitor efficiency and effectiveness of neonatal screening, 2) to provide disease surveillance, and 3) to allow identification of aetiological risk factors for CH.

Information on new cases with CH are collected in the INRICH by means specific questionnaires filled in at diagnosis. These include anonymous data concerning screening and confirmatory laboratory tests, demographic data, details on clinical state in neonatal period (included extra-thyroidal congenital malformations), diagnostic investigations, information regarding pregnancy, birth, and family background, starting and dose of the replacement therapy. It is important to note that babies with transient hyperthyrotropinemia on the basis of spontaneous normalization of TSH between screening and diagnosis are not recorded in the INRICH. The Screening Centres are responsible for collecting the questionnaires containing information from birth clinics and follow-up centers, for accuracy of their compilation, and for sending them to the INRICH. This system allows to optimize the flow of information toward the Registry by reducing sources of data concerning one CH baby. Data are coded and stored in an informed database at the Istituto Superiore di Sanità and results of data analyses are reported in a web site (www.iss.it/rnic/), presented in national and international conferences, and published in international scientific journals (FIG.1).

The INRICH surveillance activity

In the first years of the INRICH activity a strict surveillance of the Italian screening program allowed to identify some aspects which had to be improved. During the years the active and continuous collaboration between the Registry and the Italian Screening and Follow up Centres
Fig.1. Flow of information on new cases with CH collected by the INRICH has allowed to improve standardization of screening procedures with considerable improvements in terms of reduction of age at starting treatment and adequacy of dose of the replacement therapy (FIG.2). In fact, while the median value of infant’s age at starting therapy was 23 days between 1987 and 1999, a reduction of this value was observed in the period 2000-2006 (19 days) although significant differences among diagnoses were observed: ectopia: 15 days; agenesis: 16 days; hypoplasia: 20 days; normal/hyperplastic thyroid: 23 days. Moreover, the INRICH data demonstrated a high efficiency of screening program also among babies with high risk of morbidity such as twins and babies with additional congenital malformations. In fact, no delay in time of starting therapy was found when twin CH babies were compared with singletons, as well as when CH babies with extra-thyroidal congenital anomalies were compared with infants with isolated CH [7-8].

According to recent studies and available guidelines [1,9], improvements have been also observed in dose of L-T4 at starting therapy. The INRICH data showed that the median value of L-T4 dose was 8.0 μg/Kg/day between 1987 and 1999 and 9.6 μg/Kg/day between 2000 and 2006.
**Fig. 2.** Graphs illustrating improvements in standardization of screening procedures obtained in Italy during twenty years of surveillance in terms of reduction of age at screening (panel A), reduction of age at starting therapy (panel B), increase of dose of replacement therapy (panel C).
Moreover, the INRICH data showed that in our country scintigraphy and/or ultrasonography was performed in 64% of CH babies before starting therapy. Among these babies 67% had thyroid dysgenesis, and 33% normal/hyperplastic thyroid (FIG.3).

![Pie chart showing thyroid conditions](chart.png)

**Fig.3.** Thyroid scintigraphy and/or ultrasound results in the Italian population of babies with permanent CH.

As expected, the frequency of the disease is higher in female than in male babies with a F/M sex ratio = 1.7 (F/M=2.0 among babies with thyroid disgenesis; F/M=1.0 among those with normal/hyperplastic thyroid). To ascertain the impact of CH on the Italian newborn population and to avoid the danger of drawing conclusions from an overestimation of the disease incidence, only cases with permanent forms of CH were considered while all the cases with transient hypothyroidism, ascertained by means a re-evaluation of the diagnosis after a withdrawal of the replacement therapy at 3 years of age, were not included in the incidence estimation. Indeed, to avoid the possibility of including some cases with transient hypothyroidism not re-evaluated yet, only children older than 3 years at the time of analysis were included in the evaluation. The estimated CH incidence in the period 2000-2005 was 1:2036 live borns. This value was higher than that observed previously (1987-99 = 1:2990) confirming an increasing trend of CH in our country. This is at least in part explained by a reduction of cut off value of TSH at screening, as a result of a continuous analysis of distribution of
TSH values in the screened neonatal population with a consequent more correct use of TSH threshold values [10].

The INRICH data have also shown a risk of CH occurrence 3-fold higher in twin than in single deliveries. Given the high number of CH babies recorded in the Registry, for the first time it was possible to estimate the CH incidence in multiple and single pregnancies separately. It was 10.1 per 10,000 live births in multiple deliveries and 3.2 per 10,000 live births in single deliveries [7]. Moreover, the analysis of re-evaluated infants with high suspicion of transient hypothyroidism recorded in the INRICH has also shown a twin prevalence of 1.9% among infants who resulted affected by permanent CH and 13.2% in those with final diagnosis of transient CH. Taken together these findings have demonstrated an increased risk for both permanent and transient CH in multiple than in single pregnancies. This finding has important implications in terms of public health given the high number of induced pregnancies, in Italy as well as in other Western countries, because of the increasing use of techniques of assisted reproduction and drugs inducing ovulation [11-12].

