

## PROFESSIONAL NEGLIGENCE SECTION NEWSLETTER: FALL 2018

# Identifying a Potential Medical Negligence Claim for Children with Inborn Errors of Metabolism

CHARLES P. HEHMEYER AND MARTINA W. MCLAUGHLIN  
RAYNES LAWN HEHMEYER

## I. INTRODUCTION

By law, almost every baby in the United States is screened at birth for diseases known as inborn errors of metabolism (IEMs). Also called metabolic disorders, IEMs prevent the proper conversion of food and allow toxic byproducts to accumulate in the child. If an IEM is properly diagnosed, a simple diet change usually can ensure the child's health. If, however, the condition is not detected and treated, the child can suffer devastating lifetime injuries that require constant attendant care.

There are dozens of different IEMs—most with tongue-twisting names. As one leading pediatric textbook states, "IEMs are individually rare but collectively numerous."<sup>[1]</sup> Doctors estimate that 1 in every 2,500 children is born with a metabolic disorder.<sup>[2]</sup>

Like a doctor approaching a new patient, a lawyer contacted about an injured child must triage the available history and medical record, developing a "differential" of potential legal claims. What follows are guidelines based on twenty years' experience representing children with IEMs in twenty-four states.

## II. METABOLIC DISORDERS

### A. What Is a Metabolic Disorder?

Most nutrition falls into three categories: Protein, fat, and carbohydrates. The gut digests food, and the bloodstream takes these substances to organs where they are metabolized, that is, broken down and either used or stored.

Metabolism occurs within cells. There are hundreds of steps, each requiring a unique enzyme. A metabolic disorder occurs when there is a genetic mutation that impairs the body's ability to make an enzyme properly. The poorly working enzyme results in

---

---

accumulation of an intermediate metabolite, which can cross the blood-brain barrier and cause neurologic damage or death.

## B. How Are Metabolic Disorders Diagnosed?

### *1. Newborn Metabolic Screening*

Each state mandates that a newborn's blood be screened for elevations of certain metabolites indicative of an IEM. After birth, a baby's heel is pricked, usually at 24 to 36 hours of age, and blood is placed on filter paper, which is sent for laboratory analysis. Results arrive in a few days. The state's public health infrastructure is designed to assure that newborns with abnormal levels receive prompt diagnostic testing and, if necessary, treatment.

### *2. Clinical Diagnosis*

While newborn screening identifies most babies with IEMs, physicians still must be watchful for clinical signs of a metabolic disorder. By itself, screening is an imperfect process. Screening programs also do not look for all IEMs. And, critically, some babies with metabolic disorders become severely ill before the screening results are available. Thus, doctors should consider an IEM in any newborn with lethargy, poor feeding, abnormal breathing, metabolic acidosis, recurrent vomiting, or any combination of these symptoms. Many signs and symptoms of IEMs are similar to those in newborns with infection, but because the outcome of a delayed diagnosis can be catastrophic, concurrent workup to exclude an IEM is imperative.<sup>[3]</sup>

An unusual odor is strongly suggestive of a metabolic disorder, the best-known being maple syrup urine disease, so-called because an affected child's secretions often smell sweet.

There are also times when signs of a metabolic disorder do not occur until months or years after birth, particularly in children affected with a milder mutation. Genetic diseases also should be ruled out in older children with unexplained intellectual disability, development delay, motor deficits, cardiomyopathy, or recurrent vomiting.<sup>[4]</sup>

## C. Treatment for Metabolic Disorders

IEMs presently cannot be cured, so current treatment includes restricting the substance that cannot be sufficiently metabolized. For example, children with galactosemia (who cannot properly break down milk) drink soy formula. Babies with a protein metabolism defect receive a low-protein diet supplemented with a commercial formula without the problem amino acid. In addition, doctors can sometimes prescribe vitamins called "cofactors" that improve the function of the poorly working enzyme.<sup>[5]</sup>

Everyone breaks down stored fat and protein during periods of stress, illness, or fasting

---

---

– a process called “catabolism.” When children with an IEM are sick, parents or doctors provide large amounts of glucose, sometimes via an IV, to halt catabolism and prevent breakdown of substances stored in the body that the child cannot metabolize.

