Editorial

Maria Arélin and Skadi Beblo

Newborn screening of metabolic disorders

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Introduction

Inherited metabolic diseases constitute more than 100 different diagnoses which are all rare, but reach a cumulative incidence of approximately 1:1600–2000 newborns.

Many of them may present in the first days of postnatal life, but they may also become apparent in older patients at every age. Symptoms vary widely and are often non-specific. The younger the child the more diffuse is the clinical presentation, and an inborn error of metabolism must be considered in any infant with non-specific symptoms that are not explicable by a different cause. Patients are mostly critically ill during metabolic crisis, and death is not unusual. If survived, the crisis often leaves the patient with sequelae. Prognosis is highly dependent on early diagnosis and introduction of specific treatment.

Mostly inherited as autosomal recessive traits, metabolic diseases are due to an enzyme or transport protein defect. This leads to a deficiency and/or an accumulation of specific metabolites. Either the inability to eliminate precursors or the deficiency of essential products is directly or indirectly responsible for disease manifestations and clinical course.

Newborn screening of metabolic disorders

To avoid irreversible clinical defects of inherited metabolic diseases especially in the first postnatal days of life, a screening procedure was developed in the 1960 starting with phenylketonuria as the first screened disease.

By measuring elevated levels of phenylalanine in dried blood spots of the Guthrie card, a unique success story took its course. With early detection of the affected patients and a special dietary management, severe mental retardation can nowadays be avoided and the outcome of these patients changed dramatically. Phenylketonuria became a treatable disease and patients with this amino acid disorder can live normal lives.

Congenital hypothyroidism and congenital adrenal hyperplasia followed as next “screening diseases” and many others have since become part of the screening programs.

At the beginning of newborn screening in developed countries certain requirements for a screening disorder were important:

- the screened disease had to be detected by a special and easily measured parameter, with very high sensitivity and acceptable specificity – the disease must be amenable to treat
- screening and adequate treatment can prevent the effect of the disease before appearance of first clinical symptoms (e.g. physical or mental retardation, severe organic failure, death)
- nationwide implementation and near complete coverage

The development of tandem mass spectrometry screening in the early 1990s led to a large expansion of potentially detectable congenital metabolic diseases via newborn screening. This method permits the semi-quantitative detection of over 70 metabolites and their characteristic patterns.

Since the introduction of newborn screening in the developed countries, the level of knowledge concerning pathophysiology, diagnostic steps, genetic fundamentals and treatment of the different inborn metabolic diseases increased step by step (1, 2).

However, the conditions for newborn screening programs vary around the world, based on the legal requirements, prevalence of certain diseases within a population, structural and political situation, and the availability of screening techniques. Therefore, the scope and societal benefit of newborn screening programs will also vary. While industrialized countries have adopted an expanded screening program, other areas struggle with comprehensive coverage of at least the most prevalent disorders.

In the comprehensive study by Kaur et al. from India current results and future perspectives of newborn

screening in India are highlighted (3). The authors delineate the dilemma of possibilities and advances of screening programs and realization in a country with limited resources for both testing and treating detected patients.

The diversity of analyzed metabolites in modern screening programs provides extensive information about different metabolic pathways. This leads to identification of patients with diseases which may not be primary target in classical screening programs. Thodi et al. provide an example of this opportunity, describing two unrelated families with hawkinsinuria (4). By identifying elevated tyrosine levels in two out of 92 519 screened Greek newborns and consecutive genetic testing two different mutations in the *HPD* gene were found and a therapy in the two identified patients was initiated. The generally benign course would not justify screening for hawkinsinuria, however, the increase of knowledge in such situations should not be underestimated.

The publications by Kaya et al. from Turkey (5), Veselá et al. from Poland (6) and Lausten-Thomsen et al. from Denmark (7) demonstrate a new scope of newborn screening: they leave the path of analyzing specific metabolites to identify monogenetic rare diseases towards the identification of factors in early life modifying the risk of so-called civilisatory diseases.

To expand investigations of leptin and neuropeptide Y levels in newborns the Turkish group of Kaya et al. included 62 newborns (14–28 days old) in their prospective study. They divided the newborns in only breast-fed and partly formula partly breast-fed children. No differences concerning the leptin/NPY levels could be measured (5).

The Polish study assessed a possibel interaction between serum leptin levels measured in newborns, at the ages of 6 months, 1 year, 1.5 and 2 years and bone metabolism markers, especially bone mineral density (6). No major influence could be detected.

The investigation of Lausten-Thomson et al. studied the multifactorial etiology of childhood obesity by measuring the concentration of adipokines (adiponectin, leptin and sOB-R) in umbilical cord blood from 60 neonates, 30 born large for gestational age (LGA) and 30 born appropriate for gestational age (AGA). Interestingly the data in the macrosomic newborns (the LGA group) indicates a significantly higher leptin/adiponectin ratio (7).

It remains to be established whether adipokines and leptin represent the most useful candidates. However, the scene is set for a broader use of simple dried blood samples, gained at the start of life. Thus, the effort put into the study of metabolic disorders in neonatology and development of newborn screening should pay off for a much larger number of individuals.

Conclusions

The approach to the diagnosis of metabolic disorders has changed. As new testing technologies become more widely available, screening programs all over the world expand their spectrum of detectable metabolic diseases.

The issue of this journal aims to demonstrate current investigations and new possibilities in the field of newborn screening for metabolic diseases. The focus expands beyond the classical diseases.

In order to increase our chances to successfully prevent civilization disorders such as childhood obesity, screening technology can be used to identify novel risk indicators even in newborns. Such indicators can be used to estimate individual risk, but also on a population level, guiding prevention programs.

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Corresponding author: Skadi Beblo, MD, Hospital for Children and Adolescents, Department of Women and Child Health, University of Leipzig, Liebigstr. 20a, D 04103 Leipzig, Germany,
Phone: +49-341-9726242, Fax: +49-341-9726009,
E-mail: skadi.beblo@medizin.uni-leipzig.de
Maria Arélin: Hospital for Children and Adolescents, Department of Women and Child Health, University of Leipzig, Leipzig, Germany