NEWBORN SCREENING FOR RARE DISEASES IN THE NORTH-EAST PART OF ROMANIA: RESULTS OF THE NEWBORN SCREENING PROGRAM 2009-2012

Dana-Teodora Anton-Paduraru[1], Maria-Liliana Iliescu[2]
[1]3rd Clinic of Pediatrics, University of Medicine and Pharmacy "Gr. T. Popa", Iasi
[2]Public Health and Management Department,
University of Medicine and Pharmacy "Gr. T. Popa", Iasi

ABSTRACT

Objective. To evaluate the Newborn Screening Program for rare diseases – congenital hypothyroidism (CH) and phenylketonuria (PKU) – in the north-east part of Romania from 2009 to 2012.
Methods. To realize the transversal descriptive study, we studied the cohorts formed by the babies who were borne between 2009-2012 in the maternities situated in the north-east part of the country. The screening was performed for two diseases: phenylketonuria (PKU) and congenital hypothyroidism (CH). Thyroid stimulating hormone (TSH) and phenylalanine (Phe) were tested by fluorometric assay. Newborns with abnormal screening results (TSH > 9 µIU/L, Phe > 3 mg/dl) were re-examined.
Results. A total of 76,308 newborns were screened. From these, were detected 9 cases with CH and 5 cases with PKU. The incidence of CH was 1: 8,478 and of PKU1: 15,261, for the whole period.
Conclusions. Newborn screening programme represent an important public health programme that allows early diagnosis and prevention of severe consequences for PKU and CH.

Key words: newborn screening, congenital hypothyroidism, phenylketonuria, Romania

BACKGROUND

Newborn screening – an important preventive public health programme, is useful in establishing early diagnosis and timely delivery of medical interventions in newborns with rare diseases. In Romania, the tests for PKU and CH are free of charge, but, despite this, not all the babies are tested.

OBJECTIVES

The objective of this paper is to present the results of the implementation of newborn screening (NBS) program for rare diseases in the north-east of Romania.

METHODS

To realize the transversal descriptive study we studied the cohorts formed by the babies who were borne between 2009-2012 in the maternities situated in the north-east part of the country, meaning six counties (Botosani, Suceava, Iasi, Vaslui, Neamt, and Bacau), included in the National Health Programme for Newborns Screening (NBS). The panel of screening disorders includes two diseases: phenylketonuria (PKU) and congenital hypothyroidism (CH). Thyroid stimulating hormone (TSH) and phenylalanine (Phe) were tested by fluorometric assay (Victor 2D). Newborns with abnormal screening results (TSH > 9 µIU/L and Phe > 3 mg/dl) were re-assessed by measuring serum fT4 and TSH, respectively by phenylalanine in serum.

Communicating the screening positive results to parents was confidential. In the case of negative screening results, these were not communicated to the parents (only at the request), due to economic reasons (the scarcity of the screening programme budget). We adopted the „no news is a good news" policy.

Coresponding author:
Dana-Teodora Anton-Paduraru, „Gr. T. Popa", University of Medicine and Pharmacy and University, Str. Universității 16, Iasi
e-mail: antondana66@yahoo.com

RESULTS

In the north-east of Romania, the implementation of NBS programme for rare diseases was started in September 2009. At the beginning of the screening programme, in 2009, in September were tested only the newborns from Iasi county, and from October (the same year) were added Neamt and Suceava counties, with a total of 15 maternities. In 2010 the NBS extended in another county (Botosani) and from 2011 in other two counties (Bacău and Vaslui) – Fig. 1. From November 2012 were included four private maternities, so, in present, the NBS is conducted in 24 maternities.

The number of newborns tested for PKU and CH increased from 4,760 in 2009 to 19,214 in 2010; 23,540 in 2011 and 28,794 in 2012. At the beginning of the screening programme, in 2009, in September were tested only the newborns from Iasi county, and from October we added Neamt and Suceava counties.

The rate of newborns tested is mentioned in Table 1.

The denominator for calculating the rate represents the number of newborns from which was excluded the neonatal deaths occurred in maternities, before testing the babies. During 2009 and 2012, the overall rate for NBS is 72.37%.

The sources for demographic data are National Institute for Statistics from Romania, and Counties' Departments of Public Health (1).

TABLE 1. *The rate of NBS for PKU and CH in the north-east part of Romania, 2009-2012*

Year	Total newborns	Newborns died after birth, before screening	Newborns tested	Rate of NBS (%)
2009[+]	6,691	95[++]	4,760	72.16
2010	24,899	81	19,214	77.41
2011	36,401	135	23,540	64.91
2012	37,881	121	28,794	76.45
Total	105,872	432	76,308	72.37

[+] In 2009 the NBS started in September.
[++]The number represents the newborns died after birth, before screening, for the whole year 2009.

The percentage of newborns that were not included in NBS is fluctuating, while the number of counties included in the programme is increasing. The overall rate for non-included is 32.63%. The reasons are different: mothers' refuse, early discharge from hospital (on demand), cultural or religious reasons or they were simply omitted.

