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Answer Key appears on page e686.

The Newest Features and Future Direction of *NeoReviews*

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I am very excited to present this special issue to commemorate the 20th anniversary of *NeoReviews*. We begin with a perspective from Dr Alistair Philip, Editor-in-Chief from 2007 to 2017, on the past 20 years in neonatology. Then, Drs David Stevenson and William Hay Jr (the founders of *NeoReviews*), along with Ronald Wong, write about their expectations for the future of our specialty. This issue also contains state-of-the-art reviews about inborn errors of metabolism and several *NeoReviews* monthly features.

I want to take this opportunity to highlight some of the new features that *NeoReviews* has recently added and to describe the future direction of the journal.

In October 2018, *NeoReviews* launched "NeoQuest." Readers now receive an email mid-month containing a visual diagnostic challenge inspired by articles from that month's issue of *NeoReviews*. If you are a subscriber but are not receiving this email, please email us at NeoReviewsEditorial@aap.org.

As many of you know, since January 2019, *NeoReviews* articles have been included in MEDLINE and are searchable in PubMed. This indexing helps our content reach a broader audience of neonatologists, trainees, and NICU teams, beyond our 4,600 subscribers. It also enables *NeoReviews* authors to receive greater recognition for their contributions to neonatal-perinatal medicine.

In January 2020, we introduced a new feature—"Complex Fetal Care Cases." Articles in this series describe a case, starting from the referral to a fetal care center and include details about the patient's initial evaluation (emphasizing radiographic images), perspectives of multidisciplinary specialists, a summary of the fetal and neonatal outcomes, and a review of the diagnosis. For those fellows and neonatologists who practice at a hospital with a fetal care center, these articles provide insight about approaches at other centers, and for those who do not have the luxury of a nearby fetal care center, the series offers insights into these evaluations.

For the past 2 years, we have published a "Video Corner" piece every other month. We have recently broadened the scope of these videos beyond procedures to include clinical findings, diagnostic studies, and therapeutic interventions. We have also added a new feature to our site—"NeoVideos"—which contains a systems-based collection of videos from *NeoReviews* as well as other resources for both teaching and learning.

I am also pleased to note that the American Academy of Pediatrics has published 2 books based on content from *NeoReviews*. *Challenging Cases in Neonatology*, published in June 2018, contains a collection of rare diagnoses and unusual clinical manifestations of common conditions. These cases originate from "Visual Diagnosis" and "Index of Suspicion in the Newborn Nursery," with accompanying commentaries and, when available, follow-up of cases. *Questions from NeoReviews: A Study Guide for Neonatal-Perinatal Medicine* was published

AUTHOR DISCLOSURE Dr Brodsky is the Editor-in-Chief of *NeoReviews*. Dr Brodsky has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

in January 2020 and contains approximately 1,200 questions, with explanations that are organized by systems, to assist with both board review and professional development.

So where is *NeoReviews* headed? In addition to continuing to publish state-of-the-art reviews and noteworthy clinical cases, we plan to offer infographics and podcasts that highlight these articles. We anticipate publishing a new feature focused on outcomes of NICU graduates. We are exploring the possibility of creating a visual library for easier access to photographs and radiographs that we have published over the past 20 years. We also plan to collate the NeoQuest content to make it available on our website. As always, we would like to hear from you, at NeoReviewsEditorial@aap.org, with suggestions for new initiatives.

I have been honored to follow former Editor-in-Chief Alistair Philip, and I look forward to maintaining his high standards and visionary approach to the journal. It has been an honor and privilege to work alongside such an incredibly bright, hard-working, and dedicated editorial board. The staff at the American Academy of Pediatrics has also been instrumental to the success of our journal. With this foundation, I anticipate that *NeoReviews* will continue to be a valuable educational resource for health care professionals in neonatology.

Dara Brodsky, MD
Editor-in-Chief, *NeoReviews*

Anniversaries

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Although events occur in every year, we tend to concentrate on (or attach special significance to) those years which end in a zero, largely because they end (or possibly start) a decade, a century, or even a millennium.

Since this is 2020, we have reached the 20th anniversary of the publication of *NeoReviews* as an online-only journal (6 issues were published jointly with *Pediatrics in Review* at the end of 1999). This makes us think about where we have come from and where we might be going. At this point in my life, I am more inclined to reflection than to prognostication and offer some thoughts on important events that made an impact on me and my colleagues in medicine during my lifetime.

1960

This was the start of my final year at medical school, which clearly was an important time for me personally. However, the more important event that deserves recognition is that this was the year of publication of the first edition of the text by Alexander Shaffer entitled *Diseases of the Newborn* (which later became Shaffer and Avery). (1) In the introduction to his book, he hoped to be forgiven for coining the terms "neonatology" and "neonatologist." These terms are now used so frequently that it is difficult to appreciate that they were not in general use before that time.

1970

This was the year that the proceedings of a conference on assisted ventilation held in Paris were published in *Biologia Neonatorum* (which later became *Biology of the Neonate* and more recently became *Neonatology*). (2) The conference was actually held in 1969 and was organized by Professor Alex Minkowski, with whom I spent 3 months around the time that the conference was held. I was therefore privileged to be a participant in that conference and to hear discussion concerning this "new" approach to respiratory distress syndrome (RDS; hyaline membrane disease). There was considerable concern that we might be heading in the wrong direction as bronchopulmonary dysplasia secondary to assisted ventilation had been described a couple of years earlier by Northway et al. (3) The results from around the world suggested that this approach was likely to be more beneficial than harmful. At this time, it is hard to imagine that there was so much concern, but it was very real back then.

A couple of other things of major importance that occurred in this year were the publication of articles that documented the importance of parent–infant interaction (emphasis on maternal-infant interaction) by Klaus and Kennell, (4) as well as consolidation of methods for assessing gestational age, which resulted in the Dubowitz score. (5)

On a personal note, I became the first neonatologist in Hawaii, being on call 24 hours a day, 7 days a week! In that capacity, I was fortunate to welcome Bill Tooley

AUTHOR DISCLOSURE Dr Philip is Emeritus Editor-in-Chief of *NeoReviews*. Dr Philip has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

as a visiting professor (from San Francisco) and learned about (and began to use) continuous positive airway pressure, a description of which was published in the following year. (6)

1980

Another person who came to Hawaii (in 1971) as a visiting professor was Jerry Lucey, who became Editor-in-Chief of *Pediatrics* in 1974, the same year that I joined him in Vermont. In 1979, the first report of the use of head ultrasonography to detect intracranial pathology (particularly intraventricular hemorrhage) in neonates had been published. (7) In 1980, Jerry organized the first of 2 conferences on intracranial hemorrhage in Washington, DC, with several international participants. This conference had a different format for that era in that a considerable amount of time was allotted to general discussion. In subsequent years, this morphed into the annual "hot topics" conference, which drew larger and larger audiences with each passing year.

Perhaps of even greater significance, 1980 was also the year when the use of artificial surfactant to successfully treat RDS was reported by Fujiwara and colleagues in Japan. (8) This led to further evaluation of several different surfactants in multicenter trials in both North America and Europe.

1990

The Food and Drug Administration approved the use of Exosurf (an entirely synthetic product) at the end of 1990 and the following year approved Survanta (like the Japanese surfactant, it was derived from a bovine source). In Europe and Scandinavia, the main product was Curosurf.

While neonatologists were basking in new-found success in treating RDS, pediatric surgeons were beginning to have success in repairing diaphragmatic hernia before delivery. (9)

2000

NeoReviews becomes an online-only journal.

2010

To commemorate 10 years of publication, a collection of historical perspectives concerning seminal contributions in neonatal-perinatal medicine, which had been published in *NeoReviews* in earlier years, were published in book form as *Milestones in Neonatal/Perinatal Medicine*. (10).

In this brief retrospective it is only possible to touch on a few important contributions. For a more detailed consideration of how neonatology evolved, I refer you to my previous discussion of the topic. (11) I believe that during the last 20 years, *NeoReviews* has provided a useful resource for staying abreast of advances in our field, and I congratulate the current editor, who took the helm in 2017, on leading us into the next decade.

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Comments on the 20th Anniversary of *NeoReviews*

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In his introduction, "*Anniversaries,*" Alistair G.S. Philip, the editor of *NeoReviews* until 2017, reminisces about the 1960s to 1990s, highlighting various advances that long ago became a part of the scientific and professional sediment in our field. However, all of these recollections preceded the inception of the all online journal, *NeoReviews*, one of the first of its kind. At the journal's 10th birthday, Alistair assembled a collection of "seminal contributions" in neonatal-perinatal medicine that had been published in *NeoReviews*, (1) which were then subsequently published in a book, *Milestones in Neonatal/Perinatal Medicine*. (2) Moreover, Alistair's masterful and judiciously thorough recounting of the history of our field of neonatology was published in 2005, entitled "*The Evolution of Neonatology.*" (3) In this commentary, we wish to acknowledge Alistair's dedication in informing his readership about the scientific and clinical advances in neonatology. Here, we offer our own perspective on what has transpired over the last 20 years of *NeoReview's* life, but with an eye toward the future.

As Alistair has pointed out, the subfield of newborn medicine evolved within general pediatrics sometime in the late 1940s and 1950s, an unusual, but remarkable, legacy from Martin A. Couney and Pierre-Constant Budin and their "incubator babies" sideshows at amusement parks, world fairs, and exhibitions. (4) The term "*neonatology*" itself, however, was not introduced until 1960 by Alexander Schaffer (5) in close timing with the advent of intensive care nurseries, which were more than just special facilities for preterm infants. The original research defining the nascent field focused on thermoregulation, nutrition, and growth of a neonate, quickly distinguishing neonatology from general pediatrics because of the unique requirements of the newborn, especially the preterm infant. As survival of preterm infants increased over subsequent decades, advances in cardiorespiratory support and in the diagnosis and treatment of infection naturally followed, not only leading to further overall decreases in mortality and morbidities but also bringing into respite some morbidities that have persisted to this day. In particular, bronchopulmonary dysplasia (BPD), (6) intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) remain 21st century "scourges" affecting the smallest of our patients in the NICU. While advances in our understanding of fuel and waste fluxes between the pregnant mother and fetus provided scientific rationale for newborn nutrition and growth and have continued to inform our practice of newborn medicine, other advances are suggesting how we might improve outcomes further. We have learned how to use oxygen (O_2) more judiciously and avoid intubations and positive pressure ventilation by using less invasive respiratory assistance to lessen the risk of ROP (7)(8) and BPD. (9) In addition, we have learned how to use postnatal corticosteroids more judiciously in our most immature infants, to avoid adverse side effects and improve their transitional physiology. (10) We have also learned how to use inhaled nitric oxide to assist in the management of pulmonary hypertension and avoid extracorporeal membrane oxygenation in our larger and more mature patients. (11) Furthermore, we have learned how to monitor our neurologically at-risk patients more effectively with near-infrared spectroscopy and amplitude electroencephalographic monitoring,

AUTHOR DISCLOSURE Drs Stevenson and Hay are inaugural coeditors of *NeoReviews*. Drs Stevenson, Wong, and Hay have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

(12)(13) and how to ameliorate hypoxic-ischemic brain injury with cooling techniques (14)(15) and new pharmacologic approaches. (16) Finally, we have developed a better sense of when performing a laparotomy might be a better option than drainage in the context of NEC or an isolated spontaneous intestinal perforation, (17) and we have made some progress in understanding the role of microbes in the intestinal dysbiosis associated with NEC. (18) We also have moved beyond some practices that were downright damaging, such as postural drainage percussion that caused fractures and brain injury. (19)

Despite these notable advances in care based on clinical studies, the NICU scourges noted earlier persist at almost the same rates over the last 2 decades. In fact, disparities in outcomes also persist among our patients and institutions, which might be explained in part by disparate practices at our respective institutions, possibly amenable to quality improvement processes, but perhaps also rooted in the actual causes of the various conditions that we encounter mostly in our extremely preterm patients. (20) Thus, the future of our field will likely increasingly depend on us having a better understanding of how the inherited genetic capacity of a fetus or newborn is "exercised" in response to an exposome. This would begin for the fetus through the pregnant mother and would include not just biological determinants of the pregnancy, such as infection, nutrition, and exposures to toxins, but also demographic, psychosocial, and physical factors—all of which have been shown to influence pregnancy outcomes, both maternal and neonatal.

