

June/July 2010 Newborn Screening Articles

1. Pediatr Pulmonol. 2010 Jul 29. [Epub ahead of print]

Does presenting with meconium ileus affect the prognosis of children with cystic fibrosis?

Johnson JA, Bush A, Buchdahl R.

Abstract

It is a matter of debate as to what extent the long-term outcome of cystic fibrosis (CF) is affected by presenting with meconium ileus (MI). We compared long-term clinical outcomes of CF children who presented with MI, to those presenting with other symptoms (non-MI) in an era of non new-born-screening (NBS). We collected annual lung function data between the ages of 8-15 years in terms of percent predicted first second forced expired volume (FEV1%pr), percent predicted forced vital capacity (FVC%pr), and between the ages of 2-15 years annual height and weight Z-scores (HtZ and WtZ respectively) for children attending the Royal Brompton Hospital CF clinic. To be included in the study, subjects had to have at least five pulmonary function tests and five anthropometric measurements recorded over this period. Thirty-eight MI and 76 non-MI subjects were compared. There were no significant differences in genotype, sex, chronic Pseudomonas infection, or pancreatic enzyme use between the two groups. The median age of diagnosis was 1 day (MI) versus 7 months (non-MI). There was a decline in spirometry and anthropometric variables over the study period for both MI and non-MI groups apart from WtZ score in the non-MI group. Mixed model analysis adjusting for potential confounders including genotype, pancreatic status, sex, chronic Pseudomonas aeruginosa lung infection, and age of diagnosis revealed no difference between the two groups in terms of lung function and growth during the time period of the study, however there was a non-significant trend for subjects presenting with MI to do better in all four parameters. We conclude that babies presenting with MI have no worse long-term outcome than those presenting symptomatically later in infancy, despite having undergone invasive procedures in the newborn period. This underscores the importance of early diagnosis and treatment in CF.

2. Ir Med J. 2010 May;103(5):146-9.

Newborn hearing screening: a regional example for national care.

Adelola OA, Papanikolaou V, Gormley P, Lang J, Keogh IJ.

Abstract

Congenital Permanent Childhood Hearing Impairment (PCHI) is known to have a negative effect on language acquisition, cognitive development and social integration. Since 2000 our department has implemented a UNHS program in the West of Ireland. We describe our experience and detail our results to date. All neonates born from October 2000 to November 2007 were screened using a 2-stage protocol. Transient evoked oto-acoustic emissions (TEOAEs) were used to screen all neonates, followed by automated auditory brainstem response (AABR) in those who did not pass TEOAE, and all neonates at audiological risk. 26,281 babies were born over the eight year period. 25,742 underwent the screening process, achieving a coverage rate of 98%. The prevalence of PCHI in the population tested was 1.21/1000 live births (31/25,731). Our results show that a hospital based 2-stage UNHS protocol using TEOAEs and AABR is accurate, feasible and effective.

3. **Eur J Pediatr. 2010 Jul 28. [Epub ahead of print]**

Neonatal pulse oxymetry as a screening for congenital heart disease: single or double recordings?

Rosti L.

4. **Am J Med Genet A. 2010 Aug;152A(8):fmix.**

SCID added to national newborn screening standards.

5. **Eur J Pediatr. 2010 Jul 27. [Epub ahead of print]**

Post-mortem MRI reveals CPT2 deficiency after sudden infant death.

Bouchireb K, Teychene AM, Rigal O, de Lonlay P, Valavannopoulos V, Gaudelus J, Sellier N, Bonnefont JP, Brivet M, de Pontual L.

Abstract

Inherited metabolic disorders are the cause of a small but significant number of sudden infant deaths in infants. We report on a boy who suddenly died at 10 months of age during an acute illness. Parents declined autopsy; nevertheless, they accepted a whole body MRI, which revealed hepatomegaly with steatosis. Acylcarnitine profile of a blood sample from neonatal Guthrie screening led to the diagnosis of type 2 carnitine palmitoyltransferase deficiency. To conclude, whole body MRI is useful in the investigation of some inherited metabolic causes of sudden infant death, which might prevent future deaths in the family. It is a good alternative when autopsy is refused.

6. J Med Screen. 2010;17(2):66-7.

The efficacy of a neonatal screening programme in decreasing the hospitalization rate of patients with G6PD deficiency in southern Iran.

Cohan N, Karimi M, Khalili AH, Falahzadeh MH, Samadi B, Mahdavi MR.

Abstract

OBJECTIVE: To investigate whether a neonatal screening programme for G6PD deficiency has decreased hospitalization for acute haemolytic attack in the Fars province of southern Iran. **METHODS:** A total of 850 patients registered with G6PD deficiency were included in the study. Variables including age, sex, time and cause of hospitalization, cause of haemolytic crisis, positive history of blood transfusion, G6PD enzyme deficiency, blood urea nitrogen (BUN) and creatinine were recorded based on a standard questionnaire. All patients were analysed for G6PD enzyme level based on a quantitative test. **RESULTS:** Five hundred and fifty-three patients were hospitalized before the introduction of the neonatal screening programme (2001-2004) and 297 afterwards (2005-2008). Of those patients hospitalized after the introduction of the screening programme, 237 were wrongly classified as normal and 60 were recorded as having G6PD enzyme deficiency by the neonatal screening programme. The main causes of haemolytic crisis in G6PD-deficient patients were fava bean consumption (88.2%), underlying infection (10.9%) and drugs (0.8%). **CONCLUSION:** Our study showed the effectiveness of the neonatal screening programme in decreasing the hospitalization rate.

7. J Med Screen. 2010;17(2):58-65.

Implementing neonatal screening for haemoglobinopathies in the Netherlands.

Bouva MJ, Mohrmann K, Brinkman HB, Kemper-Proper EA, Elvers B, Loeber JG, Verheul FE, Giordano PC.

Abstract

BACKGROUND: The birth prevalence of severe haemoglobinopathies such as sickle cell disease (SCD) in the Netherlands has been estimated to be at least 50 newborns per year. Neonatal screening for SCD was added to the Dutch screening programme in January 2007. We here evaluated three high performance liquid chromatography (HPLC) systems for application in neonatal screening for haemoglobinopathies, and present the results of a subsequent pilot screening programme. **METHODS:** The Variant NewBorn Screening (Vnbs) HPLC system (Bio-Rad) was validated by analysing 131 blood samples and blood mixtures. Subsequently, the performance of the G7 (Tosoh BioScience) and Ultra (Primus Corporation) was compared with the Vnbs. The three HPLC analysers were tested in a pilot screening programme on 21,969 dried blood spot samples from the routine Dutch neonatal screening programme. **RESULTS:** The pilot screening resulted in 188 abnormal patterns. The three HPLC devices presented comparable within- and between-run precision and detected the abnormal samples similarly. The high throughput, sampling systems, presentation of results, and integration of the chromatograms, however, were different. **CONCLUSION:** All three analysers detected the same abnormal haemoglobins satisfactorily, but integrated the chromatograms with variable imprecision. Comparison of the results suggested that the Bio-Rad Vnbs was the preferred system. However, software adjustments were required to improve the diagnostic potential of this device for screening for beta- and alpha-thalassaemia.

8. Clin Chem. 2010 Jul 21. [Epub ahead of print]

A Multiplex Immunoassay Using the Guthrie Specimen to Detect T-Cell Deficiencies Including Severe Combined Immunodeficiency Disease.

Janik DK, Lindau-Shepard B, Comeau AM, Pass KA.

Abstract

BACKGROUND: Severe combined immunodeficiency disease (SCID)(4) fulfills many of the requirements for addition to a newborn screening panel. Two newborn screening SCID pilot studies are now underway using the T-cell recombination excision circle (TREC) assay, a molecular technique. Here

we describe an immunoassay with CD3 as a marker for T cells and CD45 as a marker for total leukocytes that can be used with the Guthrie specimen. **METHODS:** The multiplexing capabilities of the Luminex platform were used. Antibody pairs were used to capture and detect CD3 and CD45 from a single 3-mm punch of the Guthrie specimen. The assay for each biomarker was developed separately in identical buffers and then combined to create a multiplex assay. **RESULTS:** Using calibrators made from known amounts of leukocytes, a detection limit of 0.25×10^6 cells/mL for CD3 and 0.125×10^6 cells/mL for CD45 was obtained. Affinity tests showed no cross-reactivity between the antibodies to CD3 and CD45. The multiplex assay was validated against eight coded specimens of known clinical status and linked to results from the TREC assay that had identified them. All were correctly identified by the CD345 assay. **CONCLUSIONS:** The performance parameters of the CD345 assay met the performance characteristics generally accepted for immunoassays. Our assay classifications of positive specimens concur with previous TREC results. This CD345 assay warrants evaluation as a viable alternative or complement to the TREC assay as a primary screening tool for detecting T-cell immunodeficiencies, including SCID, in Guthrie specimens.

9. Clin Chem. 2010 Jul 21. [Epub ahead of print]

High-Throughput Multiplexed T-Cell-Receptor Excision Circle Quantitative PCR Assay with Internal Controls for Detection of Severe Combined Immunodeficiency in Population-Based Newborn Screening.

Gerstel-Thompson JL, Wilkey JF, Baptiste JC, Navas JS, Pai SY, Pass KA, Eaton RB, Comeau AM.

Abstract

BACKGROUND: Real-time quantitative PCR (qPCR) targeting a specific marker of functional T cells, the T-cell-receptor excision circle (TREC), detects the absence of functional T cells and has a demonstrated clinical validity for detecting severe combined immunodeficiency (SCID) in infants. There is need for a qPCR TREC assay with an internal control to monitor DNA quality and the relative cellular content of the particular dried blood spot punch sampled in each reaction. The utility of the qPCR TREC assay would also be far improved if more tests could be performed on the same newborn screening sample. **METHODS:** We approached the multiplexing of qPCR for TREC by attenuating the reaction for

the reference gene, with focus on maintaining tight quality assurance for reproducible slopes and for prevention of sample-to-sample cross contamination. Statewide newborn screening for SCID using the multiplexed assay was implemented, and quality-assurance data were recorded. RESULTS: The multiplex qPCR TREC assay showed nearly 100% amplification efficiency for each of the TREC and reference sequences, clinical validity for multiple forms of SCID, and an analytic limit of detection consistent with prevention of contamination. The eluate and residual ghost from a 3.2-mm dried blood spot could be used as source material for multiplexed immunoassays and multiplexed DNA tests (Multiplex Plus), with no disruption to the multiplex TREC qPCR. CONCLUSIONS: Population-based SCID newborn screening programs should consider multiplexing for quality assurance purposes. Potential benefits of using Multiplex Plus include the ability to perform multianalyte profiling.

10. Mol Genet Metab. 2010 Jul 24. [Epub ahead of print]

Outcome in six patients with mitochondrial trifunctional protein disorders identified by newborn screening.

Sperk A, Mueller M, Spiekerkoetter U.

