EXPANDED NEWBORN SCREENING BY TANDEM MASS SPECTROMETRY: THE MASSACHUSETTS AND NEW ENGLAND EXPERIENCE

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Abstract. In February 1999, Massachusetts introduced expanded newborn screening for 20 rare metabolic disorders by MS/MS. Medium chain acyl-CoA dehydrogenase deficiency (MCADD) was mandated, in addition to 9 previously screened disorders, while the remaining 19 were offered as an optional pilot. Approximately 98% of parents have elected to participate in the optional program. Maine added MCAD in September 1999, and the optional disorders in July 2001. The other New England states are currently studying the benefits of adding additional testing. Expanded MS/MS screening in Massachusetts has thus far yielded a prevalence of approximately 1: 10,000 [200,000 screened – 22 total cases – MCAD (7), VLCAD (1), SCAD (5), PA (2), 3-MCC (1), citrullinemia (1), ASA (1), argininemia (1), CPT11 (1) and 2 patients (argininemia and CPT11) with a severe neonatal presentation who died in the immediate newborn period]. All surviving patients have normal developmental outcomes so far. To evaluate the benefit of expanded newborn screening in the New England Region, the New England Consortium of Metabolic Centers has undertaken a prospective 3 year study, comparing the outcomes of patients identified by MS/MS with those diagnosed clinically. To date 22 screened patients (10 MCAD, 4 SCAD, 1 VLCAD, 1 CPT11, 1 3-MCC, 2 PA, 1 ASA, 1 citrullinemia and 1 argininemia) have been enrolled along with 24 clinically identified patients (7 MCAD, 1 SCAD, 1 VLCAD, 1 LCHAD, 1 argininemia, 1 tyrosinemia type 1, 6 PA, 3 GA 1, 2 GA 11, 1 MMA). Studies include: medical exam, neuropsychological assessment (Bayley Test and Stanford-Binet Test of Intelligence) and medical record review. Preliminary data suggest that the screened patients have an improved clinical outcome with fewer hospitalizations and so far, no neurological complications.

INTRODUCTION

The development of tandem mass spectrometry allows the rapid detection of over 30 inborn errors of metabolism in the newborn period. Expanded newborn screening by tandem mass spectrometry (Table 1) was introduced in Massachusetts in February 1999 (Atkinson *et al*, 2001). Approximately 80,000 newborns are screened each year.

While presymptomatic diagnosis of these disorders is expected to prevent mortality and serious morbidity, provide a positive cost/benefit ratio and provide true ascertainment of the disorders in the population, these outcome measures remain to be demonstrated in long term follow up studies. Questions have also been raised about the effect of biological false positive screening results on the parents of these infants and whether some disorders may present either too early or too late to be detected through screening. Barriers to evaluating these outcomes include small numbers of affected children with each disorder, a lack of standardized diagnostic protocols and case definitions, and the need, and lack of availability of prospective or historical controls.

A group of physicians (specializing in metabolic disease) and allied health professionals has developed the New England Consortium of Metabolic Programs (http://www.newenglandconsortium.com) as a mechanism to integrate the diagnosis and care of children with inborn errors of metabolism within the framework of the newborn screening program – specialist programs, primary care providers, public health departments, community services and parent organizations. Activities of the physician subcommittee include developing algorithms for evaluating abnormal newborn screening results, information sheets for primary care physicians, clinic protocols for the metabolic centers (for standardized evaluation and case definitions), emergency protocols for parents to take to local Emergency Rooms for acute illness and education outreach to physicians in the community.

MATERIALS AND METHODS

Preliminary data from 2 studies have been accumulated:

1. A 3-year prospective study to evaluate newborns detected by screening in Massachusetts and

Table 1. Disorders included in expanded newborn screening by tandem mass spectrometry.

Disorders included in expanded screening
• Tyrosinemia I (Fumarylacetoacetate hydrolase deficiency)
• Tyrosinemia II (Tyrosine aminotransferase deficiency)
• Citrullinemia
• Argininosuccinic acidemia (ASA)
• Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) syndrome
• Methylmalonic acidemia (Methylmalonyl-CoA mutase deficiency) (MMA)
• Propionic acidemia (Propionyl-CoA carboxylase deficiency) (PA)
• Argininemia (Arginase deficiency)
• Isovaleric Acidemia (Isovaleryl-CoA dehydrogenase deficiency)
• Glutaric acidemia I (Glutaryl-CoA dehydrogenase deficiency) (GA I)
• Glutaric acidemia II (Multiple acyl-CoA dehydrogenase deficiency) (GA II)
• ß-Ketothiolase deficiency (2-Methylacetoacetyl-CoA thiolase deficiency)
• ß-Methylcrotonyl CoA carboxylase deficiency
• 3-Hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency
• CPT deficiency (Carnitine palmitoyltransferase deficiency)
• Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
• Short chain acyl-CoA dehydrogenase (SCAD) deficiency
• Long chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
• Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency

Pennsylvania (data provided by Neo Gen Screening, Inc, Pittsburgh, Pennsylvania USA) compared to those diagnosed clinically, in terms of the interaction between the parents and the healthcare system and the health outcome of the child and the family, including the ways in which information is conveyed to the parents, parental response, types of medical care provided, psychosocial factors and legal ramifications.

2. A 3-year prospective study to assess the impact of a biological false positive screen compared to a normal screen, in terms of parental response and interactions with the health care system.

In study 1, each child was evaluated 6 months after diagnosis and 1 year later. Evaluation included a physical exam, developmental assessment by the Bayley Scales of Infant Development (2nd edition) or the Stanford-Binet Test of Intelligence and medical record review. The parents were interviewed to assess social support, satisfaction with healthcare, parental stress index, well-being scale, patient enablement instrument and demographic information. In study 2, 26 parents have been enrolled in the biological false positive group and 64 in the control group.

