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NEWBORN SCREENING IN SLOVAKIA – FROM 1985 TILL TODAY

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Regular newborn screening enables detection of severe disorders in their asymptomatic early phase and thus allows the start of early treatment and prevention of long-term sequelae. This concept is in full accordance with care for so called rare diseases. Recently, the national NBS in Europe are under the supervision of ISNS and EUNENBS to ensure the quality control and unified approach. NBS in Slovak Republic has been provided for the whole population as a governmentally guaranteed activity since 1985. The first screened disorder was congenital hypothyroidism (CH). Patients have been screened for phenylketonuria (PKU) since 1995, for congenital adrenal hyperplasia (CAH) since 2003, and for cystic fibrosis (CF) since 2009. The organizational network of NBS ensures more than 98% coverage of the population of newborns. Between 1985 and 2011, the newborn screening centre (NSC SK) examined 3,239 068 newborn infants and confirmed 413 cases of CH (1: 4 128), 157 cases of PKU (1:5 908), 51 cases of CAH (1:8 677) and 26 CF cases (1:6 315). In 2012, the expanded NBS (ENBS) was introduced. It used tandem mass spectrometry (ms/ms) to detect other nine hereditary metabolic disorders (HMDs), defect of beta-oxidation of fatty acids, carnitine disorders, and organic acidurias. Four month pilot study revealed 12 positive cases in 25 000 screened newborns as well as other HMDs not included in the screening – in "peripheral view" of ms/ms. Since 1. January, ENBS has been performed as a regular NBS in the whole population. In January, fifteen new cases were detected (prevalence even 1:763).

Keywords: *Newborn screening – Hereditary metabolic disorders – Rare Disease*

INTRODUCTION

The concept of early detection of rare congenital and hereditary disorders in newborn population by means of newborn screening arose from the fact that early detection and treatment of the screened disease in asymptomatic period warrants the normal

psychosomatic development of the child. NBS was dependent on the development of screening tests and rapid definitive confirmation of the diagnosis and treatment. Today, NBS is one of the principal activities in the concept of care for rare disorders (RDs) in EU (point 4.1. of the EUCERD statement). The International Society of Newborn Screening (ISNS) and European Union of National Experts for Newborn Screening (EUNENBS) are guarantor institutions for unification and evaluation of national NBS in Europe. Spectrum of screened disorders in NBS is chosen according to Wilson - Junger criteria, validity of which has been confirmed even after fifty years of existence.

Newborn Screening (NBS) in Slovakia

NBS in Slovakia started in Trenčín in 1978 as phenylketonuria (PKU) screening which used Guthrie test, and simultaneously as the evaluation of the possibility to introduce the congenital hypothyroidism (CH) screening by means of radioimmunoassay (RIA) of thyroxine (T_4) from dry blood spot sample (DBS) in Banská Bystrica. The retrospective analysis of CH incidence in Slovakia confirmed incidence similar to other states of the world and the development of DBS T_4 RIA test enabled CH screening to start in the central Slovakia between 1980 and1984. This organizational model was used to start the regular CH screening in Slovakia in 1985 in the Newborn Screening Centre of Slovak Republic (NSC SK). After the introduction of the quantitative fluorometric test for phenylalanine (phe) in DBS, PKU screening was shifted to NSC SR and Guthrie semi-quantitative screening was abandoned. Congenital adrenal hyperplasia (CAH) screening and cystic fibrosis screening were introduced to regular screenings in 2002 and in 2009 respectively. In Slovakia NBS is provided in one national screening centre (NSC SK). DBS samples are sent from 92 nurseries and newborn health care institutions where newborn infants should be on the 4^{th} or 5^{th} day after birth. Each of these institutions has its original code for identification of the suspected case. Positive cases in NBS are urgently recalled to three regional recall centres (west, central, east) for confirmation, or exclusion of the disease. Confirmed cases remain in the long-term care in these regional centres. This network cooperates on the basis of a close feed-back system of communication and control, and ensures almost complete coverage of population by screening. Between 1985 and 2011 this coverage was more than 98% of liveborn infants while escape from screening was recorded at the start of the screening (in 1985) and in the last years due to deliveries abroad. Results of NBS are presented in the table 1. Screening of CH was realized in 1,804 805 liveborns, and 413 cases of CH were confirmed. Incidence of CH is 1:4 128. PKU screening was realized in 927 524 newborns and 157 cases of PKU were confirmed. The incidence of PKU is 1:5 908. Since the start in 2003, 442 540 newborns have been tested for CAH and 51 cases have been proven. The CAH incidence is 1:8 677. At last, CF screening was done in 164 199 liveborns and 26 cases were confirmed, with incidence of 1: 6 315. From 1985 till 2011 the NSC SK screened 3, 239 068 newborns for four disorders with screening incidence of 1: 5 006. NSC SK ranks on the sixth place in EUNENBS evaluation of thirty four EU national NBSs.

