Molecular Genetics and Metabolism 116 (2015) 226–230

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Short-term follow-up systems for positive newborn screens in the Washington Metropolitan Area and the United States

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ARTICLE INFO

Article history:
Received 31 August 2015
Received in revised form 2 November 2015
Accepted 3 November 2015
Available online 4 November 2015

Keywords:
Newborn screen
Inherited metabolic disorders
Inborn errors of metabolism
PKU

ABSTRACT

For most inherited metabolic disorders on newborn screening (NBS) panels, prompt, expert confirmation and treatment are critical to optimize clinical outcomes for children with inherited metabolic diseases (IMD). In the Washington Metropolitan Area (WMA), 3 different short-term follow-up (STFU) systems exist for linking infants with positive newborn screens for IMD to appropriate specialty care. We diagrammed the STFU systems for the District of Columbia, Maryland and Virginia and calculated clinically relevant intervals of time between NBS collection and diagnosis/treatment initiation. We also surveyed representatives from 48 other state NBS programs to classify the STFU systems in the rest of the country. We found that in the WMA the STFU system that did not include the IMD specialist at the same time as the primary care provider (PCP) was associated with a longer median collection-to-specialist contact interval for true positive NBS for critical diagnoses ($p = 0.013$). Nationally, 25% of state NBS programs report having a STFU system that does not include the IMD specialist at the same time as the PCP. In conclusion, there is variability among the STFU systems employed by NBS programs in the US which may lead to delays in diagnosis confirmation and treatment. National standards for STFU systems that include early involvement of an IMD specialist for all presumed positive NBS results may decrease the collection-to-specialist contact interval which could improve clinical outcomes in children with IMD.

1. Background

For over 50 years state newborn screening (NBS) programs in the United States have been preventing death and disability in children with inherited metabolic disorders (IMD) through early identification and treatment. While every state NBS program shares the same goals, the specific methods for testing, reporting of abnormal results and the short-term follow-up (STFU) systems for linking screen-positive infants to appropriate specialty care can vary from state to state.

Although the disorders for which NBS programs screen are rare the impact of early intervention is well-documented and widely accepted in the public health and Medical Genetics communities [1]. In order to secure the best health outcomes for truly positive children, the efficient and reliable reporting of a positive NBS result to the appropriate local subspecialist is necessary. While all NBS programs ultimately report to specialists, in our experience the systems and time-frames vary across NBS jurisdictions. Our Program for Newborn Genetics & Metabolism at Children's National Health System (CNHS) is in the unique position of serving as a referral center for three different NBS jurisdictions – the District of Columbia (DC), Maryland (MD) and Virginia (VA) – each of which employs a different STFU process.

In this report we describe our program's experience with referrals for positive NBS in the Washington Metropolitan Area (WMA), including the various intervals of time between specimen collection and establishment (or refutation) of an IMD diagnosis. Furthermore, we describe the results of a survey designed to capture the current national landscape of NBS STFU systems in the United States.

2. Methods

2.1. Study population, definitions and NBS database

We reviewed and analyzed data from all newborns referred to CNHS from January 2012 through September 15, 2014 from each of the three WMA jurisdictions we serve. Data considered included the number of referrals from each state, origin of the referral (pediatrician, state program, etc.), and abnormal analyte category (Table 1).

For all abnormal screens which ultimately resulted in positive diagnoses' time intervals (in days) were calculated for the following: birth to collection of NBS card, collection to first contact with CNHS because of

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http://dx.doi.org/10.1016/j.ymgme.2015.11.002
1096-7192/

Table 1
Characteristics of NBS referrals to Children's National Health System for the study period.

	DC	MD	VA
Live births[a]	25,615	199,855	282,541
Total referrals	37	239	180
Females (% total)	18 (48%)	111 (46%)	73 (41%)
State program referrals	5 (14%)	186 (78%)	28 (15%)
Pediatrician referrals	11 (30%)	32 (13%)	99 (55%)
Other[b] referrals	21 (57%)	21 (9%)	53 (29%)
Disorder type			
FAO	11 (30%)	73 (30%)	43 (23%)
GALT/Gal	9 (24%)	50 (20%)	66 (35%)
OA	5 (14%)	57 (23%)	27 (15%)
AA	3 (8%)	33 (13%)	27 (15%)
UCD	5 (14%)	24 (10%)	6 (3%)
Biotinidase	2 (5%)	6 (2%)	12 (6%)
Other	2 (5%)	2 (1%)	5 (3%)
Total	37	245	186

[a] Per state during our study period (estimated).
[b] Other referral sources included commercial NBS laboratory, birth or other hospitals, including military base hospitals.

an abnormal result, contact to first visit and collection to final diagnosis. Medians were used as a better representation of central tendency and therefore less likely to be influenced by outlier cases present in our data set. In a subanalysis, we examined the intervals specifically for what we defined as "critical analytes", that is analytes that corresponded to disorders where prompt diagnosis and early intervention clearly results in better clinical and/or neurological outcomes or failure to intervene results in early death. These critical analytes included the screens for diagnoses of Arginosuccinic Aciduria, Carnitine Palmitoyltransferase Type 2, Citrullinemia, Classic Galactosemia, Cobalamin Deficiencies, Glutaric Aciduria Type 1, Holocarboxylase Synthetase Deficiency, Homocystinuria, Isovaleric Acidemia, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, MCADD, MSUD, PKU, Propionic Aciduria, and Very Long Chain Acyl-CoA Dehydrogenase Deficiency.

