A Pilot Study on an Expanded Newborn Screening Program in Palestine: Phase II
S. Khatib and A. Ayyad, Al-Quds University, Jerusalem, Palestine

Abstract

Objective: Until this day newborns in Palestine are being screened for phenylketonuria and congenital hypothyroidism only. However, a number of other metabolic diseases have been recognized amongst the population, including four main types of organic acidemias: Methylmalonic acidemia (MMA), Propionic acidemia (PA), Glutaric acidemia type1 (GA1), and Isovaleric acidemia (IVA). The study was conducted in an effort to investigate the possibility of finding such cases in newborns throughout the West Bank of Palestine by screening newborns for a number of organic acid intermediates. In addition, reference ranges for these intermediates will be established.

Study Design: A cross-sectional observational study design was used and the study was conducted in all 12 districts of the West Bank. A pilot study was done before the actual study took place. Convenience sampling was used to recognize the study newly born participants. Information regarding date of birth, weight, sex, district, and parent kinship was recorded. The sample size was 4240 and an informed consent form was collected from all parents. The study blood collection cards were collected over a one year period by Ministry of Health staff in parallel to the routine collection for the existing newborn screening program. The study cards were shipped to the University of Liege Human Genetics Department in Belgium for analysis using tandem mass spectrometry (MS/MS).

Results: Statistical analysis showed significant differences in mean newborn weight and organic acid levels. The odds ratio analysis showed no effect of gender on all organic acid levels, while independent sample t-test showed significant differences in the mean organic acid levels and gender. No significant effect was observed between parent kinship and organic acid levels. Chi-square test showed significant differences in the levels of the organic acids and districts. The reference range for the main types of organic acids tested was calculated based on the non-parametric percentile method as indicated by CLSI C28-A3.

Conclusion: Based on our established reference ranges for each analyte the results showed that 10.7% of the tested samples (455) had at least one organic acid level in the upper 2.5% of the population.

Presenter: Samir Khatib, PhD, Al-Quds University, Medical School, Beit Hanina, Jerusalem, Palestine, Phone: 972.5463.52826, Email: drskhatib@gmail.com
Summary

Introduction: Newborn screening is a universal health program which is useful in the early detection of serious metabolic and genetic diseases in newborns before symptoms begin to appear. Until this day newborns in Palestine are being screened for phenylketonuria and congenital hypothyroidism only. However, a number of other metabolic diseases have been recognized amongst the population, including amino acids, organic acids and fatty acids oxidation disorders. Therefore, a comprehensive study was undertaken to investigate the possibility of detecting these disorders through an expanded newborn screening program. Phase I of the study involved aminoacids and urea cycle disorders while the present study i.e. phase II, looked at the four main types of organic acidemias, namely methylmalonic academia (MMA), propionic academia (PA), glutaric academia type I (GA1), and isovaleric academia (IVA) by measuring the levels of their respective acylcarnitines in newborn blood samples. Phase III involved studying the levels of acylcarnitines related to fatty acid oxidation.

The study was conducted in collaboration with: a) the Palestinian Ministry of Health through the collection of samples from newborns throughout the West Bank of Palestine, and b) the Human Genetics Department at Liege University in Belgium by analyzing the collected samples.

Study Objectives:
- To assess the need for expanding the existing newborn screening program in Palestine.
- To investigate the relationship between some demographic variables such as gender, kinship, district, weight and three types of acylcarnitine levels that are related to organic acid metabolism.
- To determine the reference ranges for three acylcarnitine profiles of four main types of organic acidemias in Palestinian newborns.

Methodology: A cross-sectional observational study design was done. The study covered all 12 districts of the West Bank in Palestine during the period between January 2012 and January 2013. A pilot study was done before the actual study took place. Convenience sampling was used to recognize the study participants of newborns. Blood samples were collected on special blood collection cards in parallel to the routine collection for the existing newborn screening program. Information regarding weight, date of birth, sex, district, and kinship of parents was taken. The number of samples was 4240 and informed consent was taken from each parent participant. The collected cards were shipped to Liege by courier where analysis of acylcarnitines in the samples was done using tandem mass spectrometry (MS/MS).

Results: Of the 4240 newborns, almost half (50.4%) of the study sample were males. Most of the parents of the newborns (74.3%) were unrelated. The mean weight of the participating newborns was 3.23 +/- 0.45 kg.