The INRICH research activity

It has been demonstrated that CH is a multigenic disease in mice [13]. Indeed, the identification of genes related to gland organogenesis or thyroid hormone biosynthesis has allowed the formulation of hypotheses on molecular mechanisms causing CH [14-15]. However, although still underestimated, the occurrence of mutations in genes known to be involved in the development of the disease have been observed only in a small proportion of the CH patients. Furthermore, the aetiological role of specific environmental risk factors has not completely elucidated yet. These considerations imply that the aetiology of CH is still largely unknown and that further efforts to identify new genetic markers and environmental (modifiable) risk factors are needed to allow an efficient primary prevention of the disease. As mentioned above, the large amount and the high quality of information collected in the INRICH during more than twenty years of activity provided a unique opportunity for research into this condition. This because data collected in the INRICH are highly representative as referred to the entire Italian population of infants with CH. One of the most important studies conducted on the basis of the INRICH data is represented by a population-based
case-control study performed with the aim to identify the most important risk factors for permanent and transient forms of CH [16]. This study showed that many risk factors contribute to the aetiology of CH suggesting a multifactorial origin in which genetic and environmental (especially iodine deficiency and maternal diabetes) risk factors play a role in the development of the disease. The multifactorial origin of CH was further supported by results obtained in the above mentioned study on CH twins recorded in the INRICH between 1989 and 2000 [7]. This study showed that, despite a low concordance rate (4.3%) for permanent CH observed among twins at birth, a higher recurrence risk for the disease was present among siblings of CH babies than in babies of the general population (35-fold higher). These findings strongly suggested the occurrence of non-inheritable post-zygotic events in the aetiology of CH and that environmental risk factors may act as a trigger on a susceptible genetic background in the aetiology of the disease.

The importance of a susceptible genetic background was also supported by another study conducted on data recorded in the INRICH. This demonstrated that not all congenital malformations but only congenital anomalies of heart, nervous system, eyes, and the occurrence of multiple congenital malformations are significantly associated to CH [8]. These results strongly suggested a very early impairment in the first stages of embryo development, probably involving genes regulating first stages of differentiation, with a consequent and simultaneous involvement of different organs and structures. These findings oriented molecular biologists to focus their investigations on genes involved in heart and thyroid development. This because cardiac anomalies represented the most frequent congenital malformations observed in CH population. It was found that mutations in NKX2.5 transcription factor, a gene specifically associated to atrial septal defects [17], can contribute to thyroid dysgenesis phenotype [18]. More recently, attention was focused on JAG1 a gene associated with the Alagille Syndrome, an autosomal multisystemic disorder characterized by variable defects of several organs (mainly liver, heart, eye, bones). A genetic variation of JAG1, already described in a patient with Alagille Sindrome, has been reported in patients with CH and heart developmental defects suggesting a potential involvement of this gene in the pathogenesis of CH [19].
CONCLUSIONS

Screening, surveillance and research are vital for the optimal management of babies with CH. The information required to improve diagnosis as well as to investigate aetiology of the disease require good clinical ascertainment with the smallest amount of selection bias. In this scenario a population-based Registry for CH represents a useful epidemiological tool for surveillance of the disease and a powerful resource of information on CH babies. This because such a Registry has the potential to assess temporal and geographical trends, to identify possible clusters of the disease, and to promote development of *ad hoc* investigation of suspected exposures. Moreover, by identifying critical points in screening programme procedures it can contribute to develop recommendations to improve diagnosis, treatment and follow-up of CH babies.

In Italy the surveillance of CH carried out by the INRICH together with the early diagnosis made by the nationwide screening programme, the prompt treatment and the appropriate clinical management of the patients performed by the Italian Follow-up Centres for CH, are elements of an integrated approach to CH which has been successfully established in our country. At the same time, the results derived from epidemiological studies performed by using the INRICH data have contributed to deepen knowledge of CH, to start identifying the most important risk factors for the disease, and to orient molecular biologists towards the identification of new genes involved in the aetiology of this disease. Finally, the potential of adding data on candidate genes involved in the CH aetiology to the INRICH database will no doubt represent a great breakthrough in the disease knowledge.

At present, further collaborative research studies based on the INRICH database are going on and our efforts in the field of CH risk factors identification are continuing with hope of making possible, in a near future, primary prevention of CH which still represents the most frequent endocrine disease in infancy.

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References