Recently, there has been a revolution in the types of omic measurements: genomic, epigenomic, transcriptomic, proteomic, metabolomic, lipidomic, immunomic, and microbiomic. (21) All of the technical advances in these measurements are affording new ways to describe how a pregnant mother and fetus adapt to each other and how various stressors may affect a particular pregnancy. Integration of these omics is providing not only new insights into the causes of preterm birth, (21) preeclampsia, (22) and other complications of pregnancy, (23) but also may reveal novel ways of preventing (or at least ameliorating) such complications. Moreover, these same measurement tools, when used in various combinations, will likely provide the basis for plausible hypotheses about the causation of conditions that are still plaguing our smallest and most immature patients; this will set the stage for clinical studies to reduce and finally eliminate their occurrence. Because most of the conditions are oxidative or inflammatory in nature and involve dysregulated responses of the mother, fetus, or newborn, it is likely that a better understanding of immune responses, innate and adaptive, will help identify gene pathways that would be accessible to targeted pharmacologic interventions to avoid tissue injury and dysregulated development in the newborn. (23) Indeed, there might even be advantages that add to a woman's health, because prevention of preeclampsia could also prevent later cardiovascular disease in women with a history of preeclampsia. (24) Improving the health of the young mother, still too many of whom are teenagers, has major potential for improving her health during and after pregnancy as well as the health of her infant. Reducing obesity and type 2 diabetes and promoting a healthy diet before and during pregnancy are strong examples. (25) For newborn medicine, new and improved approaches of protection for the brain, eye, lung, and gut of neonates, based on fundamental discoveries and clinical trials, should be our goal over the next 20 years.

As we look toward the future, it is therefore important to emphasize how little is certain. There are in fact very few "on/off" switches; things change. Continued research and application of basic biological principles will be fundamental for solving the problems that exist and those yet to come. First, we need to correct mistakes and misconceptions that continue to drag us backward, not forward. For example, many concepts and practices persist that are simply downright wrong, such as the notion that preterm infants cannot tolerate the same amount of essential nutrients that the healthy growing fetus of the same gestational age does. It also is remarkable today, over half a century since Battaglia and Lubchenco noted that normal infants are small, average, and large for gestational age. (26) We define postnatal growth failure as a weight below some arbitrary weight-for-age percentile rather than a growth rate that does not match the growth rate of the normal healthy human fetus over the same period of gestation that we care for preterm infants. This is not because we do not use the right growth chart. All show the same average fractional growth rate of about 17 g/kg per day of the healthy fetus and what should be the same for the preterm infant of the same gestational age. In relation to such misinterpretations of growth, there is no evidence that catch-up growth is necessary and beneficial; nutrition that promotes normal growth rates is what is needed. For the preterm infant, aggressive nutrition is important to prevent poor growth and development and to achieve normal growth but should not be interpreted as excessive nutrition. An overabundance of body fat is not a healthy outcome.

Many opinions also persist that are simply not supported by facts, for example, the notion that glucose concentrations below some arbitrary, yet still very common value are always damaging to the brain. We still do not know how to define pathological hypoglycemia in newborn infants. Why? In large part because, while brain glucose uptake and metabolism are

directly related to plasma glucose concentration, unfortunately, the correlation between plasma glucose concentration and the consequences of insufficient brain glucose uptake and metabolism are weak. Circulating glucose concentrations are just not a good measure of the impact of insufficient brain glucose uptake and metabolism on neuronal function, neuronal viability, irreparable neuronal damage, or longer term potentially adverse neurodevelopmental outcomes. We still rely on intermittent measurements of plasma or blood glucose measurements to guide less than rigorously defined practice. We do so because we still do not have simple bedside clinical measures of brain glucose uptake and metabolism and directly related neuronal function and viability for the measure of circulating glucose concentration to be useful. We also do not have bedside measures for brain uptake or metabolism of oxygen or any of the several alternative sources of carbon for oxidation and energy production (eg, stored glycogen, lactate, ketones, amino acids). We really do not even have, other than by statistical approaches, good definitions of what is normal glycemia in neonates. The guidelines from the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) provide some help by trying to establish lower limits for routine management of infants with low glucose concentrations. (27) However, to date no prospective, randomized, controlled study has shown that glucose concentrations below these lower limit values, or for how long, consistently determines transient or permanent neurologic injury. The AAP and PES approaches have not been compared in clinical research trials to determine if one, both, or neither reduces adverse neurodevelopmental outcomes because of "significant" hypoglycemia. There has been no substantial evidence-based progress in defining what constitutes clinically significant but transient neonatal hypoglycemia. No evidence-based study has identified any specific plasma glucose concentration (or range of glucose values, or the duration of a potential or even actual pathological value or range of values) to define pathologic "hypoglycemia, and thus at what glucose concentrations interventions [*and which ones, when, and how*] should be initiated."(28) Clearly, there is still much work to be done to resolve what should be one of the most common "problems" in neonatal medicine.

Second, we need to correct misadventures. These are legion. We still overuse O_2 therapy and we continue to produce more ROP than should be tolerated. We do this despite the universal application of pulse oximetry to noninvasively monitor blood O_2 levels. This technology has become the fifth vital sign everywhere, yet there is little evidence that it has improved any single practice or reduced any single pathology. In fact, its application has documented clearly that frequent hypoxic episodes continue in nearly all preterm infants with still uncertain impact on their development. The many national and international studies of oxygen administration to preterm infants that relied on pulse oximetry O_2 saturation (SpO_2) measurements in fact showed that higher values produced more ROP; however, lower values that reduced the incidence of ROP were associated (still cause unknown) with greater risk of mortality. (29) Remarkably, we still do not know which value or range of values of blood oxygenation, whether measured by SpO_2, arterial O_2 saturation, transcutaneous O_2 levels, or arterial O_2 levels, is the one that produces the least damaging impact of O_2 toxicity or the best amount of O_2 for growth and development of all cells in the growing preterm infant. (30)

A further cautionary note on a topic that still accounts for one of the most common problems that pediatricians encounter—neonatal jaundice. We know, without a doubt, that high levels of bilirubin in the circulation of newborns, most often (but not always) in the context of hemolysis or other causes of increased bilirubin production, is associated with an increased risk for permanent brain injury, otherwise known as kernicterus (or chronic bilirubin encephalopathy). (31) However, we still do not know exactly how the mechanism of bilirubin-related neurologic injury occurs in some individuals. It is most likely related to unbound bilirubin that can move easily through membranes and into brain tissue, when binding capacity is exceeded, and especially under relatively acidic conditions. (32) Ironically, even though bilirubin itself is a powerful antioxidant, (33)(34) the underlying cause of the bilirubin-induced injury may be oxidative in nature, like many of the other injurious conditions plaguing the newborn. More research on this topic is desperately needed—and the apparent vulnerability of infants with glucose-6-phosphate dehydrogenase deficiency to bilirubin encephalopathy, if understood, might provide some important insights into the mechanism of bilirubin-related injury more generally. Nonetheless, we have learned that phototherapy, long thought to be safe, might also be injurious to our smallest, most immature, and most transparent patients, causing increased mortality, possibly once again through an oxidative injury (likely photo-oxidative, though the mechanism has not been proven), while still providing protection from bilirubin-related injury among survivors. (35) This clinical trial comparing an aggressive versus conservative approach to phototherapy revealed this provocative dilemma, and reminded us about the dangers of overgeneralization, echoing the admonition of Andersen et al. (36) This worrisome finding needs to be confirmed, but more importantly, alternative ways to apply phototherapy, such as being cycled, should be tested more thoroughly. (37) Ideally, an innovative approach that is within practical grasp would be to screen newborns for evidence of

increased bilirubin production using carbon monoxide detection in end-tidal breath or blood (carboxyhemoglobin)(38) and then treating high producers of the pigment (or perhaps all extremely low-birthweight infants) with a safe inhibitor of bilirubin production, such as zinc protoporphyrin. Zinc protoporphyrin is a naturally occurring protoporphyrin, which is not photosensitizing (unlike others that have been introduced for clinical testing) and is metabolizable and short-acting. (39)(40) Besides addressing the pressing problem of hyperbilirubinemia in extremely low-birthweight infants, such an approach would revolutionize care of newborns with jaundice around the world and reduce injury and death among the most vulnerable populations everywhere.

Other misadventures continue. We still try every possible approach to use steroids for nearly everything, but particularly chronic lung disease, despite the evidence that this practice is associated with exacerbated neuropathology. We also have used antibiotics for whatever ails patients, with an overgrowth of resistant organisms seen in nearly every NICU and hospital (and also perhaps point out that preterm birth is not an antibiotic-deficient disorder). We continue to use a lot of diuretics; calcium and phosphorous deficits, shorter bones and thus shorter adult stature, and even rickets are still with us as a result.

We still need to solve and thereby get rid of problems that are still with us, not just optimize our treatments:

- Preterm birth
- Neurodevelopmental limitations
- Intrauterine and postnatal under- and overgrowth
- Respiratory distress syndrome
- Chronic lung disease
- Intracranial hemorrhage
- Patent ductus arteriosus
- NEC
- Hypoxic-ischemic encephalopathy
- Cerebral palsy
- Maternal-infant separation
- Genetic disorders of all kinds
- Inflammatory disorders

The list could go on. We would be remiss, for example, if we did not note how unprepared we have been for the recent scourge of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its devastating disease, COVID-19. To date, while this pandemic has wreaked havoc around the world with death and disease, it has fortunately affected few neonates. It has not, though, spared neonatologists and their colleagues in obstetrics who have had to care for—with great effort—both mother and infant. This disease among many others is a stark reminder that we do not know what will come next. It also is a fundamental reminder that mothers and their infants are a unit; one does not exist without the other, and as neonatologists, we must focus on the perinatal aspect of our field. (41)

Such problems—scourges—continue to cause damage to preterm infants. But as Barker so remarkably demonstrated, (42) the pathology caused by these and many other disorders, and all too often their treatments, has major adverse impact on the later life health and prosperity of preterm infants. They have short stature later in life; they develop obesity and insulin resistance and type 2 diabetes associated with cardiovascular disease; and their intellectual development lags behind that of normal healthy infants born at term. These later life conditions produce a huge burden of disease and exponentially increased financial costs over the lifespan and life course of these infants. (43) Solving the many problems that injure and damage preterm infants has even greater potential therefore to improve their health, their lives in all respects, their productive contributions to their families and to society, and not the least, greater potential for passing on greater health to the next generation.

In summary, the last 20 years have been productive, and mothers and infants are generally better off than they were 20 years ago. However, there is still much more to be done on behalf of neonates. We hope that *NeoReviews* continues to feature the practical advances in our field while keeping us informed about the relevant fundamental science that has always been the wellspring for newborn care. Neonatology has always been at the forefront of technical innovations and more recently, evidence-based improvements in our practice since our checkered beginnings with nonexperimental empiricism and faulty expert opinions. It is likely that some of the latter influences will continue; however, we hope that fundamental discoveries in the developmental sciences and well-designed clinical trials will dominate our future.

There still is a lot of great work to do. As so eloquently expressed in 1902 by H.G. Wells (44):

> *"It is possible to believe that all the past is but the beginning, and all that is and has been is but the twilight of the dawn. It is possible to believe that all the human mind has ever accomplished is but the dream before the awakening."*

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the definition, risks to the fetus and/or newborn infant, and management of post-term pregnancy.

