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Tandem Mass Spectrometry and Newborn Screening: Pilot Data and Review

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United States legislatures are debating whether to use tandem mass spectrometry to expand the roster of inherited disorders tested in newborn screening programs. The debate is hampered because published financial data comparing charges associated with late vs early diagnosis are not readily available. We provide pilot financial data comparing late diagnosis vs presumptive diagnosis and early management taken from consecutive patients with propionic acidemia diagnosed from 1995-1998 in New Hampshire. We extrapolated from these data and the incidence of treatable inborn errors of metabolism to estimate the projected yearly savings of critical care charges if expanded newborn screening were instituted. We conclude that institution of expanded screening will bring diminished morbidity and large savings in yearly chronic care and critical care charges.

Filiano JJ, Bellimer SG, Kunz PLL. Tandem mass spectrometry and newborn screening: Pilot data and review. Pediatr Neurol 2002;26:201-204.

Introduction

Tandem mass spectrometry is a major technologic advance in screening newborns for genetic diseases. It permits expansion of screening to many disorders of organic and amino acid metabolism heretofore not included in traditional newborn screens. As with current standard newborn screening tests, only four "spots" of blood on a filter paper are required for an adequate specimen. Efforts are underway to apply tandem mass spectrometry as universally as the techniques used to screen for phenylketonuria 35 years ago and the methods used to screen for neonatal hypothyroidism 25 years ago. Legislative debate is ongoing concerning whether or when to expand newborn screening. The debate includes issues of effectiveness and budgetary burdens from the startup costs. Financial data regarding the potential benefits of expanded newborn screening are not widely available, in part because the charges associated with these diseases are difficult to compile across many institutions, hospitals, insurance companies, and states. Pediatric neurologists are becoming vocal on behalf of the patient because of their special experience in diagnosis, management, and long-term care of many of the complications of disorders of organic and amino acids (e.g., cognitive impairment, seizures, chorea, and hypotonia). We present pilot financial and clinical data on four patients with propionic acidemia as evidence that it is prudent to screen for all treatable organic and amino acid disorders using tandem mass spectrometry (see Tables 1-4).

Organic and Amino Acid Disorders in General

Organic and amino acid disorders often cause death or severe neurologic disability. If detected by a newborn screening test and treated early, however, affected children may live a functional life. Without newborn screening a patient may not be recognized as having an organic or amino acidemia until the child is admitted to the hospital with cognitive or behavioral symptoms, seizures, ataxia, movement disorder, stroke, or coma. These symptoms are costly and often permanently disabling. Without newborn screening the diagnosis of an organic or amino acid disorder can be delayed because these disorders are uncommon and can mimic more common disorders. Lack of screening may delay a clinician's thought to test for these diagnoses, even when an affected child is critically ill. In patients with these neurometabolic disorders, a minor infection in conjunction with a heavy protein load may trigger a neurologic crisis of coma and seizures. Unfortunately, it is common that a clinician may attribute the symptoms to the infection only and thereby miss the chance to diagnose and treat the more serious underlying metabolic disease. Even if an organic or amino acidemia is suspected, it may still take more than 1 week before laboratory tests establish the proper diagnosis, which may delay effective therapy.

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Received May 16, 2001; accepted October 1, 2001.

PII S0887-8994(01)00384-8 • 0887-8994/02/$—see front matter

Table 1. Clinical presentations of four patients with propionic acidemia

	Erroneous Diagnosis	Age at Presentation	Presenting Symptoms	Clinical Outcome
Patient 1, male	Cerebral palsy	Birth and later at 2 years of age	Neonatal encephalopathy. At 2 years of age had Reye-like syndrome	Deceased
Patient 2, female	Diabetic acidosis, then treated as organic acidemia	2 years of age	Febrile illness, vomiting, coma, acidosis	Normal development on diet
Patient 3, female	Birth asphyxia	First month	Coma, hypotonia	Developmental delay, seizures, microcephaly, gastrostomy
Patient 4, female	Presumed organic acidemia, early treatment	First month	Hypotonia, seizures	Mild motor delay, normocephalic, gastrostomy