RESULTS

After 2 ½ years of screening approximately 200,000 babies in Massachusetts, there have been: 14 fatty acid oxidation defects (7 MCAD, 5 presumptive SCAD, 1 VLCAD, 1 CPT2), 3 Urea cycle defects (1 ASA, 1 arginase deficiency, 1 citrullinemia) and 3 Organic acidemias (2 PA, 1 MCC).

In Study 1 (combined Massachusetts patients) there are currently enrolled 33 clinically identified study participants (6 MCAD, 1 SCAD, 2 VLCAD, 6 PA, 3 GA1, 2 GA11, 1 CPT11, 1 ASA, 3 Tyr 1, 2 MMA, 1 cobalamin C and 3 arginase deficiency), 29 screened (15 MCAD, 6 SCAD, 2 VLCAD, 2 PA, 1 3MCC, 1 citrullinemia, 1 CPT11, 1 ASA and) and 12 previously undiagnosed siblings of screened infants (11 MCAD and 1 3MCC).

Sample characteristics of the health outcomes for both groups are shown in Table 2. The screened patients so far have fewer hospitalizations and require less extra care by parent report. Data are not yet complete enough to make conclusions about developmental outcome (Table 3), however comparison of medical and developmental data for patients with MCAD and propionic acidemia (Table 3), suggest that neurological and developmental outcomes are improved in the screened group. Assessment of parental stress index shows a significantly greater mean score in the clinical group (72+/- 4) compared to the screened group (59 +/- 3). 22% of parents in the clinical group reported high levels of stress compared to 4% in the screened group.

In Study 2, preliminary results show no statistical significance (Table 4) between each group studied regarding their parental stress index results.

OUTCOME AND CONCLUSIONS

Of the Massachusetts cases thus far studied, 3 were found to be MCAD-homozygous for A985G and 4 were compound heterozygous for A985G and one other unique mutation. All are clinically well with normal development.

Table 2. Health outcomes of cases detected in Massachusetts and Pennsylvania study.

	Newborn screened group (n=33)	Clinically identified group (n=34)
Age at time of diagnosis in days (mean ± SD)	22.9 + 40.6	333.9 + 584.3
Range	(1—180)	(2—2,160)
Hospitalizations in past year or since birth	(n=33)	(n=15)
• Mean # hospitalizations	1.1	3.4*
• Mean # days in hospital	2.6	14.6*
• % needing hospitalization	45%	88%*
• % at Emergency Room	52%	81%*
Extra care requirements		
• Parental rating (1-5 scale)	1.0	2.7*
• % with g-tube	7%	31%*

Table 3. Preliminary Developmental Outcome

	NEWBORN SCREENED GROUP (n=33)	CLINICALLY IDENTIFIED GROUP (n=16)
Mean DQ or IQ	104	97 (ns)
• Bayley MDI (Cognitive)		
• Bayley PDI (Motor)	--	106
• Stanford Binet	0	0
• % Scoring 70-85	0	6%
• % Scoring < 70		
VINELAND		
• Adaptive Behavior Comp.	107	95
• % SCORING 70-85	6%	11%
• % SCORING < 70	0	17%

Table 4. Parental indices of stress and well-being

	FALSE POSITIVE GROUP (n=26)	NORMAL CONTROL GROUP (n=64)
PARENTAL STRESS INDEX		
• Mean score	62 ± 17	57 ± 12 (ns)
• % Scoring >85	8%	3% (ns)
WELL-BEING INDEX		
• Mean score	51 ± 10	52 ± 8 (ns)
• % Scoring < 40	7%	7% (ns)

One patient has had a hospital admission for emesis (blood glucose 60 mg/dl). All patients with SCAD presented with elevation of ethylmalonic and methylsuccinic acid in their urine and one was unfortunately lost to follow up. Three patients were clinically well with normal development. One patient was found to be homozygous for G625A. Two patients had abnormal fatty acid oxidation studies and with their DNA results pending. One patient had mild developmental delay, abnormal fatty acid oxidation studies, homozygous for a new mutation (N Gregersen personal communication). The patient with VLCAD was clinically well with normal development. The patient with CPT2 had multiple congenital anomalies and eventually died on the 3rd day of life. The patient with ASA was clinically well with normal development and with no hyperammonemia. The patient with Citrullinemia had mild elevation of citrulline. The patient was well with no hyperammonemia. The patient with Arginase deficiency had severe hyperammonemia and eventually died on the 3rd day of life. One patient with Propionic acidemia was well and developmentally normal with no ketoacidosis. The other patient was developmentally normal but had several hospitalizations with ketoacidosis. The patient with MCC was clinically well. Two disorders presented too early for detection through screening (1 MMA at 36 hours of life and 1 sudden death at 52 hours of life). Post mortem studies pending.

Preliminary conclusions from the consortium studies suggest that early presymptomatic diagnosis may improve morbidity and/or mortality for the inborn errors of metabolism detected through expanded screening with MS/MS, and that parental anxiety is not significantly increased 6 months after a false positive expanded newborn screening result. Tandem mass spectrometry appears to be an efficient method for screening many rare metabolic diseases. Pre-symptomatic diagnosis likely improves prognosis; however, some disorders with very early neonatal onset will not be detected pre-symptomatically. A broader spectrum of severity of some disorders exists and newborn screening will help to complete the understanding of the natural history of many of the diseases being detected.

REFERENCES

Atkinson K, Zuckerman B, Sharfstein JM, Levin D, Blatt RJ, Koh HK. A public health response to emerging technology: expansion of the Massachusetts newborn screening program. *Public Health Rep* 2001;116:122-31.