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Neonatal Presentations of Metabolic Disorders

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Practice Gaps

1. Metabolic acidosis or primary respiratory alkalosis can be an early sign of neonatal hyperammonemia.
2. Metabolic disorders in a neonate can involve any organ system and can be challenging to diagnose.
3. Early detection of treatable metabolic conditions is important for prognosis.
4. A normal newborn screening result does not exclude a metabolic disorder.

Abstract

Metabolic disorders in a neonate can present with involvement of any organ system and can be challenging to diagnose. A newborn can present with an acute metabolic crisis such as hyperammonemia or seizures needing immediate management, with a more chronic clinical picture such as cholestatic liver disease, or with structural abnormalities such as skeletal manifestations. Early detection of treatable metabolic conditions is important to improve outcomes. Newborn screening has facilitated early detection and initiation of therapy for many metabolic disorders. However, normal testing does not rule out a metabolic disorder and a high index of suspicion should remain when caring for any critically ill neonate without a diagnosis. Whole exome sequencing (WES) or whole genome sequencing (WGS) can be powerful tools in rapid diagnosis of a potentially treatable metabolic condition in a critically ill neonate. This review presents classic clinical presentations of neonatal metabolic disorders and also highlights some uncommon neonatal manifestations of metabolic disorders to improve the recognition and diagnosis of these conditions.

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ABBREVIATIONS

FAOD	fatty acid oxidation defect
FTT	failure to thrive
HFI	hereditary fructose intolerance
HIE	hypoxic-ischemic encephalopathy
IUGR	intrauterine growth restriction
LPI	lysinuric protein intolerance
MMA	methylmalonic acidemia
MRI	magnetic resonance imaging
NBS	newborn screening
PA	propionic acidemia
RUSP	Recommended Uniform Screening Panel
WES	whole exome sequencing
WGS	whole genome sequencing

Objectives

After completing this article, readers should be able to:

1. Recognize the need to order a serum ammonia evaluation in a neonate with an unexplained metabolic acidosis or respiratory alkalosis.
2. Recognize that a variety of symptoms such as a history of fetal hydrops, hypoxic-ischemic encephalopathy, cardiomyopathy, liver failure, cholestatic liver disease, skeletal dysplasia, or *Escherichia coli* sepsis can be a clue to a metabolic disorder.
3. Describe treatable metabolic disorders that present during the neonatal period.

INTRODUCTION

Inborn errors of metabolism, also known as biochemical genetic disorders or metabolic disorders (referred to as such in this article), are a group of thousands of rare genetic conditions that can present at any age from the fetal period to adulthood and can involve multiple organ systems. (1)(2)(3) Neonatologists may only see a handful of newborns with metabolic disorders during their career. Although there is no effective treatment for some metabolic disorders and the prognosis can be poor, some conditions can be effectively managed with dietary modifications, medications, supplements, or organ transplantation. Early detection of these treatable conditions is important to improve outcomes. Therefore, neonatologists should have a high index of suspicion for a metabolic disorder in any critically ill neonate with an unusual or unexplained presentation. Newborn screening (NBS) has facilitated early detection and initiation of therapy for many metabolic disorders. However, a normal test result does not rule out a metabolic disorder, and a high index of suspicion should remain when caring for any critically ill neonate without a diagnosis.

The purpose of this review is to summarize the classic clinical presentations of neonatal metabolic disorders as well as to highlight some uncommon neonatal manifestations of metabolic disorders to improve recognition of these conditions. In this review, we focus on manifestations of these disorders during the neonatal period; clinical presentations after this period are beyond the scope of this review. We will discuss symptoms that can indicate a metabolic disorder rather than listing metabolic disorders and their clinical presentations. We present several examples of metabolic disorders related to each clinical finding. For a comprehensive list of metabolic disorders associated with each clinical sign, the reader is encouraged to refer to more comprehensive publications, many of which are referenced here.

NEONATAL HYPERAMMONEMIA AND METABOLIC ACIDOSIS

In neonates, classic scenarios in which a metabolic disorder is more likely include those in which a neonate has severe metabolic acidosis with an anion gap, lactic acidosis, or hyperammonemia, which can also occur together. Severe metabolic acidosis with an anion gap occurs when a nonvolatile acid accumulates as a result of a block in a metabolic pathway. An anion gap metabolic acidosis is typical in neonates with organic acidemias such as methylmalonic acidemia (MMA) and propionic acidemia (PA) as well as mitochondrial disorders in which lactic acid accumulates.

Neonatal hyperammonemia results from either a primary or secondary defect in the urea cycle, which is responsible for converting ammonia that is produced during protein metabolism into blood urea nitrogen, which is then excreted by the kidneys. Neonates with primary defects in the urea cycle such as ornithine transcarbamylase deficiency typically do not present with metabolic acidosis but rather, have primary respiratory alkalosis resulting from tachypnea. This tachypnea is thought to be caused by stimulation of the central nervous system respiratory center by the ammonium ion. (4)(5) In a neonate with hyperammonemia and a primary respiratory alkalosis (pH >7.45, low partial pressure of carbon dioxide [P_{CO_2}]), urea cycle defects are highest on the differential. Neonatal hyperammonemia with severe metabolic acidosis is a typical presentation of organic acidemias such as MMA, PA, and isovaleric acidemia. (6)(7) Neonates with fatty acid oxidation defects (FAOD) may also present with neonatal hyperammonemia and often have a history of low/undetectable serum glucose. If the later is true, lipid administration should be avoided pending diagnosis. Mitochondrial disorders are a less common but possible cause of neonatal hyperammonemia and should be considered if there is a

TABLE 1. **Metabolic Etiologies and Laboratory Evaluation of Neonatal Hyperammonemia**

	ACIDOSIS VS ALKALOSIS	ETIOLOGY[a]	COMMENTS	DIAGNOSTIC/HELPFUL BIOCHEMICAL LABORATORY STUDIES
Neonatal hyperammonemia[a]	Metabolic acidosis (increased anion gap)	Organic acidemias	• Anion gap acidosis is severe	• Urine organic acids (diagnostic)
		• MMA	• MMA: often lactic acidosis	• Plasma acylcarnitines
		• PA	• PA: at risk for cardiomyopathy	• Plasma total and free carnitine (secondary carnitine deficiency)
		• Isovaleric acidemia		• Plasma amino acids
		• Multiple carboxylase deficiency		• Serum/plasma MMA level
		• Multiple acyl-CoA dehydrogenase deficiency		• Serum lactic acid
		• 3-Hydroxymethylglutaryl-CoA dehydrogenase deficiency		• High BUN
		• 3-Methylcrotonyl-CoA carboxylase deficiency		• Gene sequencing[b]
		Mitochondrial disorders	See "Other" for features and diagnostic studies for mitochondrial disorders	
	Respiratory alkalosis (primary)	Urea cycle defects	• Typically very low BUN	• Plasma amino acids
		• NAGS deficiency	• Hyperammonemia typically severe in NAGS, CPS, OTC and ASS deficiency	• Urine orotic acid
		• CPS deficiency	• Hyperammonemia not very common in arginase deficiency	• Urine organic acids (orotic)
		• OTC deficiency		
		• Argininosuccinate synthetase deficiency (citrullinemia)		
		• Argininosuccinate lyase deficiency		
		• Arginase deficiency		
		Amino acid transporter deficiencies	• Only a minority of patients with HHH or LPI do not present during neonatal period	• HHH and LPI: plasma amino acids, urine amino acids
		• HHH syndrome		
		• LPI		
		• Transient hyperammonemia of the newborn	• Typically <36 weeks' gestational age, birthweight <2.5 kg, respiratory distress, presents <24 hours after birth	• Typical diagnostic metabolites of urea cycle or other disorders are not present
			• May be severe and require ammonia scavengers and/or dialysis	

Continued

TABLE 1. (Continued)

ACIDOSIS VS ALKALOSIS	ETIOLOGY[a]	COMMENTS	DIAGNOSTIC/HELPFUL BIOCHEMICAL LABORATORY STUDIES
Other[c]	Fatty acid oxidation defects	• Often severe hypoglycemia on initial presentation	• Plasma acylcarnitine profile
	• Carnitine transporter deficiency	• Risk of cardiomyopathy and cardiac arrhythmias	• Plasma total and free carnitine
	• Carnitine palmitoyl transferase 2 deficiency		• Urine organic acids
	• Carnitine acylcarnitine translocase deficiency		• Gene sequencing[b]
	• Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency		• Enzyme assay from fibroblasts[d]
	• Very-long-chain acyl-CoA dehydrogenase deficiency		
	Mitochondrial disorders	• Severe lactic acidosis, multisystem involvement	• There are currently no diagnostic biochemical markers for mitochondrial disorders
	• Mitochondrial DNA defects		• Genetic testing or enzyme analysis may lead to diagnosis
	• A defect in one of the multiple nuclear mitochondrial genes		
	Pyruvate carboxylase deficiency	• Lactic acidosis, ketosis, hypoglycemia, FTT, seizures	• Plasma amino acids
			• Gene sequencing
	HIHA	• Fasting or protein (leucine) sensitive hypoglycemia	• High insulin
			• Gene sequencing

ASS= argininosuccinate synthetase; BUN=blood urea nitrogen; CoA=coenzyme A; CPS= carbamyl phosphate synthetase; FTT=failure to thrive; HHH= Hyperornithinemia-hyperammonemia-homocitrullinemia; HIHA=hyperinsulinism/hyperammonemia syndrome; LPI= lysinuric protein intolerance; MMA=methylmalonic acidemia; NAGS=N-acetylglutamate synthetase; OTC=ornithine transcarbamylase; PA=propionic acidemia.

[a]This is not a comprehensive list of all possible causes of neonatal hyperammonemia. For example, liver failure, portocaval shunt, and bacterial colonization with urease-positive organisms may also lead to hyperammonemia. This table lists the most common metabolic causes of neonatal hyperammonemia.

[b]Gene sequencing is typically done after a diagnosis has already been made via biochemical testing for confirmation and genetic counseling.

[c]These conditions can present with either metabolic acidosis or respiratory alkalosis depending on other contributing factors such as sepsis or dehydration, but often neither metabolic acidosis nor respiratory alkalosis have the same degree of severity as do organic acidemias or urea cycle defects, respectively.

[d]Skin biopsy for fibroblast culture and subsequent enzyme assay from fibroblasts may be necessary in cases in which biochemical and genetic testing do not provide a definitive diagnosis.

concurrent severe lactic acidosis. Neonates with organic acidemias, especially MMA, can also have lactic acidosis because of secondary mitochondrial dysfunction (8)(9)(10); however, typically this acidosis is not as significant as that seen in patients with a primary mitochondrial disorder. Table 1 provides a list of conditions that may present with neonatal hyperammonemia and diagnostic or helpful biochemical laboratory studies that should be performed while initiating therapy.

Treatment of neonatal hyperammonemia is beyond the scope of this review; however, keys to management, briefly, are as follows:

- Provision of energy in the form of carbohydrate and lipids to promote anabolism. Unless FAOD is suspected in which case lipids should be avoided.
- Insulin administration if hyperglycemia develops
- Correction of dehydration
- Central catheter for high dextrose (>12.5%) concentration intravenous fluids and frequent blood sampling
- Administration of an intravenous ammonia scavenger (eg, sodium benzoate/sodium phenylacetate)
- Hemodialysis or continuous renal replacement therapy, in some cases, to rapidly decrease ammonia levels

For further review of the management of hyperammonemia, we refer the reader to publications focused on the management of neonatal hyperammonemia. (6)(11)(12)(13)(14) Hyperammonemia is one of the most common neonatal presentations of metabolic disorders that will go undetected unless the ammonia level is checked. A timely diagnosis and initiation of therapy to lower ammonia levels are vital for prognosis.