Abstract

Before the newborn screening era, disorders of the mitochondrial trifunctional protein (TFP) complex including long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) presented with high morbidity and mortality. Data on outcome and prognosis of TFP deficiency disorders since implementation of screening are scarce. We here characterize 6 screened patients with a disorder of the TFP complex (3 of those with LCHADD) with respect to clinical presentation and molecular features. Three of 6 patients were symptomatic prior availability of screening results on days 4-5 of life. Of the three asymptomatic patients recognised by screening, one acutely died at 3months at home during an infection. Two patients remained asymptomatic with preventive measures during follow-up until the age of 3years. One of them had an older sibling with identical genotype born before the screening era, who became symptomatic with 15months. We conclude that newborn screening for disorders of the TFP complex allows identification of asymptomatic cases; however, the acute presentation in 3/6 babies before screening is noteworthy and troublesome. TFP and LCHAD deficiencies remain life-threatening

disorders. This is in clear contrast to other defects of long-chain fatty acid oxidation after identification by newborn screening. Copyright © 2010 Elsevier Inc. All rights reserved

11. **J Inherit Metab Dis. 2010 Jul 21. [Epub ahead of print]**

Postprandial changes of amino acid and acylcarnitine concentrations in dried blood samples.

Fingerhut R, De Jesus Silva Arevalo G, Baumgartner MR, Häberle J, Rohrbach M, Figueroa AW, Fresse EM, Polanco OL, Torresani T.

Abstract

Blood sampling for newborn screening cannot be standardized as for example blood collection in adults after an overnight fast. Therefore the influence of postprandial changes and individual variation is valuable information for the assessment of sensitivity and specificity of newborn screening for certain disorders. We have analyzed 92 pairs of dried blood samples taken pre- and one hour postprandially, respectively. We have determined the mean increase in metabolite concentration and calculated its significance. Individual variation after an overnight fast in healthy adults (n = 3) was between 12 and 32% (SD). Postprandial increases of acylcarnitines were mostly not significant and not exceeding 10%. Postprandial increase of amino acids was highly significant for most proteinogenic amino acids, but not for all. With the collected data we were able to estimate that mainly decreased levels of methionine and, to a lesser extent, of free carnitine could be "masked" by postprandial increases of the respective metabolites, and could therefore lead to false negative results for the detection of disorders of cobalamin metabolism and carnitine transporter deficiency.

12. **Acta Paediatr. 2010 Jul 16. [Epub ahead of print]**

New technologies extend the scope of newborn blood-spot screening but old problems remain unresolved.

Pollitt RJ.

Abstract

Abstract The potential of newborn blood-spot screening is expanding rapidly with the development of new analytical techniques and treatment methods. At the same time some existing programmes, particularly that for congenital hypothyroidism, are coming under scrutiny because of suspicion that they are being shaped by analytical performance rather than evidence of clinical need. Screening policy varies greatly from country to country. Conclusion: Ethical and political considerations may sometimes override formal scientific decision models.

13. Hemoglobin. 2010;34(4):354-65.

Codon 24 (TAT>TAG) and codon 32 (ATG>AGG) (Hb Rotterdam): two novel alpha2 gene mutations associated with mild alpha-thalassemia found in the same family after newborn screening.

Giordano PC, Cnossen MH, Joosten AM, Jansen CA, Hakvoort TE, Bakker-Verweij M, Arkesteijn SG, van Delft P, Weye JS, Bouva MJ, Harteveld CL.

Abstract

We report two novel alpha2-globin gene mutations found in the same Surinamese family. The proband, a newborn presenting during neonatal screening with 21.3% Hb Bart's (gamma4), proved to be a carrier of the common -alpha(3.7) deletion and a novel codon 32 (ATG>AGG) transversion that we named Hb Rotterdam. The father carried the same point mutation with borderline hemoglobin (Hb), MCV and low MCH values. The mother presented with a significant microcytic hypochromic anemia and also carried the -alpha(3.7) deletion and a second novel TAT>TAG transversion generating a stop codon at position 24. Shortly thereafter, Hb Rotterdam was again found in two unrelated adult females and in a Canadian newborn, all of African origin, suggesting that Hb Rotterdam could be a frequently occurring alpha(T) determinant in the Black population. Screening and characterization of the mutations, phenotype/genotype correlation and the issue of reporting newborn carriers of alpha-thalassemia (alpha-thal) are discussed.

14. Sex Dev. 2010 Jul 15. [Epub ahead of print]

Impact of Molecular Genetics on Congenital Adrenal Hyperplasia Management.

Balsamo A, Baldazzi L, Menabò S, Cicognani A.

Abstract

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders caused by mutations in genes encoding the enzymes involved in one of the 5 steps of adrenal steroid synthesis or the electron donor P450 oxidoreductase (POR) enzyme. Steroid 21-hydroxylase deficiency (21-OHD), the principal focus of this review, accounts for about 90-95% of all CAH cases, and its biochemical and clinical severity depends on the underlying CYP21A2 gene disruption. Molecular genetic advancements have been achieved in recent years, and the aim of this review is to attempt to highlight its contribution to the comprehension and management of the disease. When possible, we will try to achieve this goal also by providing some results from our personal experience regarding: some aspects of CYP21A2 gene analysis, with basic genotype/phenotype relationships; its crucial role in both genetic counselling and in prenatal diagnosis and treatment in families at risk for 21-OHD; its help in the comprehension of the severity of the disease in patients diagnosed by neonatal screening and possibly treated before an evident salt-loss crisis or before performing adequate blood sampling; its usefulness in the definition of post ACTH 17-hydroxyprogesterone values, discriminating between non-classic, heterozygote and normal subjects; and finally the contribution of genes other than CYP21A2 whose function or dysfunction could influence 21-hydroxylase activity and modify the presentation or management of the disease.

15. Thorax. 2010 Jul;65(7):652-3.

Positive neonatal screening for cystic fibrosis in neonates with renal failure.

Oosterveld MJ, Schilperoort JV, Lilien MR, Arets HG.

Abstract

Screening for cystic fibrosis (CF) was recently added to the neonatal screening programme in the Netherlands. Four patients with renal failure whose heel prick tests were positive for CF as defined by raised levels of immunoreactive trypsinogen (IRT) and pancreatitis-associated protein (PAP) are described. Both cystic fibrosis transmembrane conductance regulator (CFTR) DNA analysis and sweat tests were negative. Limited renal function can be a cause of false positive neonatal screening for CF using IRT and PAP

16. Pediatrics. 2010 Jul 12. [Epub ahead of print]

Challenges and Pitfalls in the Management of Phenylketonuria.

Feillet F, van Spronsen FJ, Macdonald A, Trefz FK, Demirkol M, Giovannini M, Bélanger-Quintana A, Blau N.

Abstract

Despite recent advances in the management of phenylketonuria and hyperphenylalaninemia, important questions on the management of this disorder remain unanswered. Consensus exists on the need for neonatal screening and early treatment, yet disagreement persists over threshold levels of blood phenylalanine for starting treatment, target blood phenylalanine levels, and the management of older patient groups. The mainstay of treatment is a phenylalanine-restricted diet, but its application varies between and within countries. Beyond diet treatment, there is a lack of consensus on the use of newer treatments such as tetrahydrobiopterin. Although neonatal screening and early treatment has meant that most well-treated children grow up with near-normal IQ scores, the effect of relaxing metabolic control on cognitive and executive function later in life is still not fully understood. Although it is clear from the available literature that the active control of blood phenylalanine levels is of vital importance, there are other treatment-related factors that affect outcome. A uniform and firmly evidence-based approach to the management of phenylketonuria is required.

17. Ann Saudi Med. 2010 Jul-Aug;30(4):271-7.

Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008.

Moammar H, Cheriyan G, Mathew R, Al-Sanna N.

Abstract

BACKGROUND AND OBJECTIVES: Individual inborn errors of metabolism (IEM) are rare disorders, but may not be that uncommon in our patient population. We report the incidence of IEM in a defined cohort of births at the Saudi Aramco medical facilities in the Eastern Province of Saudi Arabia over 25 years. **METHODS:** The records of all patients diagnosed with IEM from 1 January 1983 to 31 December 2008 were reviewed and categorized according to accumulated or deficient metabolites into small-molecule disorders (aminoacidemia, organic acidopathies [OA], urea cycle defects, fatty acid oxidation,

and carbohydrate metabolic disorders) and other disorders, including glycogen and lysosomal storage disorders (LSDs), and organelle disorders. RESULTS: During the study period, 165,530 Saudi Arabian infants were born at Saudi Aramco and 248 were diagnosed with an IEM, corresponding to a cumulative incidence of 150 cases per 100,000 live births. Small-molecule disorders were diagnosed in 134/248 patients (54%). OA were the most common (48/248 patients; 19%), and methylmalonic aciduria was the most frequently observed OA (13/48 patients; 27%). LSDs were diagnosed in 74/248 patients (30%), and mucopolysaccharidosis was the most frequently observed LSD (28/74; 38%). CONCLUSION: We believe that our data underestimate the true incidence of IEM in the region. Regional and national newborn screening programs will provide a better estimation of the incidence of IEM. We recommend a centralized newborn screening program that employs tandem mass spectrometry.

18. Clin Biochem. 2010 Jul 15. [Epub ahead of print]

Newborn screening for hemoglobinopathies using capillary electrophoresis technology: Testing the Capillarys(R) Neonat Fast Hb device.

Mantikou E, Hartevelde CL, Giordano PC.

Abstract

OBJECTIVES: To diagnose hemoglobinopathies in newborns by separating and measuring the Hb fractions on high throughput capillary electrophoresis. To test and validate the Capillarys Neonat Fast Hb device (Sebia) on fresh and dry blood samples. DESIGN AND METHODS: The Hb fractions in 1.600 cord blood samples from the multi ethnic Dutch population were separated and measured. Further, the sensitivity, specificity and reproducibility of the device in detecting abnormalities and measuring the Hb fractions were estimated. RESULTS: The apparatus separated all significant Hb fractions that should be detected during newborn screening (NBS) with 100% sensitivity. The reproducibility of the migrations guaranteed putative specificity for the few relevant frequent variants observed (HbS, C, and E). The estimation of the HbA and F fractions proved reliable using a well-designed integration mode. DISCUSSION: Due to the limited number of samples no cases with sickle cell disease or beta-thalassemia major were found in this cohort. However, the heterozygous state for the common variants associated with these diseases was clearly recognizable. The measurements were sufficiently precise to recognize sickle cell disease, beta-thalassemia major and intermedia and to identify carriers including

possible beta-thalassemia. Therefore, Capillarys Neonat Fast Hb (Sebia) can be considered as a valid instrument for NBS of the Hemoglobinopathies on fresh and dry blood samples.

19. **Otolaryngol Head Neck Surg. 2010 Jul;143(1):97-100. Epub 2010 May 5.**

Etiology and one-year follow-up results of hearing loss identified by screening of newborn hearing in Japan.

Adachi N, Ito K, Sakata H, Yamasoba T.