### III. THE NINE MOST COMMON MISTAKES AFFECTING CHILDREN WITH IEMs.

Proper care for a child with an IEM involves a system: newborn screening, follow-up, diagnosis and, finally, treatment, which includes acute and chronic management. In addition to the patient and family, the stakeholders in the process are the birth facility, the state newborn screening program, metabolic specialists and pediatricians/pediatric subspecialists who care for sick children. As in any system, errors occur at each level:

#### A. Failure to Offer *Expanded* Newborn Screening

Newborn metabolic screening (NBS) started in the 1960s, when Robert Guthrie, a pediatrician, invented a test that revealed high levels of the amino acid phenylalanine. Phenylalanine is elevated in the metabolic disorder phenylketonuria (PKU). Left untreated, PKU causes profound intellectual disability. Caught early, children with PKU can be and placed on a special diet and are typically unimpaired and lead productive lives.

The medical community, however, resisted Dr. Guthrie’s new test. Frustrated, he and other advocates turned to state legislatures, and over the next decade all 50 states mandated PKU screening. As part of that legislation, states delegated to health departments the job of implementing PKU screening and determining any *additional* screens that should be mandated. Over the next several decades, states implemented one or, in some cases, a handful of other newborn screens.

In the 1990s, scientists at Duke University revolutionized NBS by applying a technique called tandem mass spectrometry (MS/MS). Before then, every proposed new infant screen would require an additional test (one test for each potential disorder). The cost was difficult to justify: public health dollars are scarce and individual metabolic diseases are rare. With MS/MS, scientists proved that labs could detect dozens of IEMs reliably with one test, called “supplemental” or “expanded” newborn metabolic screening (SNS).

The question then became what IEMs should be included in the SNS panel. In the early 2000s, the federal government convened a team of experts to answer that question. The result was the Recommended Uniform Screening Panel (RUSP), consisting of 29 “core disorders.”<sup>[6]</sup> By early 2005, all relevant standards organizations endorsed the RUSP, including the American Academy of Pediatrics and the American College of Medical Genetics.

Unfortunately, many states lagged behind in mandating SNS. The federal government and many state health departments recommended that, in the interim, hospitals should offer SNS for all newborns or inform parents about private laboratories that offer SNS.

---

---

Tragically, many failed to do so. As a result, some newborns with IEMs went undiagnosed until after they suffered severe brain injury or death. That disparity left some children with the same disease literally living or dying based solely on the location of their birth hospital.<sup>[7]</sup>

If an injured child has a disorder on the RUSP for which the state had not yet mandated screening, one should consider a claim against the birth hospital and/or the child's pediatrician for not voluntarily providing SNS through a private laboratory or, at the very least informing parents of the availability and importance of SNS. This claim is particularly powerful against health care systems that operate both the affected child's birth hospital and hospitals in other states where SNS was mandated, or where the system voluntarily offers it to parents in other states.

Health care systems typically have quality-control programs requiring that doctors within their networks provide "best practices" and evidence-based medicine. By 2005, SNS qualified as both: it is an inexpensive test endorsed by the relevant experts and standards organizations, posing no risk, that saves some children from brain damage or death. An attorney for an injured child with an IEM must consider a claim that a reasonable health care system is legally obligated to offer SNS at all of its hospitals, not just some.

By 2010, virtually all states and territories had mandated SNS. Thus, the period from 2005–2009 had the greatest number of children injured because hospitals and pediatricians failed to offer SNS. Critically, many of these claims still are viable in states that toll the statute of limitations for minors.<sup>[8]</sup>

## B. Screening Process Design Mistake

When designing the NBS process, steps must be taken to avoid false negatives—missing an affected child.