FETAL MANIFESTATIONS OF NEONATAL METABOLIC DISORDERS

Nonimmune Fetal Hydrops

Because of early diagnosis and treatment of rhesus (Rh) isoimmunization, nonimmune causes now account for the majority of fetal hydrops cases. (15)(16) Metabolic disorders account for about 1% to 15% of nonimmune fetal hydrops. (15)(16)(17) In particular, patients with storage disorders such as mucopolysaccharidosis type VII (Sly syndrome), Gaucher disease, infantile galactosialidosis, and transaldolase deficiency can present with fetal hydrops. In a fetus with hydrops or a neonate with a history of fetal hydrops, a metabolic cause should be sought if more common conditions such as fetal anemia, an infection, a chromosomal disorder, and cardiac abnormalities have been ruled out. A metabolic disorder should also be considered if nonimmune hydrops is also associated with other features of storage disorders such as a large placenta, hepatosplenomegaly, or coarse features.

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR) has multiple etiologic factors, ranging from placental insufficiency to chromosomal/genetic and infectious causes. Metabolic disorders that can lead to IUGR include mitochondrial disorders (energy deficiency), peroxisomal disorders, disorders of cobalamin metabolism, and cholesterol biosynthesis defects. Typically, however, IUGR is not the only clinical manifestation of these conditions.

In the following sections, several clinical findings are presented based on organ systems; if the reason for these findings is unknown, the clinician should consider a metabolic disorder. Some of the clinical findings presented often have a fetal origin and may be detected prenatally, especially those that involve structural changes.

NEUROLOGIC

Encephalopathy

Neonatal encephalopathy is defined as abnormal brain function in a newborn manifested by decreased level of consciousness and responsiveness, such as a poor suck. Hypoxic-ischemic encephalopathy (HIE) is among the most common causes of neonatal encephalopathy. Metabolic disorders can manifest similarly to, and mimic, HIE. (18) In general, neonates with HIE are symptomatic since birth whereas newborns with metabolic disorders typically become symptomatic after an initial normal period. However, some metabolic disorders, such as mitochondrial disorders, may potentially cause a lower tolerance of stress during labor and the affected neonate may present with a clinical picture similar to HIE.

Neonatal seizures, as a result of metabolic disorders, may also cause neonatal encephalopathy and manifest immediately at birth (see next section). Brain magnetic resonance imaging (MRI) may help distinguish between HIE and metabolic causes of encephalopathy because HIE causes typical radiographic patterns of brain injury. (19)(20)(21) A metabolic cause should be considered in cases of neonatal encephalopathy if an acute perinatal event is absent (making HIE less likely), symptoms started after an initial normal period, or seizures persist without an intracranial abnormality. Neonatal hyperammonemia and related conditions (Table 1), maple syrup urine disease, and conditions that cause neonatal seizures (Table 2) should be considered when metabolic causes of neonatal encephalopathy are being considered.

Seizures

Most neonatal seizures are caused by acute brain injury, and brain MRIs can often determine the cause (eg, structural brain abnormality, intracranial bleeding, HIE). (22)(23) However, brain MRI findings in some metabolic disorders, such as molybdenum cofactor deficiency, can mimic that of HIE. (24)(25) Table 2 lists metabolic causes of neonatal seizures with treatable or potentially treatable conditions marked with an asterisk. Most of the time, however, therapy should be initiated before the onset of symptoms or very early in the course of symptoms (preferably before brain MRI findings are apparent) such as in molybdenum cofactor deficiency and serine biosynthesis defects. (26)(27)(28) Treatment before the onset of symptoms can be possible for disorders detected on NBS or if a diagnosis has been made prenatally (eg, because of a history of metabolic disorder in a previous child). Metabolic disorders should be strongly considered if the brain MRI in a neonate with

TABLE 2. **Metabolic Causes of Neonatal Seizures**

Neonatal seizures	Typically present with isolated neonatal seizures	Cerebral folate deficiency (cerebral folate receptor gene *FOLR1*)*
		Creatine metabolism disorders (various genes)*
		Folinic acid responsive seizures*
		Glycine Encephalopathy (also known as non-ketotic hyperglycinemia)[a,*]
		Glucose Transporter (GLUT1) deficiency*
		Molybdenum cofactor deficiency (3 genes)[b,*]
		Pyridoxal (activated B6) responsive seizures (pyridoxal phosphate-binding protein gene *PLBP*, pyridoxamine 5-prime-phosphate oxidase gene *PNPO*)*
		Pyridoxine (B6) responsive seizures (*ALDH7A1* gene)*
		Serine biosynthesis defect[c,*]
		Sulfite oxidase deficiency
	Typically present with other systemic symptoms (such as metabolic acidosis, lactic acidosis, hyperammonemia)	Biotinidase deficiency (though does not typically present in neonatal period)*
		Fatty acid oxidation defects (if severe hypoglycemia)*
		Maple syrup urine disease*
		Mitochondrial disorders (severe lactic acidosis, often multisystem involvement)
		Organic acidemias (eg, methylmalonic acidemia, propionic acidemia, multiple carboxylase deficiency)[d,*]
		Peroxisomal disorders (eg, Zellweger syndrome)
		Urea cycle defects (if severe hyperammonemia)*

Conditions for which a treatment may be available are marked with an asterisk.
[a]No effective therapy available but glycine reduction may relieve symptoms in some cases.
[b]Treatment available only for 1 type of molybdenum cofactor deficiency and should be started before the onset, or early (within days of onset of symptoms).
[c]No effective therapy available but serine supplementation may relieve symptoms if started early.
[d]Treatment is available for some organic acidemias. Seizures, if they do occur, mostly occur during an acute metabolic crisis (eg, hyperammonemia). Therefore, the most important approach to treatment and prevention of seizures is management and prevention of an acute metabolic crisis.

seizures does not demonstrate a structural anomaly or acute injury, if the perinatal history is normal, and especially if electroencephalography shows burst suppression. Identifying treatable conditions early is important for prognosis. Diagnosis often requires sampling of cerebrospinal fluid for neurotransmitters or amino acids and/or genetic testing (gene panels for neonatal seizures, whole exome sequencing [WES], whole genome sequencing [WGS]).

Microcephaly

Although many metabolic disorders cause microcephaly postnatally, microcephaly at birth can be found in neonates with mitochondrial disorders, pyruvate metabolism disorders, cobalamin synthesis defects, serine synthesis defects (also a cause of neonatal seizures), and sterol synthesis defects. (29) For additional information, refer to the section on maternal conditions affecting a neonate.

Hypotonia

Neonatal hypotonia is a nonspecific symptom that can arise from an abnormality in the central nervous system, peripheral nervous system, neuromuscular junction, muscle itself, or a metabolic or electrolyte abnormality. If the cause is metabolic, possible disorders include mitochondrial disorders, peroxisomal disorders, and Pompe disease.

Hydrocephalus

Hydrocephalus is not a common presentation of a metabolic disorder in a neonate but has been described in patients with cobalamin C and cobalamin D disorders. (30)(31)(32)

OPHTHALMOLOGIC

Patients with metabolic diseases often need to be followed for ophthalmologic manifestations. Furthermore, the ophthalmologic evaluation in a sick neonate may lead to a diagnosis of a metabolic disorder. Neonates with metabolic disease can have eye abnormalities because of an accumulation of an abnormal metabolic product (eg, galactosemia, mucopolysaccharidoses) or a deficient energy metabolism (mitochondrial diseases). Ocular manifestations of metabolic disorders include corneal clouding (mucopolysaccharidoses, mucolipidoses), congenital cataract (see next section), and cherry red spot (Niemann-Pick A and B, galactosialidoses, gangliosidoses). (2)(33)

Cataract

Although many metabolic manifestations in the eye present later in infancy or childhood, in the neonatal period, the finding of a cataract in a neonate with multisystem disease can be an indication of galactosemia, a peroxisomal disorder, Lowe syndrome, or multiple acyl-coenzyme A (CoA) dehydrogenase deficiency. (33)

CARDIAC

Cardiomyopathies

A cardiomyopathy diagnosis can reveal an undetected metabolic disorder or a diagnosis of a metabolic disorder can reveal an undetected cardiomyopathy or risk for it in future years. Metabolic disorders can cause a dilated, hypertrophic or left ventricular noncompaction type of cardiomyopathy. (34)(35) Metabolic disorders in which cardiomyopathy can be the presenting symptom include primary carnitine deficiency (typically associated with a dilated cardiomyopathy, though cardiac presentation is more common later in childhood), very-long-chain acyl-CoA-dehydrogenase deficiency and other long-chain FAODs (typically dilated cardiomyopathy), Pompe disease (hypertrophic cardiomyopathy), mitochondrial disorders (fatal infantile hypertrophic obstructive cardiomyopathy, also dilated cardiomyopathy), or Barth syndrome (X-linked, more common in males, associated with left ventricular noncompaction type). Neonates with PA are at risk for either dilated or hypertrophic cardiomyopathy. Furthermore, although a neonate with cardiomyopathy often has lactic acidosis because of poor perfusion secondary to cardiac dysfunction, severe intractable lactic acidosis in a neonate should prompt an evaluation for a mitochondrial disorder.

Arrhythmias

Accumulation of storage material in cardiomyocytes leading to cardiac conduction defects and arrhythmias may occur in storage disorders. Though this typically does not occur in neonates, newborns with Pompe disease can exhibit a shortened PR interval on electrocardiography. (36) Arrhythmias may also be caused by the accumulation of toxic metabolites as occurs during a metabolic crisis in patients with an FAOD. (37)(38)

RESPIRATORY

Tachypnea

Tachypnea is a common nonspecific symptom in both term and preterm infants that can have multiple causes, including central nervous system disorders, primary pulmonary processes, or physiologic disturbances such as hypoxemia or hypercapnia. A metabolic cause for neonatal tachypnea should be sought in cases of anion gap metabolic acidosis, because the tachypnea could be the result of accumulating organic acid (organic acidemias) or lactic acid (mitochondrial diseases). These infants typically have a secondary respiratory alkalosis in an attempt to compensate for their metabolic acidosis. Tachypnea associated with a primary respiratory alkalosis (pH >7.45, no anion gap) should prompt a clinician to consider hyperammonemia as a result of a urea cycle defect, especially if there is any level of encephalopathy.

Pulmonary alveolar proteinosis can occur in patients with lysinuric protein intolerance (LPI), (39) and pulmonary arterial hypertension can be seen in some neonates with glycogen storage disorders, such as type I glycogen storage disease (von Gierke), (40) but these typically do not manifest during the neonatal period.