Once critically ill with a metabolic coma or encephaloclastic lesion, the patient usually is left with permanent difficulties in cognition, walking, speaking, or eating. The patient may later develop epilepsy, recurrent coma, or a Reye-like syndrome. Untreated patients may have persistent liver, blood, kidney, or other organ dysfunction. In full and late manifestations, these are multisystem diseases. Even without critical illness at presentation, a patient with a late-diagnosed organic or amino acid disorder usually is developmentally delayed. Many complications can be avoided by simple, but early, changes in diet, specific vitamin supplementation, and vigilant avoidance of catabolism when the child has a febrile illness. Given that most of these disorders are autosomal recessive, the probability of recurrence is usually 25% for each subsequent offspring of the same parents. Neurologic abnormalities of patients with some late-diagnosed organic or amino acid disorders may be similar to symptoms in patients with cerebral palsy. As a result, sometimes the first clue that a child's presumed "cerebral palsy" or seizures might actually be caused by an undiagnosed genetic metabolic condition is when a second sibling develops the same symptoms. In such cases, use of a newborn screen would have prevented the compounding of a family tragedy.

Although each individual neurometabolic disease identified by tandem mass spectrometry is rare, when considered collectively this class of illness is not rare. Disorders identified by expanded newborn screens include more than 20 disorders of amino acids, organic acids, congenital adrenal insufficiency, disorders of fatty acid beta oxidation, hypothyroidism, and others. Three to six children with treatable genetic and metabolic disorders are likely to be identified each year in New Hampshire. That estimate is based on data from newborns screened with tandem mass spectrometry in Louisiana, North Carolina, Ohio, and Pennsylvania, from September 9, 1985 to June 30, 1997; recent published data on the incidence of neurometabolic disease screened by tandem mass spectrometry [1]; and New Hampshire's projected yearly birth rate of approximately 13,000 infants.

Propionic Acidemia

The following pilot data and discussion focus on propionic acidemia caused by propionyl CoA carboxylase deficiency. This deficiency causes cognitive and motor impairment and seizures and recurrent episodes of acidosis, vomiting, and stupor or coma if unrecognized and treated late [2]. However, patients may lead functional lives if the defect is detected and treated early. Many of the principles of diagnosis and management of propionic acidemia apply to other disorders of organic and amino acids as a class.

Methods

Four children presented to our tertiary care facility in New Hampshire in coma and acidosis and were diagnosed with propionic acidemia from 1994 to 1998. During that time, the New Hampshire newborn screen did not test for propionic acidemia (Table 1). Diagnoses were made when samples were sent out of state to perform tandem mass spectrometry testing and confirmed by urine specimens and analysis of fibroblast propionyl CoA carboxylase. (One patient died before fibroblast confirmation.) We compiled the hospital financial charges incurred by these four patients from their critical care unit admissions. These charges were designated "critical care charges." Separate from that, we compiled the outpatient and noncritical care inpatient charges in the years after 1998. These were designated "chronic medical charges." We were unable to obtain charges from outpatient or inpatient admissions at other institutions. However, as the only tertiary pediatric facility in New Hampshire, and having followed these patients closely, we believe we have compiled all of the direct critical care charges incurred by these patients between 1994 and 2000.

Results and Discussion

The in-hospital critical care charges for our four propionic acidemia patients totaled $542,400 (Table 2). This total included emergency room stabilization, intensive care, radiograms, cerebral imaging, other laboratory tests, and therapeutic procedures and drugs before the diagnosis was established and appropriate diet begun. One child died of a Reye-like syndrome during a second critical care admission, which led to diagnosis.

