NEONATAL SCREENING FOR CONGENITAL HYPOTHYROIDISM IN ROMANIA: DATA FROM MEDILOG MEDICAL INFORMATION REGISTRY

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Abstract

Objective. Congenital hypothyroidism (CH) is one of the common preventable causes of intellectual disability in neonates, by early detection through neonatal screening. We present the 8-year experience of the National Institute for Mother and Child Health (INSMC) in using MEDILOG national registry for the neonatal screening of CH.

Methods. Neonatal screening for CH, done by TSH measurement in dried blood spot, is organized in 5 regional centers, each with a reference laboratory.

Results. In 2018 80% of all the newborns, from 80% of the maternity hospitals, were registered in MEDILOG. After re-testing of TSH and T4/FT4 from venous blood in positive cases, the incidence of confirmed CH in 2018 was 1/3576 - 1/ 4746. In INSMC center (which includes 26 counties and Bucharest, out of 41 counties), in 2018 the incidence of positive CH cases at screening was 1/2094 (TSH cut-off ≥ 17 mIU/L) and of confirmed CH cases 1/3576 newborns. For positive screening cases, the median duration from birth to the INSMC laboratory result was 19 days: median of 9 days between screening and laboratory registration and 6 days between registration and test result.

Conclusion. MEDILOG registry is a practical instrument for monitoring the steps of neonatal CH screening, the incidence of CH, the evolution of the diagnosed cases, for evaluation of iodine deficiency (by neonatal TSH), and also for research, with the aim of improving early disease detection and treatment.

Key words: congenital hypothyroidism, neonatal, screening, registry, MEDILOG.

development of child psycho-intellectual abilities (1). It has an incidence of approximately 1 in 2000–4000 live births (2). The disease is usually clinically inapparent in the first few weeks after birth (3). Early detection by screening allows the initiation of a neonatal thyroid replacement therapy, ideally within the first 2 weeks of life (4), thus preventing mental retardation and neurodevelopmental complications (5). A primary T4 screening with confirmatory TSH testing or a primary TSH test strategy may be used. TSH determination is the most sensitive test for detecting primary CH and currently is more widely used (2, 4, 6). Although the primary T4 test approach is the only able to detect neonates with secondary (central) CH, the incidence of this form of CH is very low (1:16 400 to 1:160000)(1). The main objective of newborn screening programs is to detect neonates with primary CH. In a review from 2014, it is estimated that only approximately 29% of the world's birth population is screened for CH (2).

Neonatal screening for CH in Romania is implemented within the framework of a national health program (7), being organized in 5 regional centers in Bucharest, Cluj-Napoca, Iași, Timiș, Mureș (8–11). Each center has allotted a number of counties, according to the capacity of each regional laboratory designated for screening.

The newborns tested by neonatal screening for CH are recorded in the national medical information registry MEDILOG.

INTRODUCTION

Congenital hypothyroidism (CH), defined by inadequate thyroid hormone production in newborn, is a disease with debilitating effects on the growth and

OBJECTIVE

This study aims to identify the benefits of MEDILOG, the national registry for CH, in managing the screening for CH and also in tracking the course of

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Figure 1. Organization of the neonatal screening program for congenital hypothyroidism in Romania (Infant neonatal screening test for hypothyroidism, are included in the national register MEDILOG).

the disease in the affected children. The information system MEDILOG was created by a team from “Alessandrescu-Rusescu” National Institute of Mother and Child Health in 2010 with the intention of being used by the interdisciplinary team of physicians and inter-institutional team (from the maternity hospital up to the reference center for the programme) in assessing the screening process at national level and its results on patient level, based on a standardized method of information collection and data processing.

METHODS

In this paper we study data from the MEDILOG registry concerning the route followed by the screening sample for neonatal CH from collection to the result. This can be realized with the multi institutional participation of: maternity hospitals, screening laboratory, Public Health District Authority, INSMC and the endocrinology network of treating physicians (8-11). Each of these institutions has a secured access to the corresponding level within MEDILOG information system. The system is accessible through internet MEDILOG based

authentication, through a user code and password, its functioning being ensured by an internet browser and a program for opening Excel files. In maternity, a heel-prick dried whole blood spot sample is taken onto Guthrie cards (filter paper cards) at 3 (2) - 5 days after birth in normal weight term neonates. In preterm neonates, those with low birth weight or ill, not fed with milk or protein containing solutions, a repeat specimen should be collected after 2 weeks or at 2 weeks of age, as recommended also by the European Society for Pediatric Endocrinology Consensus Guidelines (4). The newborn's data are recorded in the MEDILOG information system and the sample is sent from the maternity hospital to the reference laboratory of the allocated regional center, where the TSH result is obtained and registered in MEDILOG system; the results are communicated to the regional screening coordinator.