Data was obtained from our clinical REDCap database which is used to track all relevant dates related to the patients seen in our clinic for a positive NBS. Time intervals, in whole days, were either extracted from the database or calculated using Excel. Means and medians were calculated using Excel. We excluded data for 2 children with a critical diagnosis who died prior to confirmation of disease, and for 1 child with Classic Galactosemia who was identified because of a treated sibling. In the latter case, the family chose not to come in for their initial clinic visit until the child was several weeks old, though he was already diagnosed and being treated from day of life 2, due to their familiarity with the disease and distance from clinic.

2.2. NBS reporting systems in the WMA

For DC, MD and VA we created flow-diagrams to summarize the chain of custody for NBS specimens and results. These were based on relevant state statutes and our direct observations while working those programs. Then we shared the diagrams with officials from the state newborn screening follow-up programs for comment and correction and the finalized charts were created (Fig. 1) in August 2013.

2.3. National survey of state NBS reporting systems

In order to capture the current landscape of NBS reporting systems in the United States we designed and deployed a web-based survey (SurveyMonkey). Several logistical questions were asked as well as "Please describe (in words) the information chain in your state for reporting positive newborn screening results and communicating next steps to family of a NBS-positive infant?" One of the flow-diagrams in Fig. 1 was included in the survey as an example. These surveys were distributed via two national newborn-screen email listservs: American Public Health Laboratories New Steps [2] and the University of Texas Health Science Center at San Antonio Newborn Screen Listserv [3]. Listserv members include exclusively newborn screening stakeholders, state follow-up programs and healthcare providers. Survey respondents were self-identified state NBS program officials.

Survey responses were complied, analyzed and classified into one of four categories of STFU systems. Using the results of the first survey we created and distributed a draft map indicating which of the 4 STFU systems each state had reported using. We asked for general comments and for respondents of the first survey to confirm the accuracy of the map and to reclassify their system if it had been misrepresented. Based on the second survey, five categories were ultimately concluded on and a final map was created (Fig. 2). Representatives for all states and DC responded except for South Dakota. For the state systems in the WMA, survey responses as well as previously approved flowcharts were used to help determine categorization.

2.4. Statistical analysis

Descriptive statistics for the origin of referral and type of referral were reported as proportions of the whole and calculated using Microsoft Excel 2010 for Mac as were the calculation of the time intervals of interest. Time-to-event analyses (Logrank test for trend) were done to compare the number of days from NBS collection to CNHS contact for DC, MD and VA (Fig. 3) using GraphPad Prism (v.6).

3. Results

3.1. Characteristics of referrals included in this study

Table 1 shows the characteristics of the patients referred to CNHS during the study period. There were approximately 201,023 live births in the WMA and 470 referrals to CNHS [4–6]. A slight majority of the referrals were boys and the distribution of each abnormal analyte category was similar in all 3 jurisdictions. The majority of cases from MD (77%) were referred by the state NBS program, whereas in VA, 55% were referred by the primary care provider (PCP). 57% of referrals from DC were neither from the state program or PCP, but from outside hospitals or commercial labs.

3.2. NBS reporting systems in the WMA

Reporting systems in the WMA (Fig. 1) include direct contact of the metabolic specialist in MD and indirect, or contact by a pediatrician rather than state follow-up, in DC and VA. However, while DC identifies itself as employing a serial communication chain, in practice we are notified in parallel. Due to a much smaller geographic catchment and an informally close relationship with birth hospitals and primary care providers in DC, results have been reported concurrently to both the primary care provider and CNHS.

3.3. Time intervals for abnormal NBS results in the WMA

Table 2 shows the time (in days) between major landmarks in the NBS process for DC, MD and VA. The median interval between birth and collection was 1–2 days for all 3 jurisdictions. The median interval between collection to CNHS contact was shortest for DC (5 days) and similar for MD and VA (11 and 11.5 days, respectively) when all true positive were considered; for critical true positives median interval from collection to CNHS contact for DC and MD was 5 days and for VA, 8 days. Median interval between contact and first visit at CNHS was between 0 and 1.5 days regardless of whether the screen was critical. Median interval between collection and diagnosis was quickest for DC compared to MD and VA. Time-to-event analysis (Fig. 3) demonstrated