Table 1

RESULT OF NBS SK 1985-2011

DISORDER	SINCE	No.SCREEN.	No.POSITIVE	INCIDENCE
CH	1985	1,704 805	413	1 : 4 128
PKU	1995	927 524	157	1 : 5 908
CAH	2003	442 540	51	1 : 8 677
CF	2009	164 199	26	1 : 6 315
TOTAL		3,239 068	647	1 : 5 006

Abbreviations: CH – Congenital Hypothyroidism, PKU – Phenylketonuria CAH – Congenital Adrenal Hyperplasia, CF – Cystic Fibrosis

Expanded NBS in 2012 – 13

Extension of the spectrum of rare metabolic disorders (RMDs) by means of tandem mass spectrometry (ms/ms) – introduction of so called extended NBS (ENBS) − has become the main task for the future. From wide range of RMDs detected by ms/ms, nine RMDs including defects of beta-oxidation of fatty acids, organic acidurias, and carnitine pathway defects were chosen according to W-J criteria. Their common feature is a sudden disruption of energetic metabolism after various forms of stress leading to life-threatening situations, even death. In contrast, after early detection by NBS, the prevention of such life-threatening events is relatively simple and inexpensive. Ms/ms NBS allows to detect almost 25 RMDs "in the peripheral view" of the test. Another possibility is the detection of mother´s latent disease through her newborn screening (e.g. latent form of carnitine uptake defect – CUD). Finally, selective screening in critically ill infants is another possibility in ENBS. During the first three months of year 2012 the ms/ms device was tested, and ENBS software adjusted for routine use. From June 15th to the end of October 2012 (four months), the prospective pilot study of ENBS of all newborns in SK was carried out. Out of total 25 000 screened newborns 12 positive cases were detected: Nine PKUs, 3 MCADs, 1 MSUD, were confirmed. In "the peripheral view" of ms/ms screening, eight cases of "high C4" (suspected SCAD) and two CUDs were detected. The screening prevalence was 1:2083 (considerably high), and all children are in specialized care andin a good health state. Regular population-wide ENBS started in January 1st 2013 under the guarantee

of Ministry of Health. During January 2013, 5 343 newborns were screened for a total of 13 disorders. ENBS detected total 15 positive cases: 3 CHs, 1 CF, 2 PKUs, 1 MCAD, and 1 VLCAD. On the "periphery" 1 methylmalonic aciduria (MMA), 1 maternal CUD and 4 C4s (suspected SCAD) were detected; selective screening revealed one case of MMA in critical state – patient's state has improved after the establishment of proper diagnosis and treatment. During this month of ENBS, screening prevalence was extraordinary high: 1:763 liveborns which justifies the extension of NBS in Slovakia as a highly effective step of preventive care in childhood. Definitive evaluation of ENBS effectiveness and of other additional features will be possible in the next years.

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NOVORODENCKÝ SKRÍNING NA SLOVENSKU – OD ROKU 1985 DOPOSIAĽ

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Novorodenecký skríning (NBS) svojou koncepciou zachytiť závažné zriedkavé ochorenia v ich bezpríznakovom štádiu ihneď po narodení a včasnou liečbu predísť trvalým následkom plne zapadá do koncepcie starostlivosti o zriedkavé ochorenia (rare diseases). V súčasnosti jeho vyhodnocovanie a unifikácia postupov pre garantovaná činnosťou ISNS a EUNENBS. NBS na Slovensku sa realizuje ako celoplošná aktivita od r. 1985 vyhľadávaním kongenitálnej hypotyreózy (KH), od 1995 fenylketonúrie (FKU), od 2003 vrodenej adrenálnej hyperplázie (CAH) a od 2008 cystickej fibrózy (CF). Organizácia skríningu zaisťuje dlhé roky vyšší ako 98% záchyt celej populácie narodených detí. NBS od r. 1985 do 2011 celkovo vyšetril 3,239 068 detí, zachytil 413 prípadov KH (1 : 4 128), 157 FKU (1 : 5 908), 51 CAH (1: 8677) a 26 CF (1 : 6 315). Od začiatku roka 2012 realizoval činnosti pre rozšírený NBC (ENBS) o 9 ďalších dedičných metabolických porúch (DMP), poruchy beta-oxidácie mastných kyselín, defekty karnitínu a organické acidúrie. Pilotnou štúdiou za 4 mesiace bolo z 25 000 vyšetrených 12 pozitívnych prípadov a ďalších osem porúch v „periférii metodiky ms/ms. Od 1.1. 2013 sa ENBS realizuje ako pravidelný skríning celej populácie a za mesiac január zachytil až 15 nových prípadov (prevalencia 1 : 763).