Abstract

OBJECTIVE: To evaluate the incidence of newborn hearing loss in a Japanese population and to elucidate etiological factors and one-year prognosis. STUDY DESIGN: Screening of newborn hearing. SETTING: Children's tertiary referral center. SUBJECTS AND METHODS: Between 1999 and 2008, 101,912 newborn infants were screened, with 693 infants (0.68%) referred. Etiology investigation included CT, detection of cytomegalovirus (CMV) DNA, and connexin 26 mutation. RESULTS: Abnormal results (auditory brainstem response [ABR] threshold \geq 35 normal hearing level [dB nHL] in either side) were observed in 312 infants (0.31%), and 133 subjects (0.13%) with ABR thresholds \geq 50 dB nHL on both sides were classified into the habilitation group. In this group, inner ear/internal auditory meatus anomalies were detected in 20 of 121 subjects (17%) tested, middle/external ear anomalies in 14 of 121 subjects (12%), CMV DNA in 13 of 77 subjects (17%), and connexin 26 mutation in 28 of 89 subjects (31%). In 68 subjects undergoing all three investigations (CT, CMV, and connexin 26), 41 (60%) had positive results in at least one test. With inclusion of otitis media with effusion and perinatal problems, this rate amounted to 78% (53 subjects). Of the 97 infants in the habilitation group successfully followed up to one year, 36 (37%) showed a threshold change of 20 dB or more in either ear: 11 (11%) progression and 25 (26%) improvement, and 15 infants (15%) were reclassified into a less severe classification. CONCLUSION: Considering that 26 percent of infants with bilateral moderate to severe hearing loss showed improvement in one year, habilitation protocols, especially very early cochlear implantation within one year of birth, should be reconsidered.

20. **Clin Chim Acta. 2010 Jul 6. [Epub ahead of print]**

Pilot proficiency testing study for second tier congenital adrenal hyperplasia newborn screening.

De Jesús VR, Simms DA, Schiffer J, Kennedy M, Mei JV, Hannon WH.

Abstract

BACKGROUND: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. The Newborn Screening Quality Assurance Program (NSQAP) initiated a pilot, dried-blood spot (DBS)-based proficiency testing program designed to investigate materials and laboratory performance for second tier CAH screening by tandem mass spectrometry (MS/MS). **METHODS:** The ratio of 17-alpha-hydroxyprogesterone (17-OHP), androstenedione (4-AD) and cortisol is used as an indicator of CAH in laboratory protocols for second tier analysis of DBS specimens. DBS prepared by NSQAP contained a range of steroid concentrations resulting in different clinical ratios. Laboratories received blind-coded DBS specimens and reported results to NSQAP for evaluation. **RESULTS:** Quantitative values reported by participants for 17-OHP, 4-AD, and cortisol, reflected small differences in their analytical methods. Average quantitative values for 17-OHP increased from 81% to 107% recovery over the 3.5-year period; cortisol recoveries increased from 61.9% to 89.5%; and 4-AD recoveries decreased from 184% to 68%. **CONCLUSIONS:** Laboratory participation in the CAH second tier proficiency testing program has resulted in improved analyte recoveries and enhanced sample preparation methodologies. NSQAP services for the second tier CAH analysis in DBS demonstrate the need for surveillance to ensure harmonization and continuous improvements, and to achieve sustained high-performance of newborn screening laboratories worldwide.

21. J Trop Pediatr. 2010 Jul 7. [Epub ahead of print]

Congenital Adrenal Hyperplasia in Alexandria, Egypt: A High Prevalence Justifying the Need for a Community-based Newborn Screening Program.

Tayel SM, Ismael H, Kandil H, Abd Rabuh AR, Sallam H.

22. Arch Dis Child. 2010 Jul 6. [Epub ahead of print]

Treating patients not numbers: the benefit and burden of lowering TSH newborn screening cut-offs.

Krude H, Blankenstein O.

23. J Cyst Fibros. 2010 Jun 3. [Epub ahead of print]

Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening.

Sermet-Gaudelus I, Mayell SJ, Southern KW.

Abstract

BACKGROUND: Successful implementation of newborn screening (NBS) for cystic fibrosis (CF) depends on robust protocols, good communication and appropriate management of recognised infants. In response to current varied practice, the ECFS Neonatal Screening Working Group developed a consensus on the early management of these infants using the Delphi methodology. **METHODS:** Following detailed literature review, statements were generated by a core group of experts and then assessed by a larger group using modified Delphi methodology. **RESULTS:** Forty-one statements were written by the core group. Eighty-six CF specialists contributed to the modified Delphi process. During three rounds, extra statements were added and consensus achieved on 44 (one statement did not achieve consensus).

CONCLUSIONS: These statements will provide a framework for the management of screened infants in the first year of life. This process highlights the paucity of evidence on which to base management of these infants. To improve this situation, it is important that each infant with CF identified through NBS has opportunity to be included in a randomised controlled trial. Crown Copyright © 2010. Published by Elsevier B.V. All rights reserved.

24. Pediatrics. 2010 Jul 5. [Epub ahead of print]

Why Newborn Screening for Severe Combined Immunodeficiency Is Essential: A Case Report.

Adeli MM, Buckley RH.

Abstract

Physicians caring for infants in the first months of life need to know the normal ranges for absolute lymphocyte counts (ALCs) during that age. Any ALC <2500/ μ L is potentially pathogenic in early infancy and should be evaluated. We report the case of a 4-month-old white girl with a 2-month history of an oral ulcer, intermittent fever, recurrent otitis, decreased appetite, weight loss, and a new respiratory

illness with hypoxemia. She had been in an in-home day care since birth. The patient's primary care physician had seen her frequently and obtained blood counts, but her persistent lymphopenia had not been appreciated. The infant was ultimately diagnosed with T(-)B(-)NK(+) (lacking both B and T lymphocytes and having primarily natural killer [NK] cells), recombinaase-activating gene 2 (RAG2)-deficient severe combined immunodeficiency (SCID). However, because she had already developed 2 difficult-to-treat viral infections (parainfluenza 3 and adenovirus), she did not survive long enough to receive a bone marrow transplant. Newborn screening would not only have made the diagnosis at birth but would have led to measures to protect her from becoming infected before she could receive a transplant. Newborn screening would also reveal the true incidence of SCID and define the range of conditions characterized by severely impaired T-cell development. Until screening for SCID and other T-cell defects becomes available for all neonates (either by quantifying T-cell receptor excision circles in Guthrie spots or using other tests that quantify T cells), all pediatricians should know the normal range for ALCs according to age. Recognition of the characteristic lymphopenia of SCID can facilitate early diagnosis.

25. J Chin Med Assoc. 2010 Jun;73(6):314-8.

Newborn screening for methylmalonic aciduria by tandem mass spectrometry: 7 years' experience from two centers in taiwan.

Cheng KH, Liu MY, Kao CH, Chen YJ, Hsiao KJ, Liu TT, Lin HY, Huang CH, Chiang CC, Ho HJ, Lin SP, Lee NC, Hwu WL, Lin JL, Hung PY, Niu DM.

Abstract

BACKGROUND: The clinical course of methylmalonic aciduria (MMA) is fulminant in neonates and emergency management is necessary to save lives. It is therefore very important to differentiate affected from unaffected neonates immediately when there are abnormal results regarding MMA in newborn screening. METHODS: Between January 2002 and December 2008, 598,522 newborns were screened for MMA by 2 neonatal screening centers: the Chinese Foundation of Health and the Taipei Institute of Pathology. A total of 22 newborns were referred to confirmatory medical centers, and 7 were confirmed as having MMA. The initial propionylcarnitine (C3) level, C3/acetylcarnitine (C2) ratio, plasma ammonia, liver function tests, blood pH and bicarbonate were compared between the true-positive and false-positive groups. RESULTS: The C3/C2 ratio and plasma ammonia were markedly higher in the

true-positive MMA group ($p < 0.0001$). Blood gas pH ($p = 0.029$), bicarbonate ($p = 0.019$), and aspartate aminotransferase ($p = 0.005$) also significantly differed between these 2 groups. CONCLUSION: Referred newborns with elevated plasma C3/C2 ratios > 0.4 or ammonia levels > 200 mg/dL should be highly suspected of having MMA

26. Genet Med. 2010 Jul 1. [Epub ahead of print]

Weighing the evidence for newborn screening for early-infantile Krabbe disease.

Kemper AR, Knapp AA, Green NS, Marie Comeau A, Metterville DR, Perrin JM.

Abstract

PURPOSE:: To summarize the evidence regarding screening, diagnosis, and treatment of early-infantile Krabbe disease in consideration of its addition to the core panel for newborn screening as has been done in New York state. METHODS:: Systematic review of articles indexed in MEDLINE and Embase published between January 1988 and July 2009. Thirteen articles describing studies related to screening, diagnosis, or treatment were included in this review. RESULTS:: Case series studies suggest that allogeneic hematopoietic stem-cell transplantation soon after the development of signs or symptoms of early-infantile Krabbe disease decreases early-childhood mortality and may improve neurodevelopment. However, limited data suggest there may be loss of motor function among some children who undergo transplantation. No long-term follow-up data are available from these case series. Of the approximately 550,000 newborns reported to have been screened in New York, 25 tested positive. None of these were clinically recognized to have Krabbe disease prior these results. Four were considered to be high risk for early-onset Krabbe disease. Two were subsequently diagnosed and underwent stem-cell transplantation, of whom one died from complications. No data are available regarding the impact on families of a positive newborn screen. CONCLUSIONS:: Although early treatment with hematopoietic stem-cell transplant seems to alter early-childhood mortality and some of the morbidity associated with early-infantile Krabbe disease, significant gaps in knowledge exist regarding the accuracy of screening, the strategy for establishing diagnosis, the effect of a positive screen on families, the benefits and harms of treatment, and long-term prognosis.

27. J Clin Endocrinol Metab. 2010 Jun 30. [Epub ahead of print]

Screening for Congenital Hypothyroidism: The Significance of Threshold Limit in False-Negative Results.

Mengreli C, Kanaka-Gantenbein C, Girginoudis P, Magiakou MA, Christakopoulou I, Giannoulia-Karantana A, Chrousos GP, Dacou-Voutetakis C.

Abstract

Context: In our neonatal program, a number of infants with congenital hypothyroidism (CH) had escaped diagnosis, when a spot RIA-TSH value of 20 mU/liter whole blood was used as a cutoff point. Objective: The objective of the study was to find out prospectively the additional number of newborns with CH if the TSH cutoff point is lowered to 10 mU/liter. Population and Methods: The study included 311,390 screened newborns. The children with CH were followed up for a period of 3 yr. Results: Twenty-eight percent of infants diagnosed with CH had neonatal TSH values between 10 and 20 mU/liter (56 of 200). Forty of 47 infants, who were reevaluated later on (85.1%), suffered permanent CH. A thyroid scintiscan and/or echogram revealed that eight of 40 children (20.0%) had a structural defect, and the remaining (32 of 40) had a functional defect of the thyroid gland without anatomical abnormality; 14 of 32 cases were familial. Eighteen of the 47 reevaluated infants were prematurely born (38.3%) and 15 of these 18 had permanent CH (83.3%). The lowering of TSH cutoff point from 20 to 10 mU/liter resulted in a 10-fold increase of recall rate. Conclusions: A significant number of cases with permanent CH are missed when a TSH threshold of 20 mU/liter is applied. Almost 40% of the missed CH cases were premature. A mild increase of TSH at screening is not a predictor of transient CH. The increase in recall rate constitutes a serious drawback and should be balanced against the possible consequences of thyroid dysfunction at this important developmental stage.

28. J Clin Pathol. 2010 Jul;63(7):626-9.

Positive screening and carrier results for the England-wide universal newborn sickle cell screening programme by ethnicity and area for 2005-07.

Streetly A, Latinovic R, Henthorn J.