Although the critical care charges for these patients were great, future direct and indirect costs of chronic care must also be considered in any cost-benefit analysis of expanded newborn screening. The neurodevelopmental similarity between cerebral palsy and the neurologic residua in patients with organic and amino acid disorders provide an estimate of charges for their future chronic medical care, developmental services, special education, and lost wages [3,4]. Net total medical charges accrued for

Table 2. Critical care changes for neurometabolic disease (1998 dollars)

Patient #1 (Late diagnosis, late treatment, deceased)	$ 355,000
Patient #2 (Late diagnosis, prompt treatment)	$ 8,200
Patient #3 (Late diagnosis, late treatment)	$ 135,000
Patient #4 (Late diagnosis, prompt treatment)	$ 44,200
Total Charges	$ 542,400
Average charges per patient	$ 135,600
Critical care charges if four cases/year in New Hampshire	$ 542,400
Yearly incremental screening charges/15,000 births in New Hampshire	$ 156,000
Projected critical care savings in New Hampshire because of expanded newborn screening of neurometabolic disease	$ 366,400
Projected critical care savings in United States because of expanded newborn screening of neurometabolic disease	$36,600,000

patients with cerebral palsy up to 65 years of age was $142,000 per patient in 1988 dollars (where net total charge equals gross charges minus the average charge of inpatient and outpatient medical care in the United States as of 1988) (Table 3). This means that the average charges for caring for cerebral palsy included an additional $142,000 (in 1988 dollars) beyond that of the usual health care charges for a nondisabled citizen under 65 years of age. The gross charges for medical care, developmental services, special education charges, lost household wages, and public assistance for a patient with cerebral palsy who lived to 65 years of age was between $167,000 and $1 million dollars per patient in 1988 dollars, depending on the way future salaries are estimated [3,4]. By extrapolation to the neurologic residua of organic and amino acid disorders, even if tandem mass spectrometry screening saved half the projected acute and chronic charges, the ongoing savings would be large.

If tandem mass spectrometry is added to current newborn screening, the incremental increase in charges will be approximately $12 per newborn in 1998 dollars. This totals $156,000 to test 13,000 children born in New Hampshire each year. Of our four sample patients with propionic acidemia, the average critical care charge was $135,600 per patient in 1994-1998 dollars (Table 2). These charges likely would have been less if the diagnosis had been made by early newborn screening, although the amount of reduction can only be estimated. To make this estimate, we multiply the average critical care charge per patient by the four patients expected to be born yearly with

Table 3. Lifetime charges per disabled infant (1988 dollars)

Net additional medical charges	$ 142,000
Total charges to age 65*	$167,000-$1million

* Medical charges + developmental services + special education + lost wages.

Table 4. Charges from late-diagnosed neurometabolic disease (1998 dollars)

Magnetic resonance imaging scan	$ 1,622
Electroencephalography	$ 650
Gastrostomy	$ 6,000
Achilles tendon lengthening	$ 8,000
Leg adductor muscle release	$ 2,100
Scoliosis repair	$31,600
	$49,972

a neurometabolic disorder identified by tandem mass spectrometry in New Hampshire [1]. This critical care charge totals $542,400 yearly.

There will be outpatient charges for management after diagnosis is made by screening. Such charges in New Hampshire can be estimated by these patients' current yearly medical charges, which has been approximately $5,000 in our patients since 1998 or $20,000 yearly for four patients identified by expanded screening. Therefore the $156,000 spent on expanded newborn screening with tandem mass spectrometry in New Hampshire may save ($542,400 − $20,000) − $156,000 = $366,400 in critical care charges each year (Table 2), which saves almost twice the yearly incremental increase in charges for routine tandem mass spectrometry screening.

These savings in critical care charges underestimate the total savings. For example, our estimated savings do not include charges from the primary care hospital before the patients reached our tertiary facility. They do not include savings of drug charges that accrue when late diagnosed children develop epilepsy or mental retardation. They do not consider the yearly rehabilitation and special education charges to our patients after 1998. If these were considered, our estimates of savings from expanded newborn screening would likely be much greater. On that issue, compare Patient 3 to Patient 4 in Tables 1 and 2. Patient 3 was diagnosed late and after a prolonged, severe coma. She has had more hospitalizations, much lower cognitive function, more medical interventions, and higher yearly chronic medical charges than Patient 4. Both are matched in age and sex and had the same level of enzyme dysfunction, but Patient 4 received rapid management after presumed diagnosis. Patient 3 had 10 post-1998 admissions, amounting to $89,891 in charges, compared with Patient 4 who had six brief post-1998 admissions amounting to $39,125 in charges. Similarly, Patients 2 and 4 (Table 1) were treated presumptively and early and perform at a neurodevelopmental level better than that of the average outcome for late-treated propionic acidemia published in the pretandem mass spectrometry era [2]. It is likely, therefore, that early diagnosis will diminish both critical care and chronic medical charges (Table 4).