GASTROINTESTINAL/NUTRITIONAL

Liver Failure

Metabolic disorders account for 13% to 54% of cases of neonatal liver failure. (41)(42) Galactosemia, tyrosinemia, mitochondrial disorders (especially mitochondrial DNA depletion syndromes), and congenital disorders of glycosylation are common metabolic causes of liver failure in neonates, though tyrosinemia typically presents after the neonatal period. Galactosemia can present within days of consuming galactose-containing milk (breast milk or lactose-containing formula) with signs of hepatocellular damage such as jaundice, hepatomegaly, elevated transaminases, and coagulopathy. *Escherichia coli* sepsis is relatively common in symptomatic neonates with galactosemia. Positive urine-reducing substances without the presence of glucose in the urine can be a sign of galactosemia. All galactose (lactose)–containing products must be immediately stopped if galactosemia is being considered, and soy-based formula used until a diagnosis is either confirmed or ruled out. (43) Neonatal acute liver failure with elevated transaminases, coagulopathy, and severe lactic acidosis can be seen in neonates with mitochondrial DNA depletion syndromes (typically, multiple genes involved). (44)(45) The diagnosis of hereditary fructose intolerance (HFI) should be considered in a neonate who presents with recurrent episodes of liver dysfunction (elevated transaminases, even coagulopathy) with hypoglycemia, lactic acidosis, and hyperuricemia that rapidly corrects with stopping formula and provision of

a dextrose infusion. Although an infant with HFI typically presents with the classic clinical symptoms when the child starts consuming vegetables and fruit (important sources of fructose), some infant formulas may contain fructose, sucrose, or sorbitol (the latter 2 can be metabolized to fructose) and symptoms can occur earlier. (46)

Cholestatic Liver Disease

Cholestatic liver disease is common in sick neonates, and parenteral nutrition–induced cholestasis is common in patients in the NICU. Peroxisomal disorders, mevalonic aciduria, and congenital disorders of glycosylation are also possible causes of neonatal cholestatic liver disease, especially in a neonate with multisystem involvement. Bile acid synthesis defects typically present with isolated cholestatic liver disease. (47)(48) In adults, citrin deficiency typically manifests with recurrent hyperammonemia, but neonates often present with intrahepatic cholestasis. (49)

Pancreatitis

Neonates with PA, MMA, isovaleric acidemia, and other organic acidemias are at risk for pancreatitis, especially during a metabolic crisis. Therefore, amylase and lipase should be checked in these patients with symptoms of pancreatitis such as vomiting. (6)(7)(50)

Hepatosplenomegaly

Neonates with various storage disorders (eg, GM1 gangliosidosis, I-cell disease, mucopolysaccharidosis type VII (Sly), or Niemann-Pick type A and C) can present with hepatosplenomegaly or splenomegaly. A storage disorder is more likely if there are additional findings such as fetal hydrops, ascites, coarse facial features, and skeletal abnormalities such as dysostosis multiplex. (2)

Failure to Thrive

Failure to thrive (FTT) is a nonspecific finding that can be present in multiple metabolic diseases as a result of different causes such as malabsorption (associated with exocrine pancreatic insufficiency, intestinal disaccharidase deficiencies), aminoaciduria (associated with renal Fanconi syndrome), or energy failure (found in mitochondrial diseases). Metabolic causes of FTT should be sought, especially if the patient has already been evaluated for more common causes or if there are other signs of a metabolic disorder (eg, acidosis, dysmorphic features, multisystem involvement).

Diarrhea

Diarrhea resulting from metabolic disorders can be related to deficient absorption such as rare intestinal disaccharidase deficiencies (congenital lactase deficiency or sucrase isomaltase deficiency). (51)(52) Protein-losing enteropathy in an infant with multisystem involvement (eg, cardiac, liver) can be a clue to congenital disorders of glycosylation. (53)(54)

RENAL

Hemolytic Uremic Syndrome

A metabolic etiology is not typically considered in cases of hemolytic uremic syndrome, which is well-described in patients with cobalamin synthesis pathway defects especially in cobalamin C defect. (55)(56)

Renal Fanconi Syndrome

Generalized aminoaciduria, glucosuria, and renal tubular acidosis can be seen in neonates with galactosemia, hereditary cystinosis, hereditary fructose intolerance, mitochondrial disorders, and Fanconi-Bickel syndrome (hepatorenal glycogenosis, glycogen storage disease type XI). (2)(57)

Renal Cysts

Multiple renal cysts or polycystic kidneys can be seen, even prenatally, in patients with peroxisomal disorders (eg, Zellweger syndrome), congenital disorders of glycosylation, carnitine palmitoyl transferase II deficiency, and some congenital disorders of glycosylation. (2)(58)(59)

SKELETAL

Stippled Epiphyses

Peroxisomal disorders are classic metabolic disorders associated with stippled epiphyses (chondrodysplasia punctata). These include peroxisomal biogenesis defects such as Zellweger syndrome as well as defects in peroxisomal enzymes such as rhizomelic chondrodysplasia punctata. (58)(60)(61) Of note, warfarin embryopathy can mimic some features of peroxisomal disorders, particularly structural defects such as stippled epiphyses. (62)

Orthopedic/Skeletal

Rhizomelic (proximal) shortening of limbs is typical of peroxisomal disorders. Multiple skeletal abnormalities (ie, dysostosis multiplex) such as thoracic deformity, kyphosis, hip dislocation, clubfeet, and deformed long bones can be

seen at birth in neonates with mucolipidosis type II (I-cell disease), GM1 gangliosidosis, or multiple sulfatase deficiency. (63)(64) A storage disorder should be considered in an infant with skeletal involvement, coarse features, and/or multisystem disease. Arthrogryposis multiplex congenita (ie, multiple congenital contractures) have been described in neonates with mitochondrial disorders (65) and storage disorders such as perinatal-lethal Gaucher disease. (66)

DERMATOLOGIC

Jaundice

Cholestatic liver disease can lead to jaundice (see gastrointestinal section).

Ichthyosis

Ichthyosiform or collodion skin changes are typical of the perinatal lethal form of Gaucher disease. A history of fetal hydrops, ascites, and hepatosplenomegaly in a critically ill newborn further supports this diagnosis. Congenital ichthyosis (often with congenital erythroderma) can also be seen in neonates with peroxisomal disorders, X-linked chondrodysplasia punctata, serine synthesis defects, steroid sulfatase deficiency, and multiple sulfatase deficiency. Of note, low maternal serum unconjugated estriol in prenatal screening can be an indication of X-linked ichthyosis in a male fetus. (67)(68)

DYSMORPHIC FEATURES

Dysmorphic facial features are common in many chromosomal and genetic syndromes. Neonates with metabolic disease can have coarse facial features, especially in severe forms of storage disorders such as multiple sulfatase deficiency, mucolipidosis type II (I-cell disease), infantile galactosialidosis, infantile sialidosis, GM1 gangliosidosis, and peroxisomal disorders (especially Zellweger syndrome). (2) Multisystem involvement is, again, typical of these conditions.

HEMATOLOGIC

Cytopenias

Anemia, thrombocytopenia, and neutropenia, in isolation or in combination (including pancytopenia), can occur in neonates with metabolic disorders. Cytopenia can be caused by a deficiency of a metabolite essential for cytopoiesis, bone marrow infiltration by storage material, hypersplenism, or bone marrow suppression during a metabolic crisis. Macrocytic anemia can be seen in inborn errors of cobalamin (B_{12}) or folate (folic acid) metabolism. Bone marrow infiltration and hypersplenism leading to anemia and often pancytopenia can occur in storage disorders such as Gaucher disease. Pancytopenia (often relatively mild and transient lasting a few weeks) can be found, especially in neonates with organic acidemias during and after an acute metabolic crisis and is well described in patients with MMA and PA. (6)(69)

Vacuolated Lymphocytes

Patients with diseases such as Pompe disease, mucolipidosis type II, mucopolysaccharidoses, and Niemann-Pick disease type I often have vacuolated lymphocytes that are seen on a blood smear. (2)

Coagulopathy

Any metabolic disorder that presents with liver failure typically also has an associated coagulopathy and can be caused by galactosemia and mitochondrial DNA depletion defects.

Hemophagocytic Lymphohistiocytosis

Several metabolic disorders have been described to cause a hemophagocytic lymphohistiocytosis/macrophage activation syndrome; these include LPI, multiple sulfatase deficiency, Gaucher disease, and galactosialidosis as well as some organic acidemias. (70)

ODORS

Some metabolic disorders have a classic distinctive odor in sweat, urine, or other body secretions because of the accumulating metabolite. The odor is typically stronger during a metabolic crisis or when a metabolic disorder is poorly controlled. Table 3 includes examples of typical odors that have been typically associated with metabolic disorders.

NEWBORN SCREENING

NBS, especially expanded NBS with tandem mass spectrometry, has made it possible to analyze multiple analytes simultaneously and detect several inborn errors of metabolism. Most organic acidemias, FAODs, and amino acidemias can be detected via NBS. To promote uniform and comprehensive NBS, the Department of Health and Human Services has a list of ~40 conditions called the Recommended Uniform Screening Panel (RUSP), which is periodically updated with new disorders. (3)(71)(72) It is recommended that all states screen for the conditions listed in the RUSP. However, although this list offers guidance, it is not enforced by law. Some states adopt new

TABLE 3. **Typical or Distinctive Odors Described in Metabolic Disorders**

ODOR	METABOLIC DISEASE
Maple syrup	Maple syrup urine disease
Boiled cabbage	Tyrosinemia Hypermethioninemia
Mousy, musty	Phenylketonuria
Sweaty feet	Isovaleric acidemia Glutaric acidemia type II
Rotting fish	Trimethylaminuria (odor only manifestation)
Cat urine	3-hydroxy-3-methylglutaric aciduria
Tomcat urine	Multiple carboxylase deficiency

recommendations early whereas others are still in the process of adopting them. Some states also screen for additional disorders not listed in the RUSP. This leads to slight heterogeneity of disorders screened for by each state. (73) The most recent additions to the RUSP (and adopted by many states) include Pompe disease, mucopolysaccharidosis type I (ie, Hurler syndrome), and X-linked adrenoleukodystrophy. Disorders are typically detected with either an elevated (upstream from the metabolic defect) or low (downstream from the metabolic defect) amount of analyte, or via enzyme activity. It is important to recognize that a normal NBS does not rule out a metabolic disorder because an infant's metabolite may have been above or below a cutoff value at the time the NBS was performed. Also, most metabolic disorders are not detected on NBS. Examples of disorders not detected via NBS include mitochondrial disorders, disorders of pyruvate metabolism, congenital disorders of glycosylation, and most storage diseases, as well as most conditions that cause neonatal seizures (Table 2), with some exceptions. Therefore, maintaining a high index of suspicion of an inborn error of metabolism is vital in any critically ill neonate.

MATERNAL METABOLIC DISORDERS AFFECTING THE FETUS OR NEONATE

Maternal metabolic disorders can affect the neonate because the maternal metabolite can be toxic and thus, teratogenic. Alternatively, high maternal amounts of the metabolite can be transferred across the placenta to the fetus and postnatally lead to a false-positive NBS.

Teratogenic Effect

Maternal uncontrolled phenylketonuria is a well-known cause of a metabolic disorder with adverse fetal effects. High maternal phenylalanine levels during pregnancy can lead to microcephaly, intellectual disability, congenital heart defects, esophageal atresia, and IUGR. The specific effects and extent of the impact depend on the magnitude and timing of high phenylalanine levels with the period of organogenesis (ie, first trimester) being the most sensitive for structural anomalies.

False-positive NBS Result

Two well-described maternal conditions that can cause a false-positive NBS result in a neonate are primary carnitine deficiency (carnitine transporter deficiency, low Co on NBS) and 3-methylcrotonyl-coA-carboxylase deficiency (high C5-OH). If an infant has a positive NBS result for these conditions, it could be the result of a maternal condition.

WHOLE EXOME/GENOME SEQUENCING

A comprehensive review of WES and WGS is beyond the scope of this review; however, these diagnostic modalities have proven to be powerful tools in the rapid diagnosis of genetic and metabolic disorders in critically ill neonates and can provide a diagnosis in up to 30% to 50% of critically ill infants in the NICU. (74)(75)(76)(77)(78)(79)(80) Early diagnosis can guide clinical management and improve prognosis in cases for which a therapy is available or help direct care toward palliative care in cases with a poor prognosis.

SUMMARY

Metabolic disorders can present in various ways in a neonate, ranging from a subtle symptom or finding in 1 organ system to a severe multisystem presentation requiring immediate management. Early recognition of treatable conditions can improve mortality and morbidity in neonates affected by these conditions. Furthermore, a definitive diagnosis allows for genetic counseling about recurrence risk, which is important for early recognition of these conditions in future pregnancies or early in the neonatal period. Prenatal diagnosis can help plan for a delivery at a tertiary care center with expertise in metabolic disorders. Expanded NBS with more conditions added periodically, as well as WES and WGS, will continue to lead to earlier diagnoses of metabolic disorders in a neonate. A high index of suspicion and continuous medical education about the advancing knowledge of these conditions will help neonatologists detect

metabolic conditions early and initiate treatment in those conditions for which an effective therapy is available.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology, clinical manifestations, laboratory features, and management of infants with lysosomal, peroxisomal, and mitochondrial disorders.
- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of carbohydrates.
- Know the clinical manifestations, laboratory features, and treatment of disorders of cholesterol synthesis.
- Know the clinical manifestations, laboratory features, and treatment of organic acid disorders.