If the test result is positive, the screening coordinator should immediately contact and inform the child's parents directly by phone, or in writing through the Public Health District Authority. The parents are guided towards the local network of Endocrinology or to INSMC, where the child is re-tested for TSH and T4/FT4 from venous blood. The Public Health District Authority will communicate the diagnosis confirmation or exclusion to the screening laboratory (8-11).

Children confirmed with the diagnosis of CH will have a disease record file in the computer system, which contains some standardized preformed clinical and laboratory elements. The system allows differentiation of children with positive screening tests from the false positives.

Binding the computer system with the lab equipment offers the possibility of downloading and of statistical analysis of neonatal TSH results, particularly useful not only for defining the incidence of CH, but also in the study of iodine deficiency at a national level.

The method used for TSH determination from the screening samples is fluorimetric immunoassay in

Table 1. Maternity hospitals reporting newborns screened for congenital hypothyroidism in MEDILOG registry

Year 2018 record			
Center	No. of maternity hospitals	No. of reporting maternity hospital	% of reporting maternity hospitals from total
Regional Center Bucharest (INSMC)	109	108	99%
Regional Center Timisoara	20	3	15%
Regional Center Iasi	27	24	89%
Regional Center Mures	12	11	92%
Regional Center Cluj	33	15	45%
Total	201	161	80%

Table 2. Evolution of data recording in MEDILOG registry for neonatal screening of congenital hypothyroidism during 2011 – 2018

National level	2011	2012	2013	2014	2015	2016	2017	2018
Reporting maternity hospitals	146	136	140	137	144	157	154	161
No. of counties	36	36	41	39	40	41	41	40
Recorded newborns	31383	48175	85350	82597	80003	118733	133624	138998
Total newborns	196242	201104	214932	202501	206190	203231	205835	173936
% of records from total newborns	16%	24%	40%	41%	39%	58%	65%	80%

Table 3. Incidence of congenital hypothyroidism (CH) in Regional Center Bucharest INSMC (MEDILOG data)

Bucharest INSMC Regional Center	CH Confirmed	CH Excluded in positive screening cases	Lost from diagnostic confirmation	Total no.of screened newborns	Total positive screening cases
Year 2018	24	14	3	85841	41
Year 2017	26	19	1	90427	46

Table 4. Incidence of congenital hypothyroidism (CH) in the reference regional centers for neonatal screening of CH

Year 2018	CH Confirmed	Total number of tested kids	Incidence
Cluj Regional Center	Data not available	27011	-
Iasi Regional Center *	6	28474	1/4746
Mures Regional Center **	2	8167	1/4083
Timis Regional Center **	2	8679	1/4339
INSMC Bucharest Regional Center *	24	85841	1/3576

* MEDILOG data.

** Data reported at the Management Technical Assistance Unit Programme (UATMP) from INSMC.

Figure 2. Number of newborns recorded in MEDILOG registry for neonatal screening of congenital hypothyroidism.

Bucharest INSMC, Iasi and Mures regional centers, using a TSH cut-off ≥ 17 mIU/L, while DELFIA is used in Cluj regional center and ELISA in Timisoara regional center. Confirmation of the CH diagnosis is made in INSMC Bucharest center by an enzyme linked fluorescent assay (ELFA), using the following cut-offs for the age of 3 days up to 2 months: TSH > 16 mIU/L, total T4 < 5.2 μ g/dL or FT4 < 0.8 ng/dL.

RESULTS

The registry offers the opportunity to assess the degree of screening coverage at a national, maternity hospitals and regional level (Table 1).