These financial data, derived from patients with propionic acidemia, may be different from charges associated with other diseases identified by tandem mass spectrometry. Some charges will not be altered by expanding

newborn screens. For example, the charges of genetic counseling and chronic dietary management will be part of chronic outpatient charges whether patients were diagnosed early or late. Furthermore, infrastructure is required to process the tandem mass spectrometry specimens, report the findings to health care providers, and maintain quality control. That is paid for in part by the $12 incremental charge (in 1998 dollars).

Conclusion

In the early days of screening for phenylketonuria and hypothyroidism, controversy concerning cost-effectiveness delayed the use of newborn screening. Subsequent analyses indicate that absence of newborn screening for phenylketonuria and congenital hypothyroidism resulted in great morbidity and expense to afflicted children, to their families, and to society. These costs were ameliorated by early diagnosis and management after newborn screening was implemented [5-8]. Extrapolation from that experience and our pilot data lead us to conclude that, just as with the earlier experience with newborn screening, the monetary benefits of expanded newborn screening will outweigh the monetary charges. Tandem mass spectrometry meets current guidelines for screening tests [1,7,8]: (1) tandem mass spectrometry can identify disorders that are well-defined clinically and biochemically; (2) tandem mass spectrometry is sensitive enough to find nearly all affected children but has acceptably few "false positives"; (3) the conditions screened for, collectively, have a known and significant incidence in the population; (4) early diagnosis and effective treatment will prevent or diminish markedly both morbidity and mortality; (5) tandem mass spectrometry will assist in genetic counseling; (6) the financial charge of the screening test is small compared with charges for treating late-diagnosed patients; and (7) tandem mass spectrometry screening is safe.

Vaccinations and advanced infectious disease management have been so successful in the United States that once-uncommon disorders now cause an increased proportion of health problems. For example, hospital admissions and charges for organic and amino acid disorders at our tertiary care institution exceed charges for the once-common diseases caused by *Haemophilus influenzae*. From our pilot data we conclude that expanding newborn screens to include all treatable organic and amino acid disorders may save more than $366,000 yearly in critical care charges in New Hampshire, saving approximately twice the incremental charges for expanded newborn screening. It will also diminish chronic medical care charges from symptoms such as severe seizures and spasticity. The critical care savings may not seem large because New Hampshire's health care prices are lower than in urban areas, and New Hampshire is a small state, with approximately 1% of the United States' population. If one multiplies the $366,00 savings by 100 to extrapolate to the entire nation, the national savings of critical care charges therefore may exceed 36 million dollars yearly. We conclude that spending $12-20 more per baby for newborn screening is economically valid in a society in which effective interventions in public safety and hygiene are already in place. The financial data, however, do not convey the unremitting hardships endured by families with severely disabled children. We conclude that deployment of tandem mass spectrometry in newborn screening is both economically prudent and compassionate

Thorough cost-effectiveness analysis must go beyond our pilot data. Information must be gathered among several states and include data from insurance companies, public agencies, hospitals, and outpatient clinics. Patients must be followed for at least 7 years to determine their cognitive function by first grade. Concern for patient confidentiality will require permission from identified patients' families to maintain continuity of data over many years. Data from states that opt not to expand newborn screening can be compared with data from states that deploy expanded screening. Such studies have been approximated in nations that have state-run health programs [5-8]. In the United States, such a study will require elaborate cooperation among state and private health care and educational enterprises.

We value the critiques made by George A. Little, MD, Donald Bartlett, Jr, MD, and Adam L. Hersh, PhD. The authors thank Diane M. Minard, Staci Raymond Avery, and Rhonda A. Stewart for their help in preparing this manuscript. Lynne A. Wolfe, ARNP, contributed to clinical management of three of these patients after their initial hospital admissions. We are grateful for financial assistance provided in honor of Daniel J. Hammerschmidt and Dmitra Sklavounos, and from the Susan Epply Endowment for Research in Pediatric Critical Care.

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