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1. A 2-day-old male term infant presents with lethargy, poor feeding, and tachypnea. Laboratory evaluation reveals hyperammonemia and a respiratory alkalosis. Which of the following is most likely to be a potential diagnosis for this patient?

   A. Methylmalonic acidemia.
   B. Propionic acidemia.
   C. Ornithine transcarbamylase deficiency.
   D. Lactic acid dehydrogenase deficiency.
   E. X-linked hypophosphatemia.

2. A 3-day-old term male infant presents with seizures, vomiting, poor feedings, and hyperammonemia. He is diagnosed with methylmalonic acidemia. He is admitted to the NICU. Which of the following would be an appropriate part of initial therapy?

   A. Increase protein administration via both enteral and intravenous routes.
   B. Vitamin C loading and subsequently in 4-hour intervals given intravenously.
   C. Limit fluids to half maintenance to prevent renal overloading.
   D. Insulin administration if hyperglycemia develops.
   E. Therapeutic hypothermia for 24 hours during medical coma.

3. A 1-day-old female term neonate is noted to have seizures both clinically and then confirmed on electroencephalography. Which of the following characteristics would be most consistent with the cause of seizures being a metabolic disorder?

   A. History of a perinatal event such as acute maternal hemorrhage or cord entanglement.
   B. Persistent seizures without an intracranial abnormality.
   C. Seizures that started soon after delivery, with abnormal neurologic examination findings including hypotonia and lethargy at birth that gradually improved.
   D. No other organ involvement other than neurologic symptoms.
   E. Normal laboratory evaluation including blood gas, electrolytes, and ammonia level.

4. A 2-day-old female neonate presents with jaundice, emesis, and lethargy. Newborn screening result is positive for galactosemia. Which of the following ophthalmologic findings is seen in this condition?

   A. Cataracts.
   B. Glaucoma.
   C. Optic atrophy.
   D. Microphthalmia.
   E. Iris atrophy.

5. A neonate presents with jaundice, hepatomegaly, and *Escherichia coli* sepsis at 1 week of age. Which of the following metabolic disorders is most likely to present with *E coli* sepsis?

   A. Mitochondrial depletion syndrome.
   B. Pyruvate kinase deficiency.
   C. DNA-induced encephalopathy.
   D. Methylmalonic acidemia.
   E. Galactosemia.

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Genetic Etiologies of Neonatal Seizures

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Practice Gaps

Neonatologists are regularly expected to be able to manage neonatal seizures and identify the underlying cause. These clinicians need to be aware of the possibility and likelihood of the genetic etiologies of neonatal seizures in different clinical scenarios. Neonatologists need to appropriately consult genetics and in conjunction with the consultants, order investigations and offer targeted therapies.

Abstract

Neonates presenting with seizures are frequently assessed and managed by neonatologists in the NICU. Although hypoxic-ischemic encephalopathy and infection are common underlying causes of neonatal seizures, many patients with neonatal epilepsy will have an identifiable genetic etiology. Often these cases will be evaluated in collaboration with a geneticist. The categories of genetic causes of neonatal seizures include 1) structural brain malformations; 2) inborn errors of metabolism; 3) syndromic; and 4) nonsyndromic, single gene. Evaluation of these patients involves a comprehensive history and examination, followed by appropriate investigations and diagnostic genetic testing. Components of the diagnostic process will vary based on the clinical suspicion and differential diagnoses. In certain cases, syndromic surveillance for evaluation of other congenital anomalies may be recommended. Determination of the underlying genetic diagnosis, when present, will have important implications for treatment. Targeted therapies are currently available for specific genetic syndromes, and outcomes may improve with earlier initiation of therapy. Certain genetic diagnoses may also have guideline-based management involving screening for other manifestations of the disorder.

Objectives After completing this article, readers should be able to:

1. Identify when a genetic evaluation for neonatal seizures is appropriate
2. Recognize different categories of genetic causes of neonatal seizures
3. Be able to evaluate genetic causes of neonatal seizures in a stepwise approach
4. Recognize neonatal seizure disorders and the available targeted therapies

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ABBREVIATIONS

ACC	agenesis of the corpus callosum
AEDs	antiepileptic drugs
CSF	cerebrospinal fluid
EEG	electroencephalography
GABA	γ-aminobutyric acid
IEM	inborn error of metabolism
MRI	magnetic resonance imaging
PLP	pyridoxal phosphate

INTRODUCTION

Neonatal seizures have an incidence rate of about 3 in 1,000 live births with onset ranging from birth to 4 weeks of age (44 weeks' postmenstrual age). (1) Isolated seizures can occur because of an acute temporary brain dysfunction from various perinatal factors, but neonatal epilepsy is defined by the presence of recurrent spontaneous seizures. Seizures are a common reason for a genetics consultation in the NICU, and appropriately so, because a majority of neonates with neonatal epilepsy will have an underlying genetic etiology. A recent study in 2017 found a genetic diagnosis in 34 (59%) of 58 newborns with epilepsy who underwent genetic testing. (1)(2) Various genetic conditions can cause neonatal epilepsy, including chromosomal, single gene, and metabolic disorders. The relatively new widespread availability of multigene panels, whole exome sequencing, and whole genome sequencing has increased our ability to detect genetic causes of seizures. Not only is our diagnostic yield increasing, but the potential for targeted treatment of neonatal epileptic disorders is also on the rise. Although we will focus on the genetic etiology of seizures, a broad differential must be considered, as with any other diagnostic process; in this case, the differential should include hypoxic-ischemic encephalopathy, infection, electrolyte imbalance, and intracranial hemorrhage.

TYPES OF NEONATAL SEIZURE DISORDERS

Neonatal epilepsy can be classified into the following categories: 1) structural brain malformations; 2) inborn errors of metabolism (IEMs); 3) syndromic; 4) nonsyndromic, single gene.

Structural Brain Malformations

Isolated structural malformations can cause neonatal seizures because of focal or diffuse abnormalities in the size and formation of the brain, or abnormalities of neuronal migration. Structural abnormalities such as agenesis of the corpus callosum (ACC), polymicrogyria, lissencephaly, schizencephaly, megalencephaly, holoprosencephaly, and gray matter heterotopias may cause seizures. Of these defects, ACC is a relatively common finding (~5/1000 prevalence). Although isolated seizures may be common, when they occur as part of a cranial malformation sequence, up to 13% of patients are attributed to isolated ACC. (3) All of the structural abnormalities listed herein occur because of disruption of normal embryogenesis, and often a mutation in a single gene can result in malformations of multiple structures in the brain. Detailed neuroimaging and interpretation by a pediatric neuroradiologist is required for accurate identification of the cause. A toxic insult, such as an infection or vascular deficiency, to the embryo during critical stages may mimic anomalies because of genetic defects.

Structural brain abnormalities may be isolated or part of a constellation of abnormal features in a genetic syndrome. Syndromic surveillance should be considered to look for involvement of other organ systems. Table 1 lists some common syndromic and nonsyndrome genetic causes of structural brain malformations. The age at which onset of seizures occurs because of underlying structural malformations varies greatly, but in a recent report ~28% of neonates were identified to have epilepsy because of a brain malformation. Most patients with an early presentation were found to have abnormalities of neuronal migration. (1)

Inborn Errors of Metabolism

Metabolic disorders are rarely the underlying cause of a neonate presenting with seizures, but should not be overlooked, because some are treatable with diet changes or medications (Table 2). IEMs can cause seizures because of various reasons including deficiency of energy, accumulation of toxic products, abnormalities of neurotransmitter metabolism, or accompanying brain malformations. (4)

Clues to an underlying IEM include resistance to standard antiepileptic drug (AED) therapy, features such as hypotonia or poor feeding, or brain magnetic resonance imaging (MRI) findings suggestive of a metabolic disorder. (Table 3; example shown in the Fig). Other clues on laboratory evaluation include hypoglycemia, nonanion gap metabolic acidosis, lactic acidosis, ketosis, and hyperammonemia. The standard approach to seizures, consisting of establishing the clinical type and identifying characteristic abnormalities on electroencephalography (EEG), may not be helpful, because these findings are not specific in most patients with IEMs. Seizures in metabolic disorders can be either a primary manifestation or secondary to metabolic abnormalities such as hypoglycemia or hyperammonemia. Most patients with seizures in the setting of a metabolic disorder ultimately will require long-term AED treatment. (4)

The presence of hypoglycemia is a sign of energy deficiency, and if present, the following metabolic disorders should be considered in the differential: defects of gluconeogenesis, glycogen storage disorders, disorders of fructose metabolism, fatty acid oxidation disorders, and disorders of glucose transport. All children with hypoglycemic seizures should receive a metabolic evaluation including blood glucose, serum and urine ketones, free fatty acids,

TABLE 1. **Syndromes with Structural Malformations of the Brain**

CONGENITAL MALFORMATION	ASSOCIATED SYNDROMES (GENE)
Corpus callosum agenesis/ hypogenesis	Aicardi syndrome (likely X-linked) L1 syndrome (*L1CAM*) Mowat-Wilson syndrome (*ZEB2*) Schinzel syndrome (*KIF7*) Tubulinopathies (*TUBA1, TUBB2A, TUBB2B, TUBB3, TUBB, TUBG1*)
Type I lissencephaly (agyria-pachygyria)	Miller-Dieker syndrome (17p13.3 deletion) Isolated lissencephaly sequence (*LIS1, TUBA1A, DCX*)
Type II lissencephaly	X-linked lissencephaly with abnormal genitalia (*ARX*) Walker-Warburg syndrome (*POMT1, POMT2, CRPPA, FKTN, FKRP, LARGE1*) Fukuyama congenital muscular dystrophy (*FKTN*)
Polymicrogyria (cortical dysplasia)	1p36 deletion 22q11.2 deletion Aicardi syndrome Bilateral frontoparietal polymicrogyria (*ADGRG1*) Goldberg-Shpritzen syndrome (*KIAA1279*) Joubert syndrome (many genes) mTORopathies (*AKT3, CCND2, MTOR, PI4KA, PIK3CA, PIK3R2, PTEN*) Tubulinopathies (*TUBA1A, TUBB, TUBB2A, TUBB2B, TUBB3*) Zellweger syndrome (multiple *PEX* genes)
Schizencephaly	Nonsyndromic schizencephaly (*EMX2, SIX3, SHH, COL4A1*)
Megalencephaly	Nonsyndromic megalencephaly (*MTOR, SHH*) Megalencephaly with gigantism (*NSD1*) Megalencephaly-capillary malformation syndrome, hemimegalencephaly (*PIK3CA*) Pretzel syndrome (*LYK5/STRADA* deletion)
Microcephaly	Microcephaly with pontine and cerebellar hypoplasia (*CASK*) Microcephaly, seizures, and developmental delay (*PNKP*)
Holoprosencephaly	Patau syndrome (trisomy 13) Nonsyndromic holoprosencephaly (*SHH, ZIC2, SIX3, TGIF1*)
Septo-optic dysplasia	Nonsyndromic septo-optic dysplasia (*HESX1, OTX2, SOX2*)
Dandy-Walker malformation	3q22-q24 deletion Aicardi syndrome Coffin-Siris syndrome (*ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1,* and *SOX11*) Ciliopathies Edwards syndrome (trisomy 18) Fryns syndrome Patau syndrome (trisomy 13) Smith-Lemli-Opitz syndrome (*DHCR7*) Triploidy Walker-Warburg syndrome (*POMT1, POMT2, CRPPA, FKTN, FKRP, LARGE1*)

lactic acid, plasma amino acids, plasma acylcarnitines, urine organic acids, ammonia, insulin, growth hormone, and cortisol. These laboratory tests should be performed at the time of hypoglycemia for the interpretation to be most accurate. Delayed blood draws may allow the metabolites to normalize, leading to an inaccurate interpretation and missed diagnoses.