In 2018 a percentage of 80% of the total

number of newborns from Romania are recorded in the MEDILOG system as being included in the neonatal screening for CH. It is observed an ascending trend of the MEDILOG recordings over the years, the percentage of children registered in 2018 being 5 times higher than the percentage from 2011 (Table 2, Fig. 2). However 15% of the tested infants were not reported in the data system, mainly children born in private maternity hospitals or small maternity facilities that do not have internet access. In 2018 a total of 161 maternity hospitals representing 80% of the total number of maternities in the country have used the MEDILOG system for data transfer regarding children included in the neonatal screening programme for CH, with a share of 99% in the regional center of Bucharest, 92% for Mures regional center and 89% for Iasi regional center. A low percentage of maternity hospitals using MEDILOG system were recorded in Cluj and Timisoara regional centers.

The registry allows the evaluation of the CH incidence, the ratio between positive screening cases and the false positive ones and the percentage of children lost for the diagnosis confirmation recall, distributed on centers, counties and maternity hospitals (Tables 3 and 4).

Analysis of the records reveals an incidence of CH which varies in different regional centers, from 1/3576 life births in the Bucharest INSMC regional

Figure 3. Duration (in days) between the date of newborn's recording in MEDILOG registry at INSMC and date of screening in the maternity hospital, in each newborn positive for congenital hypothyroidism at screening in 2018.

Figure 4. Duration (in days) between the date of the TSH result and the date of the newborn's recording in MEDILOG registry at INSMC, in each newborn positive for congenital hypothyroidism at screening in 2018.

Figure 5. Duration (in days) between birth date and the date of the TSH result at INSMC, in each newborn positive for congenital hypothyroidism at screening in 2018.

Table 5. Duration (in days) of screening steps for newborns detected positive for CH at neonatal screening in INSMC Bucharest Regional Center

Bucharest Regional Center	INSMC registration date vs. date of birth	INSMC registration date vs. date of screening in maternity hosp.	Screening date in maternity hosp. vs. birth date	Result date vs. INSMC registration date	Result date vs. birth date
Median	12	9	3	6	19
Average	17	9	8	8	26
Standard deviation	18	6	17	10	20
Range	3 - 99	1 - 34	1 - 88	2 - 62	5 - 104

center to 1/4746 in Iasi regional center (Table 4).

Without the data from Cluj regional center (which were not available), the incidence of CH is 1/3858 life births country-wide.

If we take a closer look at the INSMC Bucharest center, mandated with the neonatal screening for 26 counties and Bucharest (out of 41 counties), in 2018 the data of MEDILOG registry reveal an incidence of the CH positive screening cases of 1/2094 newborns, an incidence of confirmed CH of 1/3576 and 7.35% cases lost from diagnosis confirmation (possibly evaluated by physicians not using MEDILOG system) (Table 3).

In 2017 the data from MEDILOG registry show an incidence of the CH positive screening cases of 1/1966 newborns, an incidence of CH confirmed cases of 1/3478, with 1/46 (2.1%) cases lost from diagnosis confirmation.

The difference in incidence between confirmed and positive screening cases is due to false positive cases or cases with transient hypothyroidism.

Using the information registry we have monitored the different steps of the national programme for CH neonatal screening, for the newborns recorded in the INSMC Bucharest regional center that had positive screening tests. We evaluated the duration from sample collection in the maternity hospital until the test results, thus identifying the deficiencies in the step management which can delay the early detection of the disease.

In INSMC Bucharest regional center the median duration for obtaining the screening results for positive cases of newborns was 19 days from birth. Delays in all screening steps have been detected: median 9 days delay between the maternity screening and the sample registration in the laboratory, 6 days between registration of the sample in the laboratory and obtaining the result and 12 days between birth date and the registration of the sample in the laboratory (Table 5, Figs 3-5).

DISCUSSION

The 8-year experience in using the MEDILOG national registry for congenital hypothyroidism neonatal screening allows us to confirm that MEDILOG has the characteristics of the registries mentioned in the literature, merging the characteristics of an administrative registry with those of a disease registry, which helps to identify the patients, detect the incidence of the disease and also acknowledge individual aspects of the disease and its evolution under treatment (12, 13).

The MEDILOG registry can be used in practice as well as in research for epidemiological studies, not only cohort studies, but also for evaluation of individual parameters of growth and development related to the level of thyroid hormones and last but not least to assess the treatment compliance.