The reference range for each acylcarnitine (C3, C5-DC, C5) was calculated based on the non parametric percentile method (CLSI C28-A3). The mean level for C3 was 1.15 +/- 0.59 umol/L, for C5-DC was 0.13 +/- 0.05 umol/L and for C5 was 0.21 +/- 0.08 umol/L. Elevated levels of C3 were detected in 3.8% of the tested samples, for C5-DC in 3.7% and for C5 in 4.1%. Statistical analysis showed significant relationship between mean newborn weight and most acylcarnitine levels. From odds ratios test, neither gender nor kinship had any effect on the acylcarnitine levels. However, independent sample t-test showed significant differences in the mean acylcarnitine levels and gender. The results also showed that there is a significant difference between districts and acylcarnitine levels.
Conclusions: Based on our established reference ranges for each analyte the results showed that 10.7% of the tested samples (455) had at least one acylcarnitine level in the upper 2.5% of the population.
- There is a significant relationship between mean weight and gender.
- There is a significant relationship between mean weight and most acylcarnitine levels.
- Neither gender nor kinship had any effect on the acylcarnitine levels, but there is a significant difference between most acylcarnitine levels mean and gender.
- There is a significant difference between districts and acylcarnitine levels.
- The study results support further assessment of the need to expand the existing newborn screening program in Palestine.

Congenital Hypothyroidism Detected In Newborn Screening: A 3-Year Data from a Tertiary Care Centre in India
S. Khalil, A. Sharma, S. Ramji and A.P. Dubey, Maulana Azad Medical College & Associated L N Hospital, New Delhi, India

Abstract

Abstract: Aims and objective: Congenital Hypothyroidism is one of the most common treatable causes of Mental retardation. It can lead to an increased risk and earlier onset of delayed development, which if untreated can lead to mental retardation. Newborn screening and early initiation of thyroid therapy within 2 weeks of age can completely normalize the cognitive development. Therefore, we present our prospective data of newborn screening for a period of 3 years.

Methods: A total of 14746 newborns underwent newborn screening on 24-72 hours of life at genetic division of Lok Nayak hospital, New Delhi. Dried blood spots were collected by heel-prick on the blood sample collection card and analyzed by two site fluroimmunoassay based on sandwich ELISA. In screen positive cases serum (for repeat test by a different methodology other than time resolved flourimetry) as well as repeat filter paper sample were collected and forwarded to the testing lab as soon as possible. Cut-off value of TSH >20 µU/L for neonates was taken as abnormal and 10 – 20 µU/L was treated as the ambiguous zone. All babies confirmed to have CH underwent thyroid scan, radioactive iodine uptake studies and bone age estimation (x ray Knee) and started on thyroid replacement.

Results: A total of 14746 newborn were screened, 7815 (53.5%) were males and 6931(47%) were females. Amongst them, 52 (0.35%) were diagnosed with congenital hypothyroidism on first screening, followed by confirmation in 32 (0.21%) on second testing. The ones with confirmed congenital hypothyroidism, 10(30%) neonates were preterms, 18 (57%) were males and 14 (43%) were females. From the total number of neonates diagnosed with congenital hypothyroidism, 4 had ectopic thyroid gland and 8 had evidence of dyshormonogenesis and in 2 there was no uptake suggestive of athyrosis. Out of the preterm and low birth weight babies in the ambiguous zone (n=11) 2 tested positive on the second test done at 14 weeks of age.

Conclusions: Congenital hypothyroidism is a template disorder for nationwide initiation of newborn screening. This pilot study reveals an incidence of 1 in 1500 live births. Thus universal screening is highly recommended in our part of the country for congenital hypothyroidism. Early intervention with oral thyroid replacement completely normalizes the development.

Presenter: Sumaira Khalil, DNB, Maulana Azad Medical College & Associated L N Hospital, Pediatrics, New Delhi, India, Phone: 919.810.424664, Email: sumairakhailil@yahoo.com

Screening for Critical Congenital Heart Disease: Global Implementation Efforts
G. Martin and L. Hom, Children's National Health System, Washington, DC

Abstract

Background: Health and Human Services Secretary Sibelius recommended adding critical congenital heart disease (CCHD) screening to the recommended uniform screening panel in 2011. Stakeholder meetings at the Heart House in 2011 and 2012 led to a recommended protocol as well as strategies for implementation in the United States. Tremendous progress has been made at the state level with legislation passed in 36 states and pilot projects underway in the majority of the others. It is estimated that over 80% of births in the United States will be screened for CCHD by the end of 2014. Ironically, Europe has made less progress despite providing the population based studies that were critical in driving support for efforts within the United States. Efforts for global implementation on other continents are gaining momentum. The purpose of this study was to describe the progress of CCHD screening implementation efforts globally.

Methods: Congenital Heart Disease (CHD) advocacy groups, investigators in screening for CCHD and international health organizations have been meeting with health care providers and government officials on a country by country basis. Countries that are implementing or have pilot projects have been identified. A map has been created to categorize and track global implementation.

Results: The Nordic countries, Switzerland and the United Arab Emirates are closest to universal screening for CCHD in newborns. Ireland and the United Kingdom have a national recommendation in place. Significant pilot projects tailored to unique care delivery systems screen on an out-patient basis in China, through the use of midwives in the Netherlands and on maternity wards in the United Kingdom. Isolated centers or individuals in Africa, South America, Central America and Asia have expressed interest in how to implement in their individual countries but are in the early stages of organization.