For instance, labs detect certain IEMs by measuring substances called acylcarnitines. Each facility establishes its own cutoffs. Some labs utilize a two-tiered reporting system. If an acylcarnitine is highly elevated, above an "alert" cutoff, the newborn is immediately referred to a metabolic specialist. In contrast, if the acylcarnitine is just mildly elevated, a repeat screen is requested. Such borderline cases are not referred to a specialist for diagnostic testing unless the repeat screen also is elevated.

Acylcarnitine levels, however, decrease significantly after the first week of life.<sup>[9]</sup> If a screening lab requests a repeat blood spot, the baby's pediatrician will collect it after a week of age. Thus, labs must analyze repeat specimens using lower, age-adjusted cutoffs. If the NBS laboratory utilizes a two-tiered approach, but does not establish age-adjusted cutoffs for repeat screens, it is likely that it will miss babies, particularly ones with milder mutations.

---

---

Such a flawed system is clearly negligent and, in fact, has resulted in babies suffering severe injuries.<sup>[10]</sup> When evaluating a case where NBS missed an IEM, it is very important to determine why and pursue the laboratory if appropriate.

State, rather than private, laboratories conduct most NBS in the United States. Thus, it is critical to understand applicable state sovereign-immunity laws. Although most states cap or foreclose damage claims against state entities, some allow claims against individual laboratory employees responsible for laboratory errors<sup>[11]</sup> and insure their employees against such claims.

### C. Sample Collection Timing Error

One of the most common errors is mistiming the collection of the NBS sample. NBS cutoffs are age dependent. The standard of care for sample collection from a well newborn is 24 to 36 hours of age, allowing relevant metabolites sufficient time to accumulate after birth. Earlier sample collection risks missing an affected child.<sup>[12]</sup>

The converse also is true. Samples cannot be collected too late. Some IEMs strike very early. Galactosemia, for example, often causes overwhelming E. coli infection within days of birth. A sample collected at several days of age likely will not be evaluated before such children are critically ill. Other metabolites, for example acylcarnitines, used for NBS begin falling during the first week of life once the baby has recovered from the stress of birth. If a sample is collected many days or weeks after birth and grouped with newborn samples, the cutoffs will be invalid.

### D. Batching Samples

A recent newspaper article highlighted the problem of hospitals batching NBS samples.<sup>[13]</sup> To save money on shipping, some facilities will wait to send blood spots to the laboratory until they have a large number of samples, which can take many days. Compounding the problem, hospitals may use regular mail to ship rather than paying for overnight or courier service. State labs are often also closed on weekends and holidays. Because many IEMs will cause life-threatening illness during the first week or two of life, such delays are not reasonable and should be addressed legally if they injure a baby. Most states have sample-collection rules that hospitals must follow, but that some facilities do not.<sup>[14]</sup>

### E. Over-reliance on NBS/Misunderstanding IEMs

Even if NBS is done properly, some children with metabolic disorders nevertheless will become dangerously sick before screening results are available. Clinicians need to be mindful of this because hours, and certainly days, can make the difference between a good outcome and profound brain damage or death.

Although metabolic disorders are complex, most of them present in the newborn period with a similar constellation of findings that pediatricians should know: (1) a well newborn

---

---

with no risk factors for or compelling signs of infection who, shortly after feeding starts, deteriorates suddenly, beginning with lethargy and progressing to coma; and (2) unique laboratory abnormalities, including metabolic acidosis in the absence of poor perfusion, ketones in the urine, high plasma ammonia level, and/or hypoglycemia, all of which can be evaluated very rapidly in almost any hospital laboratory.

Unfortunately, even in the face of these obvious signs, many clinicians do not consider an IEM diagnosis either because they fail to recognize the signs or wrongly assume that if a child has a metabolic disorder, the newborn screening program already would have notified them.

In one case, a pediatric intensivist failed to follow up on labs she ordered that had not been returned in over a week (the lab technician who usually ran the tests was on vacation) because she wrongly assumed that IEMs are largely untreatable.