NHS Sickle Cell and Thalassaemia Screening Programme, King's College London School of Medicine, Division of Health and Social Care Research, London, UK. allison.streetly@kcl.ac.uk

Abstract

AIMS: The overall aim of the new national newborn programme is to identify infants at risk of sickle cell disease to allow early detection and to minimise deaths and complications. **METHODS:** Universal screening for sickle cell disease was introduced in England between September 2003 and July 2006. The 13 newborn laboratories each screen between 25,000 and 110,000 babies a year using the existing dried bloodspot cards. The specified conditions to be screened for include sickle cell anaemia (Hb SS), Hb SC disease, Hb S/beta thalassaemia, Hb S/D(Punjab) and Hb S/O(Arab). Data are reported on screening results by ethnic group and geographical area. **RESULTS:** The prevalence of screen positive results across England is 1:2000. There is a 25-fold variation by geographical area. African babies make up 61% of all screen positive results despite representing only 4% of total births. Combined carrier rates vary widely by ethnicity, from 1.85 per 1000 (1:540) in 'White British' to 145 per 1000 (1:7) in 'African' babies. Refusal rates for screening show variation by ethnicity. **CONCLUSIONS:** These results provide useful information both about the frequency of these conditions and the carrier state and their geographic and ethnic distribution across England. This can be used to refine counselling information and are also useful to target and plan services and public information.

29. **Mol Genet Metab. 2010 Jun 10. [Epub ahead of print]**

Rapid determination of C4-acylcarnitine and C5-acylcarnitine isomers in plasma and dried blood spots by UPLC-MS/MS as a second tier test following flow-injection MS/MS acylcarnitine profile analysis.

Forni S, Fu X, Palmer SE, Sweetman L.

Abstract

BACKGROUND: Flow-injection MS/MS methods for elevated acylcarnitines are routinely performed in most newborn screening and biochemical genetics laboratories; however this technique cannot distinguish between isobaric compounds; therefore, chromatographic separation is required to quantitate isomers for differential diagnosis of some inborn errors of metabolism. **METHODS:** A UPLC-MS/MS method has been developed for the simultaneous quantitation of isobutyrylcarnitine and butyrylcarnitine, and a second UPLC-MS/MS method for the quantitation of isovalerylcarnitine, (S) and (R) 2-methylbutyrylcarnitine, pivaloylcarnitine and valerylcarnitine. Plasma and dried blood spots samples are

extracted with methanol and derivatized with butanolic HCl. Deuterium labeled internal standards are used for quantitation. Separation is obtained using a methanol/water gradient with a C18 BEH, 1x100mm, 1.7µm UPLC column, at 60 degrees C; run time is less than 10min. The isomers are detected with a Quattro Premier triple quadrupole, with electrospray ionization in positive ion mode. RESULTS: Intra-day precision in plasma and dried blood spots ranged from 1.4% to 14% and accuracy from 88% to 114% respectively for butyrylcarnitine and isobutyrylcarnitine. Precision for the isomers of C5-acylcarnitine ranged from 1.3% to 15% and accuracy 87% to 119%, respectively in plasma or dried blood spots. Inter-day precision was within 20% at each concentration of isobutyrylcarnitine and butyrylcarnitine. Precision for 2-methylbutyrylcarnitine and isovalerylcarnitine at concentrations above the normal range was within 24%. CONCLUSIONS: Two diagnostic tests based on the separation of C4-acylcarnitine and C5-acylcarnitine isomers by UPLC-MS/MS provide fast differential diagnosis of SCAD deficiency versus IBCD deficiency and IVA versus 2-MBCD deficiency. The separation of C5-acylcarnitines can reveal false elevation due to pivalic acid-containing antibiotics. Abnormal newborn screen results due to pivalate-generating prodrug antibiotics of maternal origin were confirmed. This separation of isomers can resolve multiple diagnostic challenges in both newborn screening and in cases with ambiguous metabolic test results

30. Arch Dis Child. 2010 Jun 28. [Epub ahead of print]

The TSH threshold in neonatal screening for congenital hypothyroidism: a variable solution.

Colón C, Alonso-Fernández JR.

Abstract

An algorithm is described whereby the threshold for thyroid-stimulating hormone used in neonatal screening for congenital hypothyroidism is re-set for each run on the basis of the variation and values of measurements of certified samples.

31. Am J Med Genet A. 2010 Jul;152A(7):1605-7.

Seize the day: Newborn screening for SMA.

Swoboda KJ.

Comment on:

- [Am J Med Genet A. 2010 Jul;152A\(7\):1608-16.](#)

32. Mol Genet Metab. 2010 Jun 9. [Epub ahead of print]

Sudden death in medium chain acyl-coenzyme a dehydrogenase deficiency (MCADD) despite newborn screening.

Yusupov R, Finegold DN, Naylor EW, Sahai I, Waisbren S, Levy HL.

Abstract

INTRODUCTION: Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is the most frequent of the fatty acid oxidation disorders (FAOD), a group caused by defects in the mitochondrial β -oxidation of fatty acids. Fatty acid oxidation is critical in supplying energy during periods when glucose is limited or when energy needs are increased beyond the availability of glucose. In MCADD, this energy shortage can result in acute metabolic episodes or sudden death. The prevention of sudden death from MCADD served as the primary impetus to expand newborn screening. However, we have experienced sudden death in four children with MCADD despite their detection by newborn screening. The purpose of this report is to alert others to the danger of sudden death in MCADD even when it is detected by newborn screening, to identify the clinical symptoms that precede sudden death, and to examine the relationship between the newborn screening result and the risk for sudden death. METHODS: We describe these children and their metabolic findings with emphasis on their newborn screening octanoylcarnitine (C8) level, the primary marker for newborn detection of MCADD. We also performed a literature search of cases of sudden death in MCADD in which the clinical status preceding death is described. RESULTS: The newborn screening C8 levels in our four cases were markedly elevated, ranging from 8.4 to 24.8 $\mu\text{mol/L}$ (cut off $<0.8 \mu\text{mol/L}$). Only two of the children were homozygous for the common c.985A>G MCAD mutation; the other two were heterozygous for this mutation. Similarly, among the eight reported cases which included MCAD genotypes, five were homozygous for the c.985A>G mutation, while two were heterozygous and one was homozygous for a splice site mutation. Vomiting 12-24h before sudden death was present in all four of our cases, and the review of reported cases of sudden death in MCADD disclosed vomiting as a frequent symptom. CONCLUSION: We suggest that in MCADD (1) a newborn

screening C8 level of 6μmol/L or greater represents particular risk of sudden death; (2) that MCAD genotypes other than homozygosity for the c.985A>G mutation are also associated with sudden death; (3) that vomiting is a frequent symptom preceding sudden death; and (4) social support and medical follow-up of these families are crucial in reducing the occurrence of sudden death. Copyright © 2010 Elsevier Inc. All rights reserved.

33. Am J Med Genet A. 2010 Jul;152A(7):1608-16.

Newborn and carrier screening for spinal muscular atrophy.

Prior TW, Snyder PJ, Rink BD, Pearl DK, Pyatt RE, Mihal DC, Conlan T, Schmalz B, Montgomery L, Ziegler K, Noonan C, Hashimoto S, Garner S.

Comment in:

- Am J Med Genet A. 2010 Jul;152A(7):1605-7.

Abstract

Spinal muscular atrophy (SMA) is a common autosomal recessive neuromuscular disorder caused by mutations in the survival motor neuron (SMN1) gene, affecting approximately 1 in 10,000 live births. The homozygous absence of SMN1 exon 7 has been observed in the majority of patients and is being utilized as a reliable and sensitive SMA diagnostic test. Treatment and prevention of SMA are complementary responses to the challenges presented by SMA. Even though a specific therapy for SMA is not currently available, a newborn screening test may allow the child to be enrolled in a clinical trial before irreversible neuronal loss occurs and enable patients to obtain more proactive treatments. Until an effective treatment is found to cure or arrest the progression of the disease, prevention of new cases through accurate diagnosis and carrier and prenatal diagnosis is of the utmost importance. The goal of population-based SMA carrier screening is to identify couples at risk for having a child with SMA, thus allowing carriers to make informed reproductive choices. During this study we performed two pilot projects addressing the clinical applicability of testing in the newborn period and carrier screening in the general population. We have demonstrated that an effective technology does exist for newborn screening of SMA. We also

provide an estimate of the carrier frequency among individuals who accepted carrier screening, and report on patient's knowledge and attitudes toward SMA testing.

34. Arch Dis Child. 2010 Jun 24. [Epub ahead of print]

One-third of the new paediatric patients with sickle cell disease in The Netherlands are immigrants and do not benefit from neonatal screening.

Peters M, Fijnvandraat K, van den Tweel XW, Garre FG, Giordano PC, van Wouwe JP, Pereira RR, Verkerk PH.

Abstract

Objectives To estimate the prevalence of children with sickle cell disease (SCD) in The Netherlands. To estimate the annual number of children newly diagnosed as having SCD and the proportion with diagnoses through neonatal screening To estimate the proportion of children with SCD receiving paediatric care in a comprehensive care setting. **Design** Data from two sources, a survey of paediatric practices (n=107) and a laboratory database (n=20), were analysed by the capture-recapture method. **Participants** Children with SCD aged <18 years, either born before 2003 or newly diagnosed as having SCD between 2003 and 2007. **Main outcome measures** Prevalence, annual number of children newly diagnosed as having SCD, proportion of children with diagnoses through neonatal screening, proportion of children receiving paediatric care. **Results** The prevalence of SCD in children living in The Netherlands on 1 January 2003 was 1:5152 (95% CI 1:4513 to 1:6015). In the next 4 years, the annual incidence was 1:2011 (95% CI 1:1743 to 1:2376). Nearly one-third (27%) of the children newly diagnosed as having SCD immigrated to The Netherlands after birth and would, therefore, be missed by the neonatal screening programme. Approximately 60% of all children with SCD were not reported by paediatricians. **Conclusion** The number of children with SCD in The Netherlands is much higher than previously estimated, and the majority of these children seem not to be reviewed regularly by a paediatrician. Children born abroad (27% of new cases) do not benefit from neonatal screening and are at high risk of life-threatening complications before SCD is diagnosed. As this introduces disparities in healthcare, the initiation of adequate measures should be considered.

35. Pediatr Pulmonol. 2010 Jun 8;45(7):708-716. [Epub ahead of print]

Pseudomonas aeruginosa in children with cystic fibrosis diagnosed through newborn screening: Assessment of clinic exposures and microbial genotypes.

Hayes D Jr, West SE, Rock MJ, Li Z, Splaingard ML, Farrell PM.