The information MEDILOG system is an instrument for the coordinators of health programs (7, 14), of the neonatal screening for CH, thanks to the information it brings regarding the development of activities as a whole; however it is also useful for the treating physician in the management of a child with CH, by monitoring the clinical signs and the disease evolution.

The utility of the registry as a monitoring instrument of the national neonatal screening program was validated by the Ministry of Health by nominating it in the diagnostic and treatment guidelines for phenylketonuria (screening developed in parallel with that for CH), approved by the Ministry of Health Order 51/2017 (15).

Analyzing the data from MEDILOG, the recall rate (i.e. the percentage of tests where the physician notifies the authorities to contact the parents in order to arrange another test) at INSMC Bucharest regional center was 0.05% in 2017 and 0.047% in 2018, similar to that in the USA 0.05% (6). Recall rates in various programs differ from 0.01% to 13.3%, due to different screening strategies, laboratory techniques, iodine status, site of sample collection, different recall criteria etc. (16). Of note, 10 years after the implementation of universal salt iodization in 2003 in Romania, median urinary iodine concentration in schoolchildren was shown to be normal in previous endemic iodine deficiency areas (17) and in most pregnant women in a maternity hospital from Bucharest (18).

Significant delays have been shown by MEDILOG data between the screening date and the laboratory results, compared to the recommended

parameters for diagnosing CH using a neonatal screening (i.e. during the first 2 weeks of life). A German software (“Hypo Dok”) for the documentation of longitudinal data of patients with primary CH shows that newborn screening result was available at a mean age of 7.3 days (19). Confirmation of the diagnosis was established at 8.4 days and therapy was started at 11 days (19). Analyzing trends in neonatal screening for CH using a Scottish registry, median age at first sampling fell from 7 to 5 days between 1980 and 2014, median notification age after initial sampling was 11 days from 1990 (20). Only 8% of infants breached the ≤ 14 day standard of notification after first sample result in 2010–2014, and 14.6% of infants undergoing second sampling from 2000 onwards breached the ≤ 26 -day standard for notification (range 7–32 days in 2010–2014). Confirmed CH cases started therapy at 10.5 days after birth (20).

After analyzing every single case tested at the INSMC laboratory, the increased duration between the date of birth and the laboratory registration of the screening samples is most likely due to the late sampling of the preterm neonates and the late dispatch of the maternity samples to the reference laboratory, demonstrated also by the increased duration (median 9 days) between sample collection and its registration in the reference laboratory.

Therefore we recommended the maternity hospitals to send samples to the laboratory of INSMC twice a week, which would potentially reduce by half the time spent between the sample collection and its registration in the laboratory. Maternity hospitals have been instructed about the protocol regarding preterm newborns, in whom 2 samples should be taken at 14 days interval (as recommended also by ESPE guidelines (4)) and not only one at the discharge from the hospital.

At the INSMC laboratory level actions have been taken to improve the flow of the samples from registration to results by organizing sample assays also during weekends.

The registry has been continuously improving since its elaboration and we are presently considering an expansion of the case management component by making the registry available to more doctors in the endocrinology network who treat children with CH.

We also wish for the MEDILOG registry to be connected to the international network in the future, both for the administrative and the case component. By centralizing the etiology of CH, it may also become a valuable database for the study of rare thyroid genetic disorders (1, 21).