Aminoacidopathies, organic acidurias, and urea cycle defects present with seizures when there is accumulation of toxic products. Passage of the toxic products across the blood-brain barrier may lead to cerebral edema, such as seen in maple syrup urine disease, or direct neurotoxicity caused by hyperammonemia, as in organic acidemias and urea cycle disorders.

TABLE 2. **Neonatal-Onset Seizures of Metabolic Origin**

TYPE	CHARACTERISTIC FEATURES	DIAGNOSIS	TREATMENT
Pyridoxine-dependent epilepsy	Seizures refractory to common AEDs, hypothermia Dystonia	Low α-AASA and pipecolic acid *ALDH7A1* gene testing	Pyridoxine
PNPO deficiency		Low CSF PLP *PNPO* gene testing	PLP
Nonketotic hyperglycinemia	Prenatal hiccups Lethargy Hypotonia	Elevated CSF-plasma glycine ratio (>0.08) *GLDC/AMT* gene testing	Avoid valproic acid Sodium benzoate Dextromethorphan
Organic acidurias	Hyperammonemia High anion gap metabolic acidosis	Urine organic acids, plasma amino acids, plasma acylcarnitines Enzyme analysis Molecular testing	Low protein diet Carnitine Cofactor supplementation
Urea cycle disorders	Hyperammonemia	Ammonia Plasma amino acids, urine orotic acid Enzyme analysis Molecular testing	Low protein diet Nitrogen scavengers Citrulline/arginine supplementation
Peroxisomal disorders	Structural brain malformations Dysmorphic facies Hypotonia Liver dysfunction Hearing loss	Very-long-chain fatty acids Phytanic acid RBC Plasmalogen Molecular testing	Standard AEDs
Folinic acid–responsive seizures	Seizures refractory to common AEDs Transient response to pyridoxine	*ALDH7A1/FOLR1* gene testing	Folinic acid
Biotinidase deficiency	Alopecia, skin rash Hearing and vision abnormalities Hypotonia	Biotinidase enzyme analysis *BTD* sequencing	Biotin
Molybdenum cofactor deficiency	Cerebral edema Developmental delays	Urine sulphite Urine sulfocysteine	Clinical trials for cPNP
Sulphite oxidase deficiency	Tone abnormalities Progressive microcephaly Intellectual disability	Enzyme analysis Molecular testing	Low protein diet (controversial)
Congenital disorders of glycosylation	Hypotonia Abnormal subcutaneous fat Dysmorphic facies Structural brain malformations	N- and O- Glycan analysis Molecular testing	Symptomatic treatment Mannose-1-phosphate trials

AASA=α-aminoadipic semialdehyde; AEDs=Antiepileptic drugs; CSF=cerebrospinal fluid; cPNP= cyclic pyranopterin; PLP=Pyridoxal phosphate; PNPO=pyridoxine 5′-phosphate oxidase deficiency; RBC=red blood cell.

Neonatal seizures refractory to common AEDs may be the result of one of the vitamin-responsive neonatal epilepsies. Pyridoxine-dependent epilepsy occurs from a deficiency of α-aminoadipic semialdehyde dehydrogenase (antiquitin) in the lysine degradation pathway. This blockage leads to a buildup of α-aminoadipic semialdehyde, piperideine-6-carboxylate, and pipecolic acid. Seizures can be controlled with vitamin B_6 administration, but developmental delays may persist. Deficiency of pyridoxamine 5′-phosphate oxidase can lead to neonatal and in utero seizures with hypoglycemia and lactic acidosis. Cerebrospinal fluid (CSF) studies may demonstrate elevation of glycine, threonine, L-DOPA, and 3-methoxytyrosine. Because the defect is in conversion of pyridoxine to the activated form of pyridoxal phosphate (PLP), treatment involves supplementation with PLP. It has been suggested that premature newborns with signs of

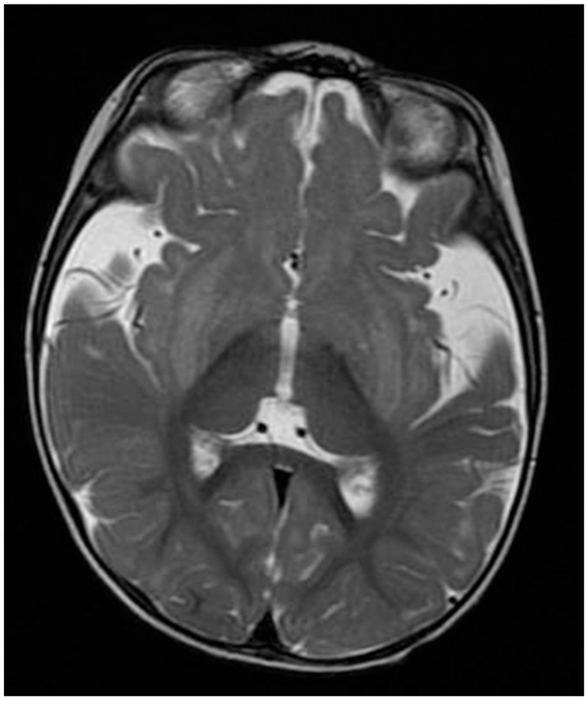

Figure. Magnetic resonance imaging scan (T2 axial) depicting frontotemporal atrophy and widened sylvian fissures in a patient with glutaric acidemia type 1.

hypoxic-ischemic encephalopathy with seizures refractory to AEDs undergo trials of PLP. Undiagnosed and untreated, these conditions may have severe morbidity and mortality because of prolonged status epilepticus. (5) Folinic acid–responsive seizures are clinically indistinguishable from the pyridoxine-dependent epilepsies and respond to folinic acid treatment.

Biotinidase deficiency, if undiagnosed and untreated, can present with severe neonatal seizures. Severe forms of fatty acid metabolism defects such as carnitine-palmitoyl transferase II deficiency and conditions of congenital lactic acidosis (such as pyruvate carboxylase deficiency and pyruvate dehydrogenase deficiency) can cause cystic changes in the brain and potentially seizures. Peroxisomal disorders and congenital disorders of glycosylation can also present with neonatal seizures and malformations of the brain such as frontal polymicrogyria and pachygyria. Severe methylenetetrahydrofolate reductase deficiency can cause neonatal seizures and is screened for by measuring homocysteine levels. Nonketotic hyperglycinemia can present with progressive seizures, initially myoclonic jerks, and isolated elevation of the CSF-to-plasma glycine ratio. Prenatal accumulation of glycine can lead to in utero brain injury and abnormal fetal movements characterized as "hiccups." Decreased activity of the glycine cleavage system in chorionic villi and elevated glycine in the amniotic fluid can be demonstrated.

Other metabolic causes of epilepsy, such as mitochondrial disorders, creatine metabolism disorders, glucose transporter deficiency type 1, and neuronal ceroid lipofuscinosis, typically present in infancy or later, but could be considered in the differential for neonatal seizures if other aspects of the clinical picture raise suspicion.

Syndromic

Syndromic epilepsies usually have multisystem involvement and may also have characteristic dysmorphic features. Chromosomal disorders such as trisomy 13, 18, or 21; 22q11.2 deletion syndrome; and Wolf-Hirschhorn syndrome can be associated with neonatal epilepsy. Some common genetic syndromes that can cause structural brain malformations often present with neonatal seizures, as listed in Table 1. Seizures can be the first symptom of neurocutaneous syndromes like tuberous sclerosis, Sturge-Weber syndrome, or incontinentia pigmenti. *COL4A1*-related vascular disorders may have neonatal seizures, either secondary to hemorrhage or resulting from underlying porencephaly or schizencephaly. Epilepsy is a feature of hundreds of other genetic syndromes, and in many, seizures may begin in infancy. Table 4 lists a selection of genetic syndromes that can present with neonatal epilepsy.

Single Gene/Nonsyndromic

Single gene epilepsy disorders can result from modifications of genes involved in ion channel regulation, synaptic function, or abnormal cell signaling.

Channelopathies can occur from variants in genes such as *KCNT1, KCNQ2, CACNA1A,* or *SCN2A*, which regulate the function of calcium, potassium, or sodium channels and play a role in action potentials and neuronal firing. Often, the expressivity associated with these genes is variable, ranging from benign familial neonatal epilepsy to severe epileptic encephalopathies, sometimes with genotype-phenotype associations. Chloride channels are regulated by γ-aminobutyric acid (GABA), and abnormalities in GABA binding and metabolism can lead to neonatal encephalopathies. Distinguishing features of disorders of GABA metabolism include presence of seizures at birth, accelerated growth, and elevated GABA in plasma and CSF. (6) Vigabatrin should be considered as a therapeutic option but may be beneficial in some patients and detrimental in others.

STXBP1 is one of several genes involved in vesicle fusion at synapses and affected patients can present with encephalopathy and seizures. Other genes involved in synaptic function are *TBC1D24* and *SIK1*.

TABLE 3. **MRI/MRS Features of Metabolic Disorders**

METABOLIC DISORDER	MRI FINDING
Disorders of creatine metabolism	Decreased/absent creatine ± increased GAMT
GABA transaminase deficiency	Elevated GABA in basal ganglia
Glutaric acidemia type 1	Frontotemporal atrophy, widened "Batwing" sylvian fissures
Maple syrup urine disease	Localized edema in cerebellar white matter, dorsal brain stem, cerebral peduncles, posterior limb of internal capsule
Mitochondrial disorders, congenital lactic acidosis	Elevated lactate peak
Peroxisomal disorders	Decrease in white matter volume, decrease of myelination, ventricular enlargement, abnormal gyration
Nonketotic hyperglycinemia	Defects of the corpus callosum, elevated glycine peak
Organic acidemias	Elevated glycine and/or lactate peaks Cerebral edema
Molybdenum cofactor deficiency	Severe cerebral edema, acute infarction of the globus pallidi and subthalamic regions

GABA=γ-aminobutyric acid; GABT=guanidinoacetate peak; MRI=magnetic resonance imaging; MRS=magnetic resonance spectrography.

CDKL5 and *BRAT1* encode proteins involved in cellular signaling, which when disrupted result in a severe epileptic phenotype with early lethality for *BRAT1*.

Epileptic encephalopathies can be defined as severe epilepsy with permanent neurologic dysfunction and are usually labeled with a clinical diagnosis such as Ohtahara syndrome, West syndrome, or Dravet syndrome. Clinical features and single genes associated with epileptic encephalopathies are listed in Table 5. They can occur as a primary feature of single gene disorders and are not necessarily caused by uncontrolled seizures. (7)(8)(9)

INVESTIGATIONAL APPROACH

Any good approach to the evaluation of a medical condition emphasizes the importance of the history and a thorough physical examination. The approach to neonatal seizures is no different. The evaluating clinician should start by obtaining information about the seizure event (onset, seizure type, provoking factors, response to treatment), as well as a detailed family history and birth history. A comprehensive physical examination should include growth parameters (specifically head circumference), and attention should be paid to the neurologic examination, skin examination, and the presence or absence of dysmorphic features. Evaluations should be considered for congenital anomalies with echocardiography, renal ultrasonography, or other studies based on clinical concern. Studies to be performed in conjunction with a neurology consultation should be an EEG and brain MRI (with magnetic resonance spectroscopy when possible). If the MRI scan is concerning for specific malformations, the evaluation should be targeted toward genetic disorders associated with those malformations. The type of seizure, other clinical characteristics, laboratory evaluation, and EEG or brain MRI findings should help narrow the differential and determine the recommended course of genetic testing.