Abstract

BACKGROUND: Chronic pulmonary infection with *Pseudomonas aeruginosa* (PA) is responsible for significant morbidity and mortality in cystic fibrosis (CF). Because of the limited studies evaluating early exposure and the progression of genetic variability of PA, our goal was to assess PA in young children with CF followed in two clinic types. **METHODS:** A total of 39 infants with CF diagnosed through newborn screening were randomly assigned to either a segregated (PA-free) or mixed (PA-positive) clinic at two different CF centers, one of which replaced an older, mixed clinic where nosocomial acquisition was suspected. Oropharyngeal (OP) swab cultures were examined with subsequent genotyping to characterize the strains of PA isolated. **RESULTS:** We found that 13/21 segregated clinic patients and 14/18 mixed clinic patients showed positive PA, with median acquisition ages of 3.3 and 2.2 years, respectively ($P = 0.57$). The median time to PA acquisition, however, was significantly longer in the new clinic with proper hygiene precautions compared to an old site (5.0 years vs. 1.7 years, $P < 0.001$). The majority of subjects isolated a single genotype of PA or AP-PCR types during the study period with eight subjects clearing the isolate after only one positive culture. The development of chronic colonization yielded the predominance of a single major genotype or AP-PCR type. **CONCLUSIONS:** Segregation of infants and young children with CF in PA-negative or PA-positive clinics did not alter the time to first PA isolation in this randomized assessment of facilities with hygienic precautions. During the early infection period where PA is first isolated in young children with CF, patients cleared different PA strains until a predominant strain established permanent colonization

36. J Inherit Metab Dis. 2010 Jun 24. [Epub ahead of print]

Diagnosis and high incidence of hyperornithinemia-hyperammonemia-homocitrullinemia (HHH) syndrome in northern Saskatchewan.

Sokoro AA, Lepage J, Antonishyn N, McDonald R, Rockman-Greenberg C, Irvine J, Lehotay DC.

Abstract

Mutations in the SLC25A15 gene, encoding the human inner mitochondrial membrane ornithine transporter, are thought to be responsible for hyperornithinemia-hyperammonemia-homocitrullinemia (HHH) syndrome, a rare autosomal recessive condition. HHH syndrome has been detected in several small, isolated communities in northern Saskatchewan (SK). To determine the incidence of HHH syndrome in these communities, a PCR method was set up to detect F188Delta, the common French-Canadian mutation. Neonatal blood spots collected from all newborns from the high risk area were genotyped for the F188Delta mutation for seven consecutive years. Using DNA analysis, we estimated that the heterozygote frequency for the mutant allele for HHH syndrome to be about 1 in 19 individuals, predicting one affected child with HHH syndrome for approximately every 1,500 individuals (1 in 1,550 live births; 1 child every 12 years) in this isolated population. The frequency for the mutant allele for HHH syndrome in this isolated community is probably the highest in the world for this rare disorder. We determined that ornithine levels, by tandem mass spectrometry, were not abnormal in newborns with F188Delta mutation, carriers and normals. Ornithine rises to abnormally high levels at some time after birth well past the time that the newborn screening blood spot is collected. The timing or the reasons for the delayed rise of ornithine in affected children with HHH syndrome have not been determined. Newborn screening for HHH Syndrome in this high risk population is only possible by detection of the mutant allele using DNA analysis.

37. J Inherit Metab Dis. 2010 Jun 22. [Epub ahead of print]

Nationwide survey of extended newborn screening by tandem mass spectrometry in Taiwan.

Niu DM, Chien YH, Chiang CC, Ho HC, Hwu WL, Kao SM, Chiang SH, Kao CH, Liu TT, Chiang H, Hsiao KJ.

Abstract

In Taiwan, during the period March 2000 to June 2009, 1,495,132 neonates were screened for phenylketonuria (PKU) and homocystinuria (HCU), and 1,321,123 neonates were screened for maple syrup urine disease (MSUD), methylmalonic academia (MMA), medium-chain acyl-coenzyme A (CoA) dehydrogenase (MCAD) deficiency, isovaleric academia (IVA), and glutaric aciduria type 1 (GA-1) using tandem mass spectrometry (MS/MS). In a pilot study, 592,717 neonates were screened for citrullinemia,

3-methylcrotonyl-CoA carboxylase deficiency (3-MCC) and other fatty acid oxidation defects in the MS/MS newborn screening. A total of 170 newborns and four mothers were confirmed to have inborn errors of metabolism. The overall incidence was approximately 1/5,882 (1/6,219 without mothers). The most common inborn errors were defects of phenylalanine metabolism [five classic PKU, 20 mild PKU, 40 mild hyperphenylalaninemia (HPA), and 13 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency]. MSUD was the second most common amino acidopathy and, significantly, most MSUD patients (10/13) belonged to the Austronesian aboriginal tribes of southern Taiwan. The most frequently detected among organic acid disorders was 3-MCC deficiency (14 newborns and four mothers). GA-1 and MMA were the second most common organic acid disorders (13 and 13 newborns, respectively). In fatty acid disorders, five carnitine transport defect (CTD), five short-chain acyl-CoA dehydrogenase deficiency (SCAD), and two medium-chain acyl-CoA dehydrogenase (MCAD) deficiency were confirmed. This is the largest case of MS/MS newborn screening in an East-Asian population to date. We hereby report the incidences and outcomes of metabolic inborn error diseases found in our nationwide MS/MS newborn screening program.

38. J Inherit Metab Dis. 2010 Jun 22. [Epub ahead of print]

Medium-chain acyl-CoA dehydrogenase deficiency in Saudi Arabia: incidence, genotype, and preventive implications.

Al-Hassnan ZN, Imtiaz E, Al-Amoudi M, Rahbeeni Z, Al-Saved M, Al-Owain M, Al-Zaidan H, Al-Odaib A, Rashed MS.

Abstract

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD), caused by mutated ACADM gene, is a potentially fatal fatty acid oxidation defect. Detection of MCADD is now part of tandem mass spectrometry (MS-MS)-based newborn screening programs worldwide. To date, more than 67 mutations have been reported to cause MCADD with a single allele, c.985A>G, being the most common in patients of northwestern European descent. In Saudi Arabia, the Newborn Screening Program, officially launched in 2005, screens for 16 disorders including MCADD. Over a period of 3 years, 237,812 newborns were screened; 13 were identified to have MCADD giving an incidence of 1:18,293. Since the introduction of MS-MS to our institution, however, a total of 30 patients were detected to have MCADD. These cases

were either newborns, at high-risk family members, or clinically suspected. The C8-carnitine levels (median 3.31, range 0.81-16.33 microM) were clearly diagnostic in all analyzed samples. Sequencing ACADM in 20 DBS revealed two novel mutations: c.362C>T (p.T121I) and c.347G>A (p.C116Y) substitutions, neither of which were detected in 300 chromosomes from controls. Eighteen (90%) patients were homozygous for the T121I mutation and two (10%) were compound heterozygous (T121I/C116Y). Our molecular data lend further support to MS-MS biochemical screening for MCADD and provide evidence for the relatively high incidence of MCADD in the Arab population. The identification of a founder mutation for MCADD has important implications for the preventive screening programs not only in Saudi Arabia but potentially also in other countries in the region.

39. J Epidemiol Community Health. 2010 Jun 16. [Epub ahead of print]

Newborn screening programmes including genetic analyses: limits and risks of negative consequences?

Thauvin-Robinet C, Munck A, Roussey M, Huet F, Binquet C, Girodon E.

40. nt J Audiol. 2010 Aug;49(8):535-41.

Ambient noise levels and infant hearing screening programs in developing countries: an observational report.

Olusanya BO.

Abstract

Considering that current newborn/infant hearing screening (NHS) instruments were designed primarily for use in developed countries, this study set out to ascertain the potential effects of higher ambient noise levels on transient-evoked otoacoustic emissions (TEOAE) in sub-Saharan Africa. Data was drawn from two hospital-based and community-based NHS programs in Lagos, Nigeria, with a total screened population of 11 893 infants. Two automated TEOAE screening devices-Echo-Screen and ECHOCHECK-were available for this study. Ambient noise levels ranged from 61.0-90.5 dBA in the hospital wards and 55.6-82.5 dBA in the community health centers. One TEOAE model could not be

activated at the prevailing noise levels. No significant pattern was observed in average noise levels and overall TEOAE referrals across all screening sites. However, the false-positive rates ranged from 1.4-13.8%. This study suggests that valid TEOAE screening is attainable in the Negroid race in settings with ambient noise levels up to 68 dBA but the associated high false-positive rates may necessitate additional screening with auditory brainstem response to achieve acceptable overall referral rates for timely diagnostic evaluation.

41. Hum Mutat. 2010 Jun 15. [Epub ahead of print]

Analysis of mutations causing biotinidase deficiency.

Pindolia K, Jordan M, Wolf B.

Abstract

Biotinidase deficiency is an inherited disorder in which the vitamin, biotin, is not recycled. Individuals with biotinidase deficiency can develop neurological and cutaneous symptoms if they are not treated with biotin. Biotinidase deficiency screening has been incorporated into essentially all newborn screening programs in the United States and in many countries. We now report 140 known mutations in the biotinidase gene (BTD) that cause biotinidase deficiency. All types of mutations have been found to cause biotinidase deficiency. Variants have been identified throughout the coding sequence. Essentially all the variants result in enzymatic activities with less than 10% of mean normal enzyme activity (profound biotinidase deficiency) with the exception of the c.1330G>C (p.D444H) mutation, which results in an enzyme having 50% of mean normal serum activity. The putative three-dimensional structure of biotinidase has been predicted by homology to that of nitrilases/amidases. The effect of the various missense mutations can be predicted to affect various important sites within the structure of the enzyme. This compilation of variants causing biotinidase deficiency will be useful to clinical laboratories that are performing mutation analysis for confirmational testing when the enzymatic results are equivocal for children identified through newborn screening.

42. Thyroid. 2010 Jun;20(6):639-45.

New cases of isolated congenital central hypothyroidism due to homozygous thyrotropin beta gene mutations: a pitfall to neonatal screening.

Ramos HE, Labedan I, Carré A, Castanet M, Guemas I, Tron E, Madhi F, Delacourt C, Maciel RM, Polak M.

Abstract

BACKGROUND: Congenital central hypothyroidism (CCH) is a rare condition that is often diagnosed in late childhood in countries where neonatal screening programs rely solely on detecting thyrotropin (TSH) elevation. TSHbeta gene mutation is one of the causes of CCH. We describe two cases of c.Q49X mutation and three cases of c.C105Vfs114X mutation in exon 3 of the TSH beta-subunit gene.

SUMMARY: We found two different TSHbeta gene mutations in two families. In one family, we identified a missense mutation in exon 3 leading to a premature stop at position 49 (c.Q49X) in the two affected twins. In the other family, the three affected siblings had a 313delT nucleotide deletion leading to a frame shift responsible for premature termination at codon 114 (c.C105Vfs114X); neonatal screening showed very low TSH levels in all three patients. The presence of inappropriately low TSH levels at birth in the three affected members of the second family raises questions about the value of the TSH level for CCH screening. **CONCLUSIONS:** The marked phenotypic variability in patients with the c.Q49X mutation suggests modulation by interacting genes and/or differences in the genetic background. TSHbeta gene mutations should be suspected in neonates with inappropriately low TSH levels.

43. Arch Dis Child. 2010 Jul;95(7):531-3.

Declining prevalence of cystic fibrosis since the introduction of newborn screening.

Massie J, Curnow L, Gaffney L, Carlin J, Francis I.

Abstract

OBJECTIVES: Newborn screening for cystic fibrosis (CF) facilitates early diagnosis and genetic counselling for parents of affected infants. Many parents elect to use prenatal testing for subsequent pregnancies, and this may affect the prevalence of CF. The aim of this study was to assess the evidence for changes in the live-birth prevalence of CF since the introduction of newborn screening for CF.

