NEW TRENDS IN NEWBORN SCREENING
THE EXAMPLE OF LYSOSONAL STORAGE DISORDERS

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Newborn screening has been implemented worldwide for many different inherited disorders, including inborn errors of metabolism, endocrinopathies, hemoglobinopathies, cystic fibrosis and others. While expanded newborn screening by tandem mass spectrometry for analysis of acylcarnitine species, and amino acids is widely available, additional novel applications are currently being developed and tested. With the advent of novel treatment modalities in lysosomal storage diseases (LSD) such as bone marrow transplantation and/or enzyme replacement therapies, newborn screening for some of the LSD for example Pompe Disease, Fabry Disease, Gaucher Disease, Krabbe Disease and others has become a focus point. From a technological perspective high-throughput newborn screening for LSD may be feasible using different analytical approaches, such as the analysis of enzyme activities by fluorometric assays, tandem mass spectrometry or analysis of protein (enzyme) concentrations by protein binding assays, respectively. Routine newborn screening for Fabry and Pompe Diseases is currently been done in parts of Taiwan and for Krabbe Disease in New York State. Additional programmes are in the process of being implemented. However prior to wide spread implementation of neonatal screening programmes for LSD, strategies for confirmatory testing, treatment, follow-up care and scientific evaluation have to be defined and agreed upon at an international level.

Descriptors: NEWBORN SCREENING, NEW TRENDS, LYSONOSMAL STORAGE DISORDERS
same laboratory provides Pompe diagnostic services for all of Taiwan. Between October 2005 and March 2007 more than 130,000 newborn infants were screened and PD was diagnosed in 4 infants during their first month of life. In contrast 3 infants were diagnosed during the same time period based on clinical symptoms alone between 3 and 6 months of age. All infants except one in the screening group had infantile-onset PD and were started on enzyme replacement therapy (6). The recall rate for repeat blood tests was 0.82% and for clinical recall 0.091% (6, 7). Outcome in the newborn screening group is excellent with all children achieving normal to near-normal psychomotor development. These data will be published soon (Paul Hwu personal communication).

The MS/MS technique for GAA analysis in DBS was further evaluated and validated on more than 10,000 anonymous newborn infants in Austria and 29 known patients with PD (2). The recall rate in this study was 0.03%, which compares very low to the results of newborn screening by fluorometry (2, 6). The MS-MS technique for newborn screening of PD needs to be evaluated in a larger, preferably nationwide pilot study.

Krabbe Disease (KD)

New York State Laboratories, Wadsworth Center Albany, NY has started newborn screening for KD using MS/MS technology in August 2006. Through June 2008 the Wadsworth Center has tested more than 550,000 newborn infants and identified four infants at high risk for developing early onset KD (4, 8, 9). Two of these infants with severe pathogenic mutations in the galactocerebroside gene and neuroradiologic findings received umbilical chord transplantation within the first 4 weeks of life. Unfortunately one infant died during transplantation due to procedure related complications (8). The other infant has not developed any signs or symptoms related to early onset KD but are developmentally delayed (8). The 2 high-risk infants who were not transplanted, show age-appropriate psycho-motor development at 8 and 16 months of life, respectively (8).

Mucopolysaccharidosis Type I (MPS-I)

The microplate adapted fluorometric, iduronidase assay is easy to perform and seems to be suitable for large scale pilot newborn screening (10). We have done a small pilot study using this protocol on 460 anonymous infants and demonstrated a median iduronidase activity of 0.8 µmol/l/h while the single MPS-I patient tested, had no measurable enzyme activity (Figures 1 and 2). Based on our limited experience recall rates appear low so that this protocol may be suitable for large scale newborn screening.

Fabry Disease (FD)

Two pilot studies using a fluorometric assay for FD were done or are still ongoing. A pilot study in northern Italy identified 12 neonates with FD among 37,000 male infants. The vast majority of infants (11/12) with FD had mutations compatible with a mild disease course. In addition affected family members were detected. A similar pilot study for Fabry disease in Taiwan is ongoing, details are currently not available.

Figure 1
α-Iuronidase activity in 460 newborn infants; one infant with a severe form of MPS-I (Hurler Phenotype) had no detectable enzyme activity

Slika 1.
α-Iuronidazna aktivnost kod 460 novorođenčadi; jedno novorođenče sa teškim oblikom MPS-I (Hurler Phenotype) nije imalo prepoznatljivu enzimnu aktivnost

Figure 2
Calibration line of the α-Iuronidase fluorometric assay

Slika 2.
Linija kalibracije α-Iuronidazne fluorometrijske analize
Conclusions

Although newborn screening for LSD using different analytical approaches may be technically feasible, it is still a long way to go. Careful planned pilot studies in large newborn populations are needed to assess test characteristics, define population specific cut-off values and diagnostic algorithms. Prior to formal implementation of newborn screening for LSD recommendations and guidelines for confirmatory testing, management and long-term follow up have to be agreed upon, preferably at an international level. The Krabbe Disease newborn screening and follow-up programme in New York State may serve as a model (8).

LITERATURE


Sažetak

NOVI TRENDI U SKRININGU NOVOROĐENČADI
PRIMJER POREMEĆAJA LIZOSOMNIH BOLESTI

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Skrining novorođenčadi se primjenjuje u čitavom svijetu za mnoge različite nasljedne poremećaje, uključujući urođene greške u metabolizmu, endokrinopatije, hemoglobinopatije, cističnu fibrozu i drugo. Dok je prošireni skrining novorođenčadi putem tandemske spektrometrije masa za analizu acilokarnitinskih vrsta i aminokiselina širom dostupan, trenutno se razvijaju i testiraju neke nove aplikacije. Dolaskom novih modaliteta liječenja lisozomnih bolesti (LSD), kao što su transplantacija koštane srži i/ili terapije zamjene enzima, skrining kod novorođenčadi za neke LSD kao što su Pompe bolest, Fabry bolest, Gaucher, Krabbe i dr. su postali interesantni. Tehnološki gledano, visoko propusni skrining novorođenčadi na LSD može biti izvediv koristeći se raznim analitičkim pristupima, kao što su analiza enzimnih aktivnosti putem fluorometrijske analize, tandemske spektrometrije masa ili analiza proteinske (enzimske) koncentracije putem analize vezivanja proteina. Rutinski skrining novorođenčadi za Fabryevu i Pompeovu bolest se trenutno obavlja u nekim dijelovima Taiwana a za Krabbeovu bolest u državi New York. Dodatni programi su u procesu uvode. Međutim, prije široke primjene programa neonatalnih skrininga na LSD, moraju se definirati strategije i odrediti međunarodni konsenzus za testiranje, liječenje, oporavak i znanstvenu evaluaciju.

Deskriptori: NOVOROĐENAČKI SKRINING, NOVI TRENDI, LIZOSOMNE BOLESTI