#### F. Follow-up Failure

The standard of care requires that all babies with an abnormal NBS be referred to a metabolic specialist for confirmation and treatment. Usually, the state reports NBS results to both the birth hospital and the baby's pediatrician. If the results are abnormal, the state will emphasize the need for immediate follow-up with a metabolic specialist.

If a metabolic specialist did not promptly evaluate a baby following a positive NBS, an investigating attorney must uncover whether there was a parent-notification failure or a failure to assure that the appointment was made and kept. The standard of care requires that the child's primary care providers check in the first month of life to assure that NBS results were reported and acted upon appropriately.<sup>[15]</sup>

Another care failure may occur when a metabolic specialist fails to timely complete a work-up. Some IEMs require specialized testing to reach a definitive diagnosis. For example, an elevated phenylalanine level may indicate classic PKU, a related and very dangerous co-factor disorder, or, a benign condition called "hyperphenylalaninemia." Further testing of the blood and urine is necessary to differentiate. Failure to order or send follow-up specimens or otherwise complete the metabolic workup is another area to investigate. One hospital did not obtain diagnostic testing for an affected baby because its personnel simply assumed the child had the benign condition.

#### G. Delay in Diagnosis

Some babies with an IEM become symptomatic before the NBS results are received. A trip to the hospital emergency room with a sick infant who is lethargic, feeding poorly, breathing abnormally and/or vomiting will lead to a working diagnosis of rule-out-sepsis and -dehydration. ER doctors sometimes fail to recognize that this also is the classic presentation of a metabolic disorder. Sometimes, a physician will order a sepsis work-

---



---

up without considering a metabolic disorder, which should be ruled out *concurrently* by ordering some simple tests (for example, an ammonia level). For an ill infant with a metabolic disorder, every minute without diagnosis and treatment is critical.

It is important when investigating a claim of a missed IEM diagnosis to review the medical chart for findings inconsistent with dehydration (good skin turgor, normal capillary refill, moist mucous membranes) and sepsis (normal WBC, negative cultures, normal spinal tap) and consistent with a metabolic disorder (metabolic acidosis, ketones in urine, unusual body odor).

#### H. Failure to Establish/Follow Emergency Treatment Protocols

Children with IEMs should receive an emergency treatment protocol/letter to guide schools, first-responders, and hospitals when the child faces a rapid, life threatening metabolic decompensation, which is often triggered by a common viral illness.<sup>[16]</sup>

An emergency protocol is a document signed by an expert—usually a metabolic doctor—that outlines the initial steps necessary to stabilize someone with an IEM who is decompensating. It also must contain contact information for relevant experts. The doctor should also date and issue a new letter at least every year, since emergency providers may be less inclined to follow out-of-date letters.

Affected children and their parents should carry the letter with them. Usually the protocol is provided in advance to the child’s school and local hospital. It can be carried electronically and as part of a medical alert system. A treating doctor’s failure to provide an emergency letter to parents is clear substandard care for many types of IEMs.

Most doctors don’t know how to treat specific metabolic disorders. Consequently, without an emergency protocol letter, they may respond too slowly to a sick child, with catastrophic results. Sometimes the correct treatment is counterintuitive. The first response to almost any metabolic decompensation must include providing a large amount of dextrose. Because children with IEMs can crash so rapidly, a bolus and a large maintenance infusion are the rule *even for children with a blood glucose level within the laboratory reference range*. Emergency department providers, however, are quite resistant to providing massive glucose infusions to babies with a “normal” blood glucose level. Thus, a protocol letter or a call to the child’s treating metabolic doctor can be lifesaving.

Protocol deviation is an important area to investigate in cases involving children with IEMs, both to determine whether doctors provided a protocol (or an inadequate protocol) to the family and whether an emergency responder failed, without cause, to follow a valid protocol.