METHODS: The authors reviewed the records of the Victorian newborn screening programme and the clinical records of the three centres caring for patients with CF in Victoria, Australia, in order to determine the live-birth prevalence of patients with CF; before (1979-1988) and after (1989-2006) the

introduction of newborn screening. The authors reviewed the records of the Victorian Clinical Genetics Service to ascertain the number and outcome of prenatal tests for CF (1979-2006). Live births in Victoria were obtained from the state birth register. FINDINGS: Between 1979 and 1988, the live-birth prevalence of CF was 3.96 (95% CI 3.48 to 4.49) per 10 000 live births. Following the introduction of newborn screening (1989-2006) the live-birth prevalence of CF was 3.28 (95% CI 2.97 to 3.63) per 10 000 live births, representing a reduction of 17% (95% CI 2% to 29%, $p=0.025$). In the prescreening period, there were 10 prenatal tests, which identified three affected pregnancies, all of which were terminated. In the later period, there were 304 prenatal tests (mean 17/year), of which 76 were affected, and 70 of these pregnancies were terminated. CONCLUSION: The authors observed a modest reduction in the live-birth prevalence of CF since the introduction of newborn screening. This is principally due to at-risk couples detected by newborn screening electing to use prenatal testing on subsequent pregnancies.

44. Eur J Pediatr. 2010 Jun 12. [Epub ahead of print]

Interdisciplinary approach to design, performance, and quality management in a multicenter newborn hearing screening project : Introduction, methods, and results of the newborn hearing screening in Hamburg (Part I).

Rohlfs AK, Wiesner T, Drews H, Müller F, Breitfuß A, Schiller R, Hess M.

Abstract

From the actual point of view, the "sensitive period" for the effects of hearing impairment on speech and language development is within the first year of life. Early exposure to acoustic or electric stimulation can compensate for the acoustic deficit. A regional-based, specifically designed concept of a universal newborn hearing screening (UNHS) was started in Hamburg in the year 2002. For the first time in Germany, a comprehensive protocol including screening measurement, follow-up procedures, tracking, and early intervention was implemented. An interdisciplinary approach from the very beginning could be realized. Sixty-three thousand, four hundred fifty-nine out of 65,466 births were registered during the period August 2002 to July 2006, 93% were primarily screened. 3.3% failed the test and 31.3% were lost to follow-up. A total of 118 children were diagnosed with hearing loss in the follow-up. The median age at time of diagnosis was 3.5 months. Seventy-four children received hearing aids. Out of these 74

children, 6 were subsequently supplied with cochlear implants. The high lost-to-follow-up rate is the biggest challenge for the tracking. Our results will be discussed in part II

45. Genet Med. 2010 Jul;12(7):396-410.

A systematic review of population screening for fragile X syndrome.

Hill MK, Archibald AD, Cohen J, Metcalfe SA.

Comment in:

- Genet Med. 2010 Jul;12(7):411-2.

Abstract

PURPOSE: To conduct a systematic review of literature regarding population-based screening for fragile X syndrome in newborns and women of reproductive age, either before or during pregnancy. **METHODS:** Seven electronic databases were searched for English language studies published between January 1991 and November 2009. Data extraction was performed for all included studies. Results were synthesized using a narrative approach. **RESULTS:** One article that examined offering newborn screening for fragile X syndrome and 10 that examined the offer of fragile X syndrome screening to women of reproductive age were identified. Two of these articles also addressed psychosocial aspects of population screening for fragile X syndrome such as attitudes to screening and experiences of screening, and a further nine addressed these issues alone. Studies exploring psychosocial issues demonstrated challenges for counseling arising from a lack of awareness or personal experience with fragile X syndrome in the general population. **CONCLUSIONS:** Targeted counseling and educational strategies will be essential to support women from the general population. It is crucial that future studies offering screening for fragile X syndrome explore a range of psychosocial aspects in addition to looking at uptake of testing and mutation frequency.

46. J Pediatr. 2010 Jun 12. [Epub ahead of print]

Tandem Mass Spectrometry Screening for Very Long-Chain Acyl-CoA Dehydrogenase Deficiency: The Value of Second-Tier Enzyme Testing.

Spiekerkoetter U, Haussmann U, Mueller M, Ter Veld F, Stehn M, Santer R, Lukacs Z.

Abstract

OBJECTIVE: To evaluate newborn screening (NBS) for very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), we further characterized newborns with elevation of one or all C14-carnitine derivatives on NBS from a total of 90 338 newborns. STUDY DESIGN: Palmitoyl-CoA oxidation was performed in lymphocytes to define very long-chain acyl-CoA dehydrogenase function. Molecular analysis followed in children with residual activities <50%. The acylcarnitine pattern on days 2 to 3 of life was evaluated thoroughly to define possible discrimination markers. RESULTS: Forty newborns with increased C14:1-carnitine were identified (1:2500). In 2 newborns, VLCADD was confirmed with enzyme and molecular analyses (prevalence, 1:50 000). One of these newborns had normal results on a second screening. Also, the combination of absolute acylcarnitine values and acylcarnitine ratios did not allow correct identification of the newborn as a patient with VLCADD. CONCLUSIONS: Reliable diagnosis is not feasible with acylcarnitine analysis alone. Enzyme analysis in lymphocytes is a reliable and rapid method for correctly assessing all newborns with VLCADD and should be carried out in all newborns identified during the first screening, regardless of the results of a later acylcarnitine profile

47. Mol Genet Metab. 2010 Aug;100(4):333-8. Epub 2010 May 23.

Characterization of new ACADSB gene sequence mutations and clinical implications in patients with 2-methylbutyrylglycinuria identified by newborn screening.

Alfardan J, Mohsen AW, Copeland S, Ellison J, Keppen-Davis L, Rohrbach M, Powell BR, Gillis J, Matern D, Kant J, Vockley J.

Abstract

Short/branched chain acyl-CoA dehydrogenase (SBCAD) deficiency, also known as 2-methylbutyryl-CoA dehydrogenase deficiency, is a recently described autosomal recessive disorder of isoleucine metabolism. Most patients reported thus far have originated from a founder mutation in the Hmong Chinese population. While the first reported patients had severe disease, most of the affected Hmong have remained asymptomatic. In this study, we describe 11 asymptomatic non-Hmong patients brought to medical attention by elevated C5-carnitine found by newborn screening and one discovered because of

clinical symptoms. The diagnosis of SBCAD deficiency was determined by metabolite analysis of blood, urine, and fibroblast samples. PCR and bidirectional sequencing were performed on genomic DNA from five of the patients covering the entire SBCAD (ACADSB) gene sequence of 11 exons. Sequence analysis of genomic DNA from each patient identified variations in the SBCAD gene not previously reported. Escherichia coli expression studies revealed that the missense mutations identified lead to inactivation or instability of the mutant SBCAD enzymes. These findings confirm that SBCAD deficiency can be identified through newborn screening by acylcarnitine analysis. Our patients have been well without treatment and call for careful follow-up studies to learn the true clinical impact of this disorder

48. Eur J Pediatr. 2010 Jun 11. [Epub ahead of print]

Interdisciplinary approach to design, performance, and quality management in a multicenter newborn hearing screening project : Discussion of the results of newborn hearing screening in Hamburg (Part II).

Rohlfs AK, Wiesner T, Drews H, Müller F, Breitfuß A, Schiller R, Hess M.

Abstract

Previously presented results of the newborn hearing screening in Hamburg and the perspectives are subsequently discussed. Minimum standards referring a participation of 95% of the neonates and a fail rate of less than 4% hearing-impaired children at the primary screening are fulfilled in Hamburg. Systematic screening of newborn hearing by an interdisciplinary approach provides early identification and intervention for children with permanent unilateral and bilateral hearing loss. But a newborn hearing screening on a voluntary basis alone cannot be maintained in the long run. Further, an anonymous data collection is not sufficient in regard to an uninterrupted tracking of conspicuous and unscreened neonates. A lost-to-follow-up rate of 31.3% at primary screening in Hamburg is much too high and emphasizes the need for a public health approach to a population-based newborn hearing screening with an elaborate and name-based tracking system. The legislation and implementation of a nationwide newborn hearing screening program in Germany and the association of German newborn hearing screening centers are highlighting long efforts of hearing professionals. But the implementation of a newborn hearing screening only makes sense if there exists an efficient tracking system. Sad to say, we are still a long way from the implementation of such a tracking system.

49. J Inherit Metab Dis. 2010 Jun 11. [Epub ahead of print]

Expanded newborn screening: social and ethical issues.

Dhondt JL.

Abstract

Newborn screening and genetic testing have expanded rapidly in the last decade with the advent of multiplex (e.g., tandem mass spectrometry) and/or DNA technologies. However, screening panels include a large number of disorders, which may not meet all of the traditional screening criteria, established in late 1960s, and used for years to justify screening programs. After a period of expansion driven by technological advances, many reports have reconsidered the justification of expanded programs. Many factors have contributed to test-panel discrepancies between countries. The test-panel review methodology, the way health benefits are weighed against harms, and the socioeconomic-political environment all play a role. Expansion of screening also requires reconsideration of the infrastructure (ideally, in the context of national plans for rare diseases) to support testing, counselling, education, treatment, and follow-up. Consequently, economic aspects cannot be ignored and can be a limitation for expansion. New ethical questions have emerged: risks of discrimination or stigmatization, respect of the autonomy of persons to make decisions, parental anxiety resulting from a false positive test (especially when reporting to parents screening results for untreatable conditions identified as by-products of screening), etc. For disorders where there is not yet confirmation of benefit, it may be prudent to recommend pilot screening and to have a mechanism that can be used to adapt or even to stop a program.

50. J Perinatol. 2010 Jun 10. [Epub ahead of print]

Implementation and analysis of a pilot in-hospital newborn screening program for glucose-6-phosphate dehydrogenase deficiency in the United States.

Nock ML, Johnson EM, Krugman RR, Di Fiore JM, Fitzgerald S, Sandhaus LM, Walsh MC.

Abstract

Objective: The purpose of this study was to analyze a targeted screening program for glucose-6-phosphate dehydrogenase (G6PD) deficiency (G6PDdef) and clinical outcomes of G6PD-deficient vs G6PD normal

newborns. Study Design: Retrospective chart review for 1578 male newborns was performed. The study group was those screened for G6PDdef. Comparisons between G6PD-deficient and normal infants were made with chi (2)-test and unpaired t-test. Result: A total of 1095 male newborns were screened, 11.1% had G6PDdef. 97.8% of screen results were reported by 48 h. Total bilirubin (TB) levels in deficient infants were significantly higher than in normal infants throughout birth hospitalization and they were more likely to receive phototherapy. Nineteen screened newborns were rehospitalized for hyperbilirubinemia, 47% had G6PDdef. Conclusion: In-hospital newborn screening for G6PDdef with rapid turnaround time is possible. G6PDdef is a risk factor for hyperbilirubinemia in American newborns. US centers with large at-risk populations can identify newborns at risk for severe hyperbilirubinemia with similar screening

51. Genet Med. 2010 Jul;12(7):464-70.

Technical standards and guidelines for the diagnosis of biotinidase deficiency.

Cowan TM, Blitzer MG, Wolf B; Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee.

Abstract

Biotinidase deficiency is an autosomal recessively inherited disorder of biotin recycling that is associated with neurologic and cutaneous consequences if untreated. Fortunately, the clinical features of the disorder can be ameliorated or prevented by administering pharmacological doses of the vitamin biotin. Newborn screening and confirmatory diagnosis of biotinidase deficiency encompasses both enzymatic and molecular testing approaches. These guidelines were developed to define and standardize laboratory procedures for enzymatic biotinidase testing, to delineate situations for which follow-up molecular testing is warranted, and to characterize variables that can influence test performance and interpretation of results.