In conclusion, MEDILOG information registry for the neonatal screening of CH, created in 2010, allows the collaboration of the different institutions involved in the screening process, including maternity hospitals, reference laboratories, Public Health District Authority and the treating physicians, with the aim of improving early disease detection and treatment. MEDILOG registry is a practical instrument for monitoring the steps of neonatal CH screening, the incidence of CH, the evolution of the diagnosed cases, for evaluation of iodine deficiency (by neonatal TSH), and also for research.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Peters C, van Trotsenburg ASP, Schoenmakers N. Diagnosis of endocrine disease: Congenital hypothyroidism: update and perspectives. *Eur J Endocrinol* 2018;179(6):R297-R317.
2. Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. *Best Pract Res Clin Endocrinol Metab* 2014;28(2):175-187.
3. Vulsma T, Gons MH, de Vijlder JJ. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989;321(1):13-16.
4. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Butler G; ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE; Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *J Clin Endocrinol Metab* 2014;99(2):363-384.
5. Grosse SD, Van VG. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? *Arch Dis Child* 2011;96(4):374-379.
6. American Academy of Pediatrics, Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics* 2006;117(6):2290-2303.
7. Ministry of Health. National Health Strategy 2014 - 2020. <http://www.ms.ro/strategia-nationala-de-sanatate-2014-2020/>. 2019. Romania. Ref Type: Online Source
8. Ministry of Health, President of the National House of Health Insurance. Order no. 1591/1110/2010 for the approval of the technical standards to achieve National Public Health Programmes for the years 2011 and 2012, with subsequent amendments. *Monitorul Oficial* 2011;I(53 and 53 bis).
9. Ministry of Health. Order no. 422/2013 for the approval of the technical standards to achieve National Public Health Programmes for the years 2013 and 2014, with subsequent amendments. *Monitorul Oficial* 2013;I(173).
10. Ministry of Health. Order no. 386/2015 for the approval of the technical standards to achieve National Public Health Programmes for the years 2015 and 2016, with subsequent amendments. *Monitorul Oficial* 2015;I(221).
11. Ministry of Health. Order no. 377/2017 for the approval of the technical standards to achieve National Public Health Programmes for the years 2017 and 2018, with subsequent amendments. *Monitorul Oficial* 2017;I(223).
12. Gladman DD, Menter A. Introduction/overview on clinical registries. *Ann Rheum Dis* 2005;64 Suppl 2:101-102.
13. Pop B, Fetica B, Blaga ML, Trifa AP, Achimas-Cadariu P, Vlad CI, Achimas-Cadariu A. The role of medical registries, potential applications and limitations. *Med Pharm Rep* 2019;92(1):7-14.
14. Ministry of Health. Activity Report for 2018. <http://www.ms.ro/Raport-de-activitate-MS-2018-2.pdf>. 2018. Romania. Ref Type: Online Source
15. Ministry of Health. Order 51/2017 for the approval of the diagnostic and treatment guidelines for phenylketonuria. *Monitorul Oficial* 2017;I(246 bis).
16. Mehran L, Khalili D, Yarahmadi S, Amouzegar A, Mojarrad M, Ajang N, Azizi F. Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism. *Int J Endocrinol Metab* 2017;15(3):e55451.
17. Ursu HI, Toader OD, Podia-Igna C, Delia CE, Firta AR, Tupea CC, Tudor LM, Gheorghiu ML, Suciu N. Iodine status after a decade of Universal Salt Iodization in Romania: a bicentric study in urban areas. *Acta Endo (Buc)* 2014;10(1):9-20.
18. Ursu HI, Toader OD, Podia-Igna C, Delia CE, Firta AR, Tupea CC, Tudor LM, Gheorghiu ML, Suciu N. Iodine status in pregnant women after a decade of Universal Salt Iodization in Romania. *Acta Endocrinol (Buchar)* 2016;12(2):161-167.
19. Ellerbroek VL, Bonfig W, Dörr HG, Bettendorf M, Hauffa B, Fricke-Otto S, Rohrer T, Reschke F, Schönau E, Schwab KO, Kapelari K, Röhl FW, Mohnike K, Holl RW. Long-term Surveillance of Children with Congenital Hypothyroidism: Data from the German Registry for Congenital Hypothyroidism (AQUAPE "Hypo Dok"). *Klin Padiatr* 2015;227(4):199-205.
20. Mansour C, Ouarezki Y, Jones J, Fitch M, Smith S, Mason A, Donaldson M. Trends in Scottish newborn screening programme for congenital hypothyroidism 1980-2014: strategies for reducing age at notification after initial and repeat sampling. *Arch Dis Child* 2017;102(10):936-941.
21. Ali SR, Bryce J, Cools M, Korbonits M, Beun JG, Taruscio D, Danne T, Dattani M, Dekkers OM, Linglart A, Netchine I, Nordenstrom A, Patocs A, Persani L, Reisch N, Smyth A, Sumnik Z, Visser WE, Hiort O, Pereira AM, Ahmed SF. The current landscape of European registries for rare endocrine conditions. *Eur J Endocrinol* 2019;180(1):89-98.