#### I. Administrative Error

Most NBS reporting is computerized, which minimizes the chance of error. There are

---

---

still occasions, however, when an abnormal NBS result is not communicated to medical providers or the family simply because there is a human mistake, as when a value is flagged as abnormal and the laboratory does not report it.

#### IV. CONCLUSION

Mistreated IEMs cause severe, lifelong injuries with a huge burden to affected individuals and their caregivers. Even old cases should be reviewed carefully since statutes of limitations typically are extended for minors, and most claims involving metabolic disorders will fall into one of the foregoing paradigms.

*Charles P. Hehmeyer and Martina W. McLaughlin practice at Raynes Lawn Hehmeyer in Philadelphia, Pennsylvania.*

---

- [1] Jean-Marie Saudubray et al., *Principles of Inborn Errors of Metabolism*, in Rudolph's Pediatrics 541 (Colin D. Rudolph et al. eds., 22nd ed. 2011).
- [2] Reid Sutton, Inborn Errors of Metabolism: Epidemiology, Pathogenesis, and Clinical Features, <https://www.uptodate.com/contents/inborn-errors-of-metabolism-epidemiology-pathogenesis-and-clinical-features/print> (last visited September 26, 2018).
- [3] Barbara K. Burton, *Inborn Errors of Metabolism in Infancy: A Guide to Diagnosis*, 102 Pediatrics, Vol. 6, at 1.
- [4] Iraj Rezvani et al., *An Approach to Inborn Errors of Metabolism*, in Nelson Textbook of Pediatrics at 634–35 (Robert M. Kliegman et al. eds., 20th ed. 2016).
- [5] *Id.* at 636.
- [6] U.S. Department of Health and Human Services' Recommended Uniform Screening Panel, *available at* <https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html> (last visited September 26, 2018).
- [7] Michael Waldholz, *A Drop of Blood Saves One Baby; Another Falls Ill*, Wall St. J., June 17, 2004, at A1.
- [8] For example, Arizona, Ariz. Rev. Stat. Ann. § 12-502; Colorado, Colo. Rev. Stat. § 13-81-103; Kentucky, Ky. Rev. Stat. Ann. § 413.170; Texas, Tex. Civ. Prac. & Rem. Code Ann. § 16.001; Utah, Utah Code Ann. § 78B-2-108; and Washington, *Schroeder v. Weighall*, 316 P.3d 482 (Wash. 2014).
- [9] Piero Rinaldo et al., *Acylcarnitine Profile Analysis*, 10 Genetics in Med. 151–56 (2008).
- [10] Ellen Gabler, *The Price of Being Wrong*, Milwaukee J. Sentinel, Dec. 9, 2016, *available at* <https://projects.jsonline.com/news/2016/12/11/the-price-of-being-wrong.html>.
- [11] *See, e.g., Block v. County of Person*, 540 S.E.2d 415 (N.C. App. 2000).
- [12] A large verdict for such a mistake occurred in *Cook v. Stanford Heath Svcs.*, Case No. 324905 (Cal. Super. Ct. 2003).
- [13] Ellen Gabler, *Delays at Hospitals Across the Country Undermine Newborn Screening Programs, Putting babies at risk of disability and death*, Milwaukee J. Sentinel, Nov. 16, 2013, *available at* <http://archive.jsonline.com/watchdog/watchdogreports/Deadly-Delays-Watchdog-Report-Delays-at-hospitals-across-the-country-undermine-newborn-screening-programs-putting-babies-at-risk-of-disability-and-death-228832111.html>.
- [14] For information regarding each state's newborn screening program, see <http://genes-r-us.uthscsa.edu/home>.
- [15] Newborn Screening Authoring Committee, *Newborn Screening Expands: Recommendations for Pediatricians and Medical Homes—Implications for the System*, 121 Pediatrics 192, 208–09 (2008).
- [16] William L. Nyhan et al., *Emergency Treatment of Inherited Metabolic Diseases*, in *Inherited Metabolic Diseases* at 125–31 (2d. ed. 2017).
-