52. Int J Pediatr Otorhinolaryngol. 2010 Aug;74(8):926-9. Epub 2010 Jun 9.

Newborn hearing screening and genetic testing in 8974 Brazilian neonates.

Nivoloni Kde A, da Silva-Costa SM, Pomílio MC, Pereira T, Lopes Kde C, de Moraes VC, Alexandrino F, de Oliveira CA, Sartorato EL.

Abstract

OBJECTIVE: An early diagnosis has been a priority in the audiological practice. Identifying hearing loss until 3 months old through Universal Newborn Hearing Screening and intervention before 6 months old, minimize the impact of auditory loss in the health and communication development of these children.

However, in the clinical practice, despite the help of the risk indicators in the audiological and etiological diagnosis, the integrated services have come up against the challenge of determining the causes of auditory loss, bearing in mind that approximately 50% of the subjects who have congenital loss do not show risk factors in their clinical history. The current research aims introduce together etiologic and audiological diagnosis of newborns. METHODS: We eluted dried blood spots from paper and performed genetic testing for 35delG mutation in 8974 newborns that were also screened for transient otoacoustic emissions (TOAE). In addition, the A1555G and A827G mutations in the MTRNR1 mitochondrial gene were screened in all newborns. RESULTS: We have found 17 individuals who failed in TOAE. Among them, we detected 4 homozygous newborns for 35delG mutation and 3 individuals with A827G mutation in the MTRNR1 mitochondrial gene. The frequency of 35delG carriers was 0.94% [84/8974]. In all 17 individuals who failed in OAE no other mutation besides those mentioned above was found.

CONCLUSIONS: The results greatly contribute to the public health area indicating the etiologic diagnosis, allowing family counseling as well as the early rehabilitation treatment or surgical intervention. Over time that will help to reduce the costs of rehabilitation considerably.

53. Orphanet J Rare Dis. 2010 Jun 10;5:17.

Congenital hypothyroidism.

Rastogi MV, LaFranchi SH.

Abstract

Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. The clinical manifestations are often subtle or not present at birth. This likely is due to trans-placental passage of some maternal thyroid hormone, while many infants have some thyroid production of their own. Common

symptoms include decreased activity and increased sleep, feeding difficulty, constipation, and prolonged jaundice. On examination, common signs include myxedematous facies, large fontanelles, macroglossia, a distended abdomen with umbilical hernia, and hypotonia. CH is classified into permanent and transient forms, which in turn can be divided into primary, secondary, or peripheral etiologies. Thyroid dysgenesis accounts for 85% of permanent, primary CH, while inborn errors of thyroid hormone biosynthesis (dysmorphogeneses) account for 10-15% of cases. Secondary or central CH may occur with isolated TSH deficiency, but more commonly it is associated with congenital hypopituitarism. Transient CH most commonly occurs in preterm infants born in areas of endemic iodine deficiency. In countries with newborn screening programs in place, infants with CH are diagnosed after detection by screening tests. The diagnosis should be confirmed by finding an elevated serum TSH and low T4 or free T4 level. Other diagnostic tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin determination may help pinpoint the underlying etiology, although treatment may be started without these tests. Levothyroxine is the treatment of choice; the recommended starting dose is 10 to 15 mcg/kg/day. The immediate goals of treatment are to rapidly raise the serum T4 above 130 nmol/L (10 ug/dL) and normalize serum TSH levels. Frequent laboratory monitoring in infancy is essential to ensure optimal neurocognitive outcome. Serum TSH and free T4 should be measured every 1-2 months in the first 6 months of life and every 3-4 months thereafter. In general, the prognosis of infants detected by screening and started on treatment early is excellent, with IQs similar to sibling or classmate controls. Studies show that a lower neurocognitive outcome may occur in those infants started at a later age (> 30 days of age), on lower l-thyroxine doses than currently recommended, and in those infants with more severe hypothyroidism.

54. J Clin Endocrinol Metab. 2010 Jun 9. [Epub ahead of print]

Two Novel Mutations of the TSH- β Subunit Gene Underlying Congenital Central Hypothyroidism Undetectable in Neonatal TSH Screening.

Baquedano MS, Ciaccio M, Dujovne N, Herzovich V, Longueira Y, Warman DM, Rivarola MA, Belgorosky A.

Abstract

Context: Patients with TSH-beta subunit defects and congenital hypothyroidism are missed by TSH-based neonatal screening. Objective: Our objective was to report the molecular consequences of a novel splice-junction mutation and a novel missense mutation in the TSH-beta subunit gene found in two patients with congenital central hypothyroidism and conventional treatment-resistant anemia. Results: Patient 1 had a homozygous G to A nucleotide change at the 5' donor splice site of exon/intron 2. This resulted in a silent change at codon 34 of the mature protein. In vitro splicing assays showed that the mutant minigene dramatically affected pre-mRNA processing, causing exon 2 to be completely skipped. The putative product from a new out-of-frame translational start point in exon 3 is expected to yield a nonsense 25-amino-acid peptide. In patient 2, sequence analysis revealed a compound heterozygosis for the already reported 313delT (C105Vfs114X) mutation and for a second novel mutation in exon 3, substituting G for A at cDNA nucleotide position 323, resulting in a C88Y change. This cysteine residue is conserved among all dimeric pituitary and placental glycoprotein hormone-beta subunits. Data from in silico analysis confirmed that the C88Y mutation would affect subunit conformation. Indeed, two different bioinformatics approaches, PolyPhen and SIFT analysis, predicted C88Y to be a damaging substitution. Conclusions: In isolated TSH deficiency, the exact molecular diagnosis is mandatory for diagnosis of isolated pituitary deficiency, delineation of prognosis, and genetic counseling. Moreover, diagnosis of central hypothyroidism should be considered in the face of severe infant anemia of uncertain etiology.

55. J Inherit Metab Dis. 2010 Jun 8. [Epub ahead of print]

The clinical manifestation of MCAD deficiency: challenges towards adulthood in the screened population.

Schatz UA, Ensenauer R.

Abstract

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common fatty acid oxidation disorder. Typically, undiagnosed individuals are asymptomatic until an episode of increased energy demand and fasting occurs, resulting in metabolic derangement. Phenotypic heterogeneity has been increasingly realized, with reports of both neonates and adults manifesting with life-threatening symptoms including encephalopathy, rhabdomyolysis, and cardiac failure. If diagnosed presymptomatically, outcome is favorable basically by avoidance of fasting. Early detection by newborn

screening (NBS) has significantly reduced the incidence of severe adverse events including deaths. In this manuscript we focus on the natural course of the disease in both children and adults. Although NBS for MCADD has been successfully established, continuing efforts need to be made to avoid acute crises and deterioration of outcome in screened patients entering adolescence and adulthood.

56. J Inherit Metab Dis. 2010 Jun 8. [Epub ahead of print]

Public health and laboratory considerations regarding newborn screening for congenital cytomegalovirus.

Dollard SC, Schleiss MR, Grosse SD.

Abstract

Congenital cytomegalovirus (CMV) infection is the most common infection in newborns worldwide and causes hearing loss and other neurological disability in 15-20% of infected infants. Only about half of the hearing loss resulting from congenital CMV infection is currently detected by universal newborn hearing screening because of late-onset hearing loss. Thus, much of the hearing loss and the majority of other CMV-associated disabilities remain undetected for years after birth and are never connected to CMV infection. Congenital CMV may be appropriate to include in national newborn screening (NBS) programs because it is more common than other disorders tested for by NBS programs and is a major cause of disability. Significant obstacles to the implementation of screening for congenital CMV include the lack of a standardized, high-throughput screening test and a protocol for follow-up of CMV-infected children. Nonetheless, screening newborns for congenital CMV infection merits further consideration

57. J Inherit Metab Dis. 2010 Aug;33(4):381-6. Epub 2010 Jun 8.

Newborn screening for neuropathic lysosomal storage disorders.

Hwu WL, Chien YH, Lee NC.

Abstract

Interest in newborn screening (NBS) for lysosomal storage disorders (LSDs) has increased significantly due to newly developed enzyme replacement therapy (ERT), the need for early diagnosis, and advances in

technical developments. Since the central nervous system cannot be treated by ERT, neuronopathic LSDs are generally not the primary target of NBS. An exception is Krabbe disease, in which hematopoietic stem cell transplantation before the onset of symptoms has benefits. However, NBS for LSD relies on measuring enzyme activities, so the most severely affected individuals (usually patients with neuronopathic subtypes) will be detected together with patients with less severe disease. In the near future, NBS is likely to be developed for diseases such as Gaucher, Niemann-Pick A/B, and certain mucopolysaccharidoses. The ability to predict phenotypes (neuronopathic or not) by enzyme activity and genotyping will therefore be critical for adequate patient management. This article reviews the status of LSD screening and issues concerning detection of neuronopathic LSDs by screening.

58. Folia Histochem Cytobiol. 2010 Jan 1;48(1):163-5.

Cystic fibrosis newborn screening enables diagnosis of elder siblings of recalled infants--additional benefit.

Sands D, Zybert K, Nowakowska A.

Abstract

The different clinical manifestations of cystic fibrosis, with variable intensity and timing, often delay the diagnosis of this genetic autosomal recessive disorder. Many countries have introduced newborn screening for cystic fibrosis to facilitate diagnosis prior to the development of the disease. The advantages and harms of such screening programmes are regularly reassessed. In the five families presented in this article the elder siblings of screened infants were diagnosed thanks to CF NBS. This is an example of a benefit for children not even directly covered by the screening programme, adding another CF NBS advantage to the balance.

59. Eur J Haematol. 2010 May 26. [Epub ahead of print]

Detection of non-deletional alpha-thalassemia in prenatal screening program.

Liao C, Li DZ.

60. Neonatology. 2010 Jun 4;99(1):1-9. [Epub ahead of print]

It Is Time for Routine Neonatal Screening by Pulse Oximetry.

Hoffman JJ.

Abstract

Most pediatric cardiologists believe that pulse oximetry helps to diagnose critical congenital heart disease in neonates who might otherwise be discharged from the newborn nursery undiagnosed. Some of these patients develop catastrophic cardiac and multi-system failure after the ductus closes and die or suffer severe morbidity. Nevertheless, pulse oximetry is not universally used in the newborn nursery. Some pediatricians believe that they can always detect these patients from physical findings, many believe that oximeters are unreliable, and others are concerned about costs of investigating false positive tests. Recent studies, however, show that even cardiologists miss critical congenital heart defects, modern oximeters are stable and reliable, and that the false positive rate is very low, lower than the false positive rate based on physical examination. The benefits probably exceed the cost, and evidence is provided to confirm this. There is no reason not to use pulse oximetry routinely in the newborn nursery.

61. J Inherit Metab Dis. 2010 Jun 3. [Epub ahead of print]

Cystic fibrosis newborn screening: using experience to optimize the screening algorithm.

Hale JE, Parad RB, Dorkin HL, Gerstle R, Lapey A, O'Sullivan BP, Spencer T, Yee W, Comeau AM.