Data contributed by: A. Granelli, A. Saarinen & A. Ewer

Presenter: Gerard Martin, MD, Children's National Health System, Heart Institute/Cardiology, Washington, DC, Phone: 202.476.2020, Email: gmartin@cnmc.org

Summary

Background: Congenital Heart Disease (CHD) is the most common birth defect impacting nearly one in every 100 live births. Health and Human Services Secretary Sibelius recommended adding critical congenital heart disease (CCHD) screening to the Recommended Uniform Screening Panel (RUSP) in 2011. Stakeholder meetings at the Heart House in 2011 and 2012 led to a recommended protocol as well as strategies for implementation in the United States.

Tremendous progress has been made at the state level with legislative or regulatory requirements in 42 states and pilot projects underway in the majority of the others. It is estimated that well over 80% of births in the United States will be screened for CCHD by the end of 2014. Ironically, Europe has made less progress despite providing the population based studies that were critical in driving support for efforts within the United States. Efforts for global implementation on other continents are gaining...
momentum. The purpose of this study was to describe the progress of CCHD screening implementation efforts globally.

Methods: Congenital Heart Disease advocacy groups, investigators in screening for CCHD and international health organizations have been meeting with health care providers and government officials on a country by country basis. Experts gathered in Torino, Italy for a second time to discuss and strategize the creation of a uniform recommendation to screen for CCHD in Europe. A recent recommendation paper from the European Union Committee of Experts on Rare Diseases (EUCERDS) identifies newborn screening for congenital heart defects as an opportunity for collaboration and improvement. Countries that are implementing or have pilot projects have been identified. A map and table have been created to categorize and track global implementation.

Results: The Nordic countries, Switzerland, the United States and the United Arab Emirates are closest to universal screening for CCHD in newborns. Ireland, Norway, Switzerland, and Poland all have a recommendation to screen at the national level. Significant pilot projects tailored to unique care delivery systems screen on an out-patient basis in China, through the use of midwives in the Netherlands and on maternity wards in the United Kingdom. The Monterrey region in Mexico has screened over 74,000 infants with 78 identified as requiring specialty care. Using a train the trainer method in the UAE, Abu Dhabi reports successful screening of over 80,000 babies with 34 cases of CCHD detected. Isolated centers or individuals in Africa and South America have expressed interest in how to implement in their individual countries but are in the early stages of organization.

As implementation progresses, it will be important to analyze and track results at the population level as well as harness local expertise working in a variety of care delivery models such as hospital versus home births. The trend toward earlier discharge in several countries like France and the UK may prove challenging as most effective protocols currently recommend screening at or around 24-48 hours of age. Australia and New Zealand have shown early promising results with improvements in detection rates after implementing screening for both normal and early discharges.

Conclusion: Coordination and data sharing will be important as CCHD screening implementation continues to gain momentum around the globe. Impact on newborn health and mortality rates will vary particularly in developing countries where pulse oximetry screening as a tool for identifying CCHD may also have an equal impact by identifying secondary targets such as infectious or respiratory causes for hypoxia.
World Map of Critical Congenital Heart Disease Screening Implementation

September 2014

Data contributed by: A. Granelli, A. Saarinen & A. Ewer

European Map of Critical Congenital Heart Disease Screening Implementation

September 2014

Data contributed by: A. Granelli, A. Saarinen & A. Ewer
Further Expansion of NBS in European Countries: Horse Carriages vs Bullet Trains
J.G. Loeber, ISNS Office, Bilthoven, The Netherlands

Abstract

Virtually all European countries have introduced neonatal screening over the last 50 years as an important public health feature. Depending on health care structure, available funds, local politics, input from professional groups and the general public, this introduction has led to different approaches in the way the screening programmes have been set up, financed and governed (Loeber 2007). In 2010 an online survey, commissioned by the EU, was compiled in which the whole screening programme was...
covered by a questionnaire. This survey covered the EU member states, (potential) candidate member states and European Free Trade Association countries, in total 38 countries.

Results showed, as expected, no consensus concerning 1) information for parents including informed consent; 2) panel of screened conditions, ranging from 2 to more than 30 conditions; 3) specimen collection time postpartum; 4) screening methodology; and 5) storage of residual specimens, varying from 1-1000 years. In addition, confirmatory diagnostics, treatment, and follow-up showed large discrepancies. Finally, not all countries view long term epidemiological evaluation as essential, which is needed for constant quality improvement (Loeber et al. 2012; Burgard et al. 2012). In 2011 the project group provided a list of 60 recommendations to the EU Commission, but so far none of them have been taken up.

Recently, the same colleagues from 2010 were re-surveyed about new developments in their country concerning the above topics. In some, mostly smaller, countries considerable changes have been implemented, mainly concerning the number of ms/ms detectable conditions. In contrast, in other mainly larger, countries very little has changed, if at all. In contrast to the US, in Europe national public health policies are either not at all, or only marginally, influenced by developments in neighbouring countries.


**Presenter:** J. Gerard Loeber, PhD, ISNS Office, Bilthoven, The Netherlands, Email: gerard.loeber@gmail.com