A proportion of 0.83% newborns were recalled for testing due to human errors in the processing of specimens (in majority of cases blood drops too small).

The laboratory test' results for NeoTSH values were elevated in 30 infants. Serum fT4 and TSH assay confirmed hypothyroidism in 9 cases. The rate of positive results was 30%. Phenylalanine values were elevated in 12 cases. The chromatography confirmed PKU in 5 cases. The rate of positive results was 41.6% – table 2.

FIGURE 1. *The extension of NBS for PKU and CH in north-east part of Romania, 2009-2012 (2009 – Suceava, Neamt, Iasi; 2010 – Botosani; 2011 – Bacau, Vaslui)*

TABLE 2. *Rate of confirmed cases for NBS in the north-east part of Romania, 2009-2012*

Disease	Screening positive values	Confirmed cases	Rate of confirmed cases
CH	30	9	30.00%
PKU	12	5	41.66%

According to data obtained inside the NBS, the incidence of the diseases included in NBS in the north-east of Romania was 1: 8478 for CH, and 1: 15261 for PKU.

Samples from newborns are kept for 5 years.

The incidence of these two diseases in other European countries is mentioned in table 3 (2,3,4,5,6,7).

TABLE 3. *Incidence of PKU and CH in other European countries*

Country	CH	PKU
Slovakia	1: 2506	1: 3676
Republic of Moldavia	–	1: 7326
Russia	1: 2941	1: 7142
Bulgaria	1: 2676	1: 28000
Belarus	1: 6349	–

In order to reduce the rejection rate of the screening it isnecessary to inform prospective parents on. Various authors believe that it is best for parents to receive information even during pregnancy or at the latest when the pregnant woman go tot he hospital for delivery, thus having time to read them, to think, to examine and receive an explanation (8,9). On the other hand, in 1998 WHO was in favor of mandatory screeningif early diagnosis and treatment are of benefit to the child. In Romania, screening is mandatory, but the families have the option to refuse. Parents who refuse NBS sign in the observation sheet that they understand the potential risk of the disease on the child's later development.

Outside of positive effects (detection of serious diseases and treated before symptoms appear, preventing mental retardation, genetic counseling for future pregnancies) screening has a downside: parental anxiety, overprotection child, feelings of guilt, family misunderstandings). Also, false-positive reactions had a negative impact on the family: increased parental stress.

DISCUSIONS

Romania – situated in Eastern Europe, has a population that decreased from 21.431.298 peoples in 2010 to 19.043.767 in 2012 according to the last national census. The number of births per year varied, in the last four years being: 222,388 in 2009; 228,427 in 2010; 196,242 in 2011; 201,104 in 2012. In Iasi and Suceava counties the birth rates, in 2012, were higher than the national average value (11.2‰ and, respectively 11.5‰ compare to 11.0‰) (1)

In Romania there are four centers for NBS situated in Bucharest, Cluj-Napoca, Timisoara, and Iasi. The NBS Center from Iasi (situated in the north-east) is the last center included in the National Health Programme for NBS.

The disciplines involved in NBS are: Neonatology, Pediatrics, Laboratory Medicine, Endocrinology, Public Health and Management, Neurology and Psychology.The screening tests are free of charge for the family, the cost per test (3 euro) being provided from the budget of this National Health Program.

Comparatively with the European countries mentioned in table 3, in Romania, the incidence of CH, respectively PKU is smaller (except PKU in Bulgaria).

After the diagnostic is clearly confirmed, the babies are followed-up, and specific treatment is provided.

Till now, all the patients with these two diseases follow the treatment recommended:

- specific nutritional therapy for PKU: according to the tolerance of phenylalanine, with different food (PKU formula, aproteic products – baking mix, "low protein" biscuits and pasta, egg, rice and potatoes replacer).
- substitutive hormonal therapy (Euthyrox) for CH.

By making timely medical interventions, neuropsychicological developmentof the patients detected with these two diseases was normal. This is supported by examinations performed regularly (clinical examination, neurological, psychological, neuropsychiatric).

The value of the phenylalanine is periodically measured, on a specific schedule, depending on babies' age:

- 0-6 months: weekly;
- 6-12 months: twice/month;
- 1-3 years: 1-2 times/ month;
- over 3 years: monthly.

The patients return in the 3rd Clinic of Pediatrics (specialized in Nutrition and Metabolic Diseases) every three months for clinical and biological control and for adapting the treatment. They will be registered in the National Unique Registry for the evidence of newborns included in NBS and diagnosed with PKU/CH, which was introduced in 2012.

The impossibility to run controlled clinical randomized trials for new-borns rises the discussion of

finding the ballance point between having too many diseases in the screening panel for new-borns (without certain benefits for the last ones) and the lack of early diagnosis (provided by screening tests) for the diseases which are treatable (10). Cost-effectiveness analysis underlines that the best strategy is that which has the optimal cost-effectiveness rate, not the cheapest one. In the particular case of NBS for CH and PKU, we must compare the specific testing with the strategy of „doing nothing".