Abstract

Newborn screening (NBS) for cystic fibrosis (CF) offers the opportunity for early diagnosis and improved outcomes in patients with CF and has been universally available in the state of Massachusetts since 1999 using an immunoreactive trypsinogen (IRT)-DNA algorithm. Ideally, CF NBS is incorporated as part of an integrated NBS system that allows for comprehensive and coordinated education, laboratory screening, clinical follow-up, and evaluation so that evidence-based data can be used to maximize quality improvements and optimize the screening algorithm. The New England Newborn Screening Program (NENSP) retrospectively analyzed Massachusetts's CF newborn screening data that yielded decisions to eliminate a screen-positive category, maintain the IRT cutoff value that prompts the second tier DNA

testing, and communicate CF relative risk to primary care providers (PCPs) based on categorization of positive CF NBS results.

62. **Public Health Rep. 2010 May-Jun;125 Suppl 2:88-95.**

Implementing routine testing for severe combined immunodeficiency within Wisconsin's newborn screening program.

Baker MW, Laessig RH, Katcher ML, Routes JM, Grossman WJ, Verbsky J, Kurtycz DF, Brokopp CD.

Abstract

Severe combined immunodeficiency (SCID) is the result of genetic defects that impair normal T-cell development. SCID babies typically appear normal at birth, but acquire multiple life-threatening infections within a few months. Early diagnosis and treatment with a bone-marrow transplant markedly improves long-term outcomes. On January 1, 2008, the newborn screening (NBS) program in Wisconsin became the first in the world to routinely test all newborns for SCID. A realtime quantitative polymerase chain reaction assay measures T-cell receptor excision circles (TRECs), which are formed during the maturation of normal T-cells. A lack or very low number of TRECs is consistent with T-cell lymphopenia. The development and validation of the TREC assay and the results of the first year of screening have been published. This article describes the process used to add SCID to the NBS panel, the establishment of follow-up capacity, and the integration of SCID screening into routine NBS workflows. The development of this expanded NBS program is described so that other states might benefit from the processes used in Wisconsin.

63. **Eur J Hum Genet. 2010 May 26. [Epub ahead of print]**

Uptake of carrier testing in families after cystic fibrosis diagnosis through newborn screening.

McClaren BJ, Metcalfe SA, Aitken M, Massie RJ, Ukoumunne OC, Amor DJ.

Abstract

Newborn screening (NBS) for cystic fibrosis (CF) provides the opportunity for cascade carrier testing of relatives. Uptake of testing by adult non-parent relatives of children diagnosed with CF through NBS has not been previously described, and this study describes uptake by both parents and adult non-parent relatives in Victoria, Australia. Pedigrees were taken from parents of children who were born in 2000-2004 and diagnosed with CF. A total of 40 families were eligible for the study and 30 (75%) were recruited. In all, 716 non-parent relatives were identified from the pedigrees as eligible for carrier testing, and 82 (adjusted uptake percentage: 11.8%; 95% confidence interval 8.0-15.7) have had carrier testing by March 2009. On average, 2.7 non-parent relatives per family had CF carrier testing after diagnosis through NBS. The odds of being tested were greater for females than males (adjusted odds ratio 1.61; 95% confidence interval 1.11-2.33; P=0.01) and greater for those more closely related to the child with CF (adjusted odds ratio 5.17; 95% confidence interval 2.38-11.24; P<0.001). Most relatives who undergo testing are tested immediately after the baby's diagnosis; however, some testing is undertaken up to 8 years later. These results indicate that in a clinical setting, the diagnosis of a baby with CF by NBS does not lead to carrier testing for the majority of the baby's non-parent relatives. We suggest re-contact with parents to offer cascade carrier testing

64. J Pediatr (Rio J). 2010 May 27;86(4). [Epub ahead of print]

Mortality of children with sickle cell disease: a population study.

Fernandes AP, Januário JN, Cangussu CB, de Macedo DL, Viana MB.

Abstract

OBJECTIVE: To describe the deaths of children with sickle cell disease (SCD) in Minas Gerais, Brazil, and followed up at the Fundação Hemominas. METHODS: Cohort of children diagnosed by the Neonatal Screening Program in Minas Gerais (March/1998 - February/2005). Deaths were identified by searching for children who did not attend scheduled consultations at hemocenters. Clinical and epidemiological data were abstracted from death certificates, the newborn screening database, individual medical records, and from interviews with families. RESULTS: During the period, 1,833,030 newborns were screened; 1,396 had SCD (1:1,300). There were 78 deaths: 63 with SS genotype, 12 with SC genotype, and three with Sbeta+thalassemia genotype. Fifty-six children (71.8%) died before 2 years of age; 59 died in hospitals

and 18 at home or during transportation. Causes of death according to certificates (n = 78): infections: 38.5%; acute splenic sequestration: 16.6%; other causes: 9%; did not receive medical care: 15.4%; and not identified on certificates: 20.5%. According to interviews (n = 52) acute splenic sequestration was responsible for one third of deaths, in contrast with 14% recorded on death certificates. Survival probabilities at 5y (SEM) for children with SS, SC, and Sbeta+thalassemia were 89.4 (1.4), 97.7 (0.7), and 94.7% (3.0), respectively (SS vs. SC, $p < 0.0001$). CONCLUSIONS: Even with a carefully controlled newborn screening program, the probability of SS children dying was found to be still high. Causes not identified on death certificates may indicate difficulties recognizing SCD and its complications. Educational campaigns directed at health professionals and SCD patients' families should be boosted in order to decrease SCD mortality.

65. Am J Med Genet A. 2010 Jun;152A(6):fmvii-fmviii.

The AJMG SEQUENCE: Decoding news and trends for the medical genetics community SCID suggested for uniform newborn screening panel.

Levenson D.

66. Pediatr Pulmonol. 2010 Jun;45(6):601-7.

Long-term effects of birth order and age at diagnosis in cystic fibrosis: a sibling cohort study.

Sliker MG, van den Berg JM, Kouwenberg J, van Berkhout FT, Heijerman HG, van der Ent CK.

Abstract

BACKGROUND: Siblings with cystic fibrosis (CF) share many genetic and environmental factors but may present different phenotypes. Younger sibs are mostly earlier diagnosed with CF than their older sibs, but might be at risk for an earlier colonization with *Pseudomonas aeruginosa* (PA) than their older counterparts due to cross-infection within families. **AIMS:** To analyze the effects of birth order and age at diagnosis on lung function, PA colonization, nutritional status, and survival during the first two decades of life in siblings with CF. **METHODS:** A retrospective cohort study of 52 sibling pairs was performed in two Dutch CF centers. Data were analyzed both cross-sectionally and longitudinally using Kaplan-Meier curves and modified log-rank tests. **RESULTS:** Median age at diagnosis was significantly higher in the

older sib compared with the younger sib (3.0 and 0.2 years, respectively, $P < 0.0001$). At the age of 5, 10, and 15 years no difference in lung function was found. However, at the age of 20 years, forced expiratory volume in 1 sec (FEV(1)) in older sibs was 19.4% (95% CI: 5.9-32.9%, $P = 0.007$) lower than in younger sibs. In the younger sibs group, FEV(1) at age 20 years was significantly better in those who had a diagnosis before the age of 6 months (difference 22.9%, 95% CI: 0.1-45.8%, $P < 0.05$). In the first 10 years of life the younger sibs tended to be earlier colonized with PA than their older counterparts. No differences in nutritional status and survival were observed. CONCLUSION: In this sibling cohort study, an early diagnosis of CF was associated with better lung function after two decades of life. Although younger siblings tended to be colonized with PA at an earlier age, they showed better lung function outcomes. This underscores the importance of early diagnosis with newborn screening and early referral to a specialized center in the prevention of long-term deleterious effects on lung function.

67. Clin Biochem Rev. 2010 May;31(2):57-68.

Newborn screening.

Pitt JJ.

Abstract

Early detection of many disorders, mainly inherited, is feasible with population-wide analysis of newborn dried blood spot samples. Phenylketonuria was the prototype disorder for newborn screening (NBS) and early dietary treatment has resulted in vastly improved outcomes for this disorder. Testing for primary hypothyroidism and cystic fibrosis (CF) was later added to NBS programs following the development of robust immunoassays and molecular testing. Current CF testing usually relies on a combined immunoreactive trypsin/mutation detection strategy. Multiplex testing for approximately 25 inborn errors of metabolism using tandem mass spectrometry is a relatively recent addition to NBS. The simultaneous introduction of many disorders has caused some re-evaluation of the traditional guidelines for NBS, because very rare disorders or disorders without good treatments can be included with minimal effort. NBS tests for many other disorders have been developed, but these are less uniformly applied or are currently considered developmental. This review focuses on Australasian NBS practices.

68. J Genet Couns. 2010 May 22. [Epub ahead of print]

Patient and Family Experiences and Opinions on Adding 22q11 Deletion Syndrome to the Newborn Screen.

Bales AM, Zaleski CA, McPherson EW.

Abstract

22q11 deletion syndrome (22qDS) has recently been proposed for addition to the newborn screening panel in Wisconsin and it seems likely that it may soon be considered in other states as well. Input from patients with 22qDS and their family was gathered from 21 phone interviews. Cardiac, palate, hypocalcemia, and multiple anomalies were common reasons for involved patients to be diagnosed, though age at diagnosis ranged from birth to adulthood. Many commented on their struggles with 22qDS, including worries about the future and the patient's independence. In general, respondents favored newborn screening for 22qDS because it would help prevent some medical problems, increase access to services, explain existing problems, and identify mild cases. However, a minority expressed reservations, including concerns that it would disrupt bonding, could be too costly, and would not be useful for mild cases.

69. J Dev Behav Pediatr. 2010 Jun;31(5):414-26.

Task-oriented and bottle feeding adversely affect the quality of mother-infant interactions after abnormal newborn screens.

Tluczek A, Clark R, McKechnie AC, Orland KM, Brown RL.

Abstract

OBJECTIVE: To examine effects of newborn screening and neonatal diagnosis on the quality of mother-infant interactions in the context of feeding. **METHODS:** Study compared the quality of mother-infant feeding interactions among 4 groups of infants classified by severity of newborn screening and diagnostic results: cystic fibrosis (CF), congenital hypothyroidism, heterozygote CF carrier, and healthy with normal newborn screening. The Parent-Child Early Relational Assessment and a task-oriented item measured the quality of feeding interactions for 130 dyads, infant ages 3 to 19 weeks ($M = 9.19$, $SD = 3.28$). The Center for Epidemiologic Studies Depression Scale and State-Trait Anxiety Inventory measured maternal depression and anxiety. **RESULTS:** Composite Indicator Structure Equation Modeling showed that infant

diagnostic status and, to a lesser extent, maternal education predicted feeding method. Mothers of infants with CF were most likely to bottle feed, which was associated with more task-oriented maternal behavior than breastfeeding. Mothers with low task-oriented behavior showed more sensitivity and responsiveness to infant cues, as well as less negative affect and behavior in their interactions with their infants than mothers with high task-oriented scores. Mothers of infants with CF were significantly more likely to have clinically significant anxiety and depression than the other groups. However, maternal psychological profile did not predict feeding method or interaction quality. **CONCLUSIONS:** Mothers in the CF group were the least likely to breastfeed. Research is needed to explicate long-term effects of feeding methods on quality of mother-child relationship and ways to promote continued breastfeeding after a neonatal CF diagnosis.