Even the cost per one screening test is 3 euro (for a new-born), in our case, in the northeast region screening 2009-2012, the cost for one HC diagnosis is 76.308 x 3 euro/9 positive cases = 25436 euro and 76.308 x 3/5 = 45784,8 euro for PKU. Despite these economic debates, the benefits for newborns are real (early treatment and avoidance of specific complications), and the „savings" are visible on long term, taking into consideration the (tangible and intangible) costs linked to healthcare for children who did not receive (and benefit) the specific treatment in the incipient phases of the disease (CH or PKU).

CONCLUSIONS

1. Neonatal screening is an important public health program that requires early diagnosis and providing information that could change the course of a child's life by preventing severe consequences of congenital hypothyroidism and phenylketonuria.

2. We consider that is necessary to analyze the causes conducing to non-inclusion in NBS, in order to prevent such situations and to increase coverage. In this respect, mothers will be better informed about the importance of NBS for their babies and for their families, too.

3. It is also necessary to give more importance to the quality of screening procedures.

ACKNOWLEDGEMENTS

The authors thank to the local leaders from the maternities subordinated to the Regional Centre Iasi: Prof.dr.Maria Stamatin, dr. Meda Brădeanu, dr. Corneliu Dumitrache, dr. Luminita Apostu, dr. Laura Murariu, dr. Perla Bereznitchi, dr. Rodica Tănăsache, dr. Sorana Iftimie, dr. Cristina Imireanu, dr. Tania Arosoaie, dr. Cristina Vasian, dr. Agneta Pal, dr. Zenovica Bădărău, dr. Anca Croitor, dr. Elena Matei, dr. Mariana Sigmund, dr. Carmen Grecu, dr. Mihaela Nicolau, dr. Camelia Husac, dr. Mariana Vasilică, dr.Marilena Tubucanu, dr. Viorica Luchian, dr. Cornelia Cămărasu, dr. Viorica Balcan, dr. Eliza Vainberg, dr. Melania Ursu, and to the laboratory personal from Children's Emergency Hospital "Sf. Maria" Iasi: chemist Adriana Rusu, assistant Liliana Nastasa, assistant Mihaela Bucur.

REFERENCES

1. **Romanian National Institute of Statistics,** Archives of Monthly Counties' Statistical Bulletins, available online at http://www.insse.ro/cms/rw/pages/arhivabuljud.ro.do
2. **Chodunova A., Novikov P., Mitkin V.** The first results of expanded newborn screening for inherited metabolic diseases in the Russian Federation (abstract). The 8thISNS European Neonatal Screening Regional Meeting, 4-6 November 2012, Budapest, Hungary. *ORVOSI HETILAP* (Suppl):19.
3. **Gusina Nina, Zinovik A., Kolkova Tatyana.** The results of population neonatal screening for congenital hypothyroidism in Belarus(abstract). The 8thISNS European Neonatal Screening Regional Meeting, 4-6 November 2012, Budapest, Hungary. *ORVOSI HETILAP* (Suppl):25.
4. **Knapkova Maria, Dluholucky S., Zahorcova Miroslava.** Newborn screening in Slovakia – what news. (abstract). The 8thISNS European Neonatal Screening Regional Meeting, 4-6 November 2012, Budapest, Hungary. *ORVOSI HETILAP* (Suppl):16.
5. **Stoeva Iva, Kostova Antoaneta, Emilova Radoslava, Aroyo Ani.** The Bulgarian Neonatal Thyroid Screening Programme 1993-2011 (abstract). The 8thISNS European Neonatal Screening Regional Meeting, 4-6 November 2012, Budapest, Hungary. *ORVOSI HETILAP* (Suppl):24.
6. **Usurelu Natalia, Burgoci V., Boiciuc K., Halabudenco Elena, Stratila M.** Phenylketonuria in Moldova –neonatal screening about 20 years (abstract). The 8thISNS European Neonatal Screening Regional Meeting, 4-6 November 2012, Budapest, Hungary. *ORVOSI HETILAP* (Suppl):17.
7. **Vazharova Radoslava, Bradinova Irena, Ivanova Maria et al.** Bulgarian mass newborn screening programme for PKU and other inborn errors of metabolism – new perspectives (abstract). The 8thISNS European Neonatal Screening Regional Meeting, 4-6 November 2012, Budapest, Hungary. *ORVOSI HETILAP* (Suppl):34.
8. **Baily Mary Ann, Murray T.** Ethics, Evidence, and Cost in NEWBORN Screening. The Hastings Center Report 2008; 38(3):23-31.
9. **Nelson R., Botkin J., Kodish E.,** Levetown Marcia, Truman J., Wilfond B. Ethical Issues With GeneticTesting in Pediatrics. *PEDIATRICS* 2001; 107 (6): 1451-1455.
10. **Wilken B.** Newborn Screening: Gaps in the Evidence. *SCIENCE* 2013; 342 (6155):197-198.