If a specific genetic condition is suspected, targeted testing for that disorder should be ordered. A karyotype can screen for chromosomal abnormalities, such as trisomies or large rearrangements. A chromosomal microarray will evaluate for microdeletions or duplications. If a particular syndrome is suspected, testing for the known associated gene(s) can be sent. If an IEM is suspected, biochemical evaluations should be sent (as discussed earlier).

If the history, physical examination, EEG, and brain MRI findings are nonspecific, broad screening for metabolic and genetic etiologies of the seizures should be considered. (10) A multigene seizure panel, which evaluates dozens (sometimes hundreds) of genes associated with seizures, is often sent. Panels continue to increase in size, often including genes that may still have limited evidence of correlation with seizures. Results must be analyzed in the setting of the patient's phenotype, before assigning

TABLE 4. **Genetic Syndromes Associated with Neonatal Epilepsy**

TYPE OF CONDITION	SYNDROME	GENETIC ETIOLOGY/GENE	OTHER ASSOCIATED FEATURES (IN THE NEONATAL PERIOD)
Chromosomal	Down syndrome	Trisomy 21	Hypotonia Congenital heart disease Dysmorphic features
	Patau syndrome	Trisomy 13	Cleft lip/palate Omphalocele Holoprosencephaly Congenital heart disease Dysmorphic features
	Edwards syndrome	Trisomy 18	Clenched hands, overlapping fingers Rockerbottom feat Congenital anomalies Dysmorphic features
	22q11.2 deletion syndrome	Deletion of 22q11.2	Congenital heart defects Palate abnormalities Hypocalcemia Immune deficiency
	Wolf-Hirschhorn syndrome	Deletion of 4p16.3	Poor growth Hypotonia Dysmorphic features
Neurocutaneous	Tuberous sclerosis	*TSC1, TSC2*	Skin abnormalities: Hypopigmented macules, shagreen patches, angiofibromas Hamartomas in the brain, heart, kidneys, retina
	Sturge-Weber	*GNAQ*	Port wine stain Glaucoma Leptomeningeal angioma
	Incontinentia pigmenti	*IKBKG*	Blistering rash in neonatal period (evolves eventually into linear hypopigmentation)
	Hypomelanosis of Ito	Mosaicism for aneuploidy or other chromosomal anomalies	Hypopigmented whirls along lines of Blaschko Other congenital anomalies
Other	*COL4A1*-related	*COL4A1*	Small vessel disease Porencephaly Eye defects
	Pitt-Hopkins	*TCF4*	Episodic hyperventilation Feeding issues, constipation Eye abnormalities Microcephaly
	Coffin-Siris	*ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1,* and *SOX11*	Hypoplasia of 5th digit Dysmorphic features Brain malformations Poor growth Hypotonia
	Aicardi-Goutieres	*ADAR, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1,* or *TREX1, IFIH1*	Early-onset encephalopathy Glaucoma Liver dysfunction

causality to an identified mutation. Whole exome sequencing, which evaluates all of the exons (protein-coding regions) in all known genes, is often considered. Whole genome sequencing, as named, evaluates the entire genome, and is becoming more widely available. In the acute intensive care unit setting, urgent whole exome or whole genome sequencing can be considered, because obtaining a diagnosis may affect immediate management.

TABLE 5. **Neonatal Epileptic Encephalopathies**

	CLINICAL CHARACTERISTICS	ASSOCIATED GENES
Ohtahara syndrome	Intractable seizures Developmental delay EEG: burst suppression	*STXBP1* *ARX* *SLC25A22* *KCQN2* *SCN2A*
Early myoclonic encephalopathy	Erratic myoclonus, refractory partial seizures Psychomotor developmental delay, hypotonia, peripheral neuropathy EEG: burst suppression	*SLC25A22* *MOCS1* *SEPSECS*
Epilepsy of infancy with migrating focal seizures	Refractory focal seizures Severe psychomotor delay EEG: frequent slow waves shifting from one hemisphere to another	*KCNT1* *SCN2A* *SCN1A* *SLC25A22*

West syndrome and Dravet syndrome usually have an age at onset of more than 1 month. (9) EEG=electroencephalography.

Note that whole exome and whole genome sequencing can have some drawbacks, including missing parts of the genome (leading to falsely reassuring normal results) and the discovery of incidental or unrelated genetic conditions.

THERAPEUTIC OPTIONS

Advances in translational research have given hope for the development of gene-specific targeted therapies for seizure disorders. Therapies focus on control of clinical and subclinical seizures as well as the improvement of long-term neurodevelopmental outcomes. Many of the AEDs commonly used now may have adverse effects in neonates. For example, with the use of phenytoin or phenobarbital, the preliminary concern is apoptosis in developing brains. (11) Targeted therapies are important, because only drugs known to be effective could be preferentially used over the common nonspecific AEDs. Some targeted therapies currently in use are listed in Table 6.

TABLE 6. **Seizure Disorders with Targeted Therapies**

DISORDER	TREATMENT
Pyridoxine-dependent epilepsy (*ALDH7A1*)	Vitamin B6
DEPDC5-related epilepsy	mTOR inhibitors (sirolimus, everolimus)
Cerebral folate transport deficiency (*FOLR1*)	Folinic acid
Guanidinoacetate methyltransferase deficiency (*GAMT*)	Creatine, ornithine
Early-onset epileptic encephalopathy **(***KCNQ2*)	Retigabine, carbamezapine
KCNT1-related epilepsy	Quinidine
Molybdenum cofactor deficiency (*MOCS1*)	Clinical trial for cyclic pyranopterin
SCN1A-related epilepsy	Avoid sodium channel blockers
Early infantile epileptic encephalopathy 11 (*SCN2A*)	Phenytoin, sodium channel blockers
Tuberous sclerosis (*TSC1, TSC2*)	Vigabatrin, mTOR inhibitors (sirolimus, everolimus)

mTOR=mammalian target of rapamycin.

Vitamin-dependent epilepsies can be treatable with vitamin supplementation. These are typically resistant to conventional AEDs but demonstrate a prompt response to vitamin administration. Pyridoxine-dependent epilepsy can be treated with intravenous or oral pyridoxine, but this may result in central respiratory depression in 20% of patients. (12) Every neonate with seizures should undergo a pyridoxine trial even if metabolic disorders are not high on the differential as an etiology. Pyridoxine 5′-phosphate oxidase deficiency is a similar disorder that requires treatment with the active form of pyridoxine, PLP. Folinic acid–responsive seizures, as aptly named, resolve with folinic acid supplementation.

Because of abnormal excitation of potassium or sodium channels, channelopathies are examples of epilepsies with a genetic etiology that may benefit from targeted (channel specific) therapy. Retigabine has been shown to be beneficial for patients with alterations of the potassium current at the KCNQ channels because of specific mutations in *KCNQ2*. Retigabine activates potassium channels, reducing neuronal excitability, thereby decreasing seizure activity. Care is needed in the use of this drug, because it may have a detrimental effect in patients with gain-of-function mutations. (13)(14)

A high degree of suspicion (based on family history) and prompt initiation of targeted therapy is critical for infants with certain seizure disorders. For example, in molybdenum cofactor deficiency, outcomes have a broad spectrum based on timing of the intervention. These outcomes can range from "near-normal" if therapy is initiated early, to severe developmental disability if initiated after irreversible brain injury has occurred.

CONCLUSION

As our knowledge of genetics continues to progress, we are learning more about the etiology of neonatal epilepsy. Neonatal epilepsy may be caused by structural brain malformations, which frequently have an underlying genetic cause. IEMs can cause neonatal epilepsy because of hypoglycemia, toxic substances, or structural malformations. There are many single-gene causes of epilepsy, including channelopathies and genes involved in neurotransmitter metabolism. Epilepsy is a common feature in many other genetic syndromes. As our ability to diagnose genetic causes of seizures improves, so does our ability to treat these seizures using targeted therapy. Neonates presenting with epilepsy without clear-cut provoking perinatal factors should undergo genetic testing as a part of routine clinical practice.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the differential diagnosis and evaluation of neonatal seizures.
- Understand the spectrum of seizures in the newborn infant.

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1. Neonatal seizures occur in 3 per 1,000 live births and can be classified as structural malformation, inborn errors of metabolism (IEMs), syndromic, and nonsyndromic single gene disorders. What is the proportion of neonatal seizures for which a genetic cause can be identified?
   A. About 20% of cases.
   B. About 30% of cases.
   C. About 40% of cases.
   D. About 50% of cases.
   E. About 60% of cases.
2. Polymicrogyria is a structural brain malformation of cortical development associated with seizures, including neonatal seizures. Which of the following syndromes is caused by *PEX* gene mutations and is associated with polymicrogyria?
   A. Aicardi syndrome.
   B. Miller-Dieker syndrome.
   C. Zellweger syndrome.
   D. Walker-Warburg syndrome.
   E. Coffin-Siris syndrome.
3. IEMs are an uncommon cause of neonatal seizures, but some are treatable with diet modifications and medications, emphasizing the need to maintain a high index of suspicion to avoid diagnosis delays. Which of the following features is not a clue that an underlying IEM may be present?
   A. Presence of hypotonia on physical examination.
   B. Hypoglycemia.
   C. Anion gap metabolic acidosis.
   D. Resistance to standard antiepileptic drugs.
   E. Hyperammonemia.
4. Channelopathies are examples of single gene, nonsyndromic disorders causing neonatal seizures. Mutations in genes that regulate action potentials and neuronal firing via calcium, potassium, or sodium channels are implicated in the pathophysiology of channelopathies. Which of the following patients with a channelopathy may benefit from treatment with retigabine?
   A. A patient with a *KCNT1* channelopathy.
   B. A patient with a *KCNQ2* channelopathy.
   C. A patient with a *CACNA1A* channelopathy.
   D. A patient with an *SCN2A* channelopathy.
   E. A patient with a *CHRNA4* channelopathy.
5. Vitamin-responsive neonatal epilepsies are important to recognize, because early diagnosis and treatment are key to improve long-term outcomes and decrease mortality. Which of the following statements regarding vitamin-responsive epilepsies is correct?
   A. Pyridoxine-dependent epilepsy can be treated with intravenous or oral pyridoxine.
   B. Pyridoxine-dependent epilepsy is characterized by increased cerebrospinal fluid levels of glycine, threonine, L-DOPA, and 3-methoxytyrosine.
   C. Folinic acid–responsive seizures are caused by α-aminoadipic semialdehyde dehydrogenase deficiency.
   D. Pyridoxine administration can result in central respiratory depression in 40% of cases.
   E. Pyridoxine 5′-phosphate oxidase deficiency can be treated with pyridoxine.

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Mediastinal Air Collection in a Preterm Male

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THE CASE

A male neonate born at 24 2/7 weeks' gestation is transferred to our facility at 81 days of age to receive bilateral diode laser photocoagulation therapy for high-risk retinopathy of prematurity. The infant is requiring a high amount of ventilator support secondary to diffuse, persistent pulmonary interstitial emphysema and bronchopulmonary dysplasia (BPD). The infant's chest radiograph on admission to our facility is shown in Fig 1.

Prenatal and Birth Histories

- Male infant born to a 29-year-old gravida 6, para 2 woman
- Prenatal laboratory screening: Normal
- Prenatal course complicated by maternal end-stage renal disease secondary to type 1 diabetes requiring dialysis and associated with intrauterine growth restriction
- Ultrasonography 2 days before delivery demonstrated normal fetal anatomy with absent end-diastolic flow of umbilical artery
- Maternal presentation at 24 weeks' gestation with uncontrolled severe pre-eclampsia that prompted an emergent cesarean section at 24 2/7 weeks' gestation
- Apgar scores of 1, 1, and 6 at 1, 5, and 10 minutes, respectively. Cord clamping was delayed for 60 seconds. Because of apnea and cyanosis, positive pressure ventilation was started and then the infant quickly underwent intubation; surfactant was administered 16 minutes after birth.
- Infant's birthweight=451 g (2nd percentile), head circumference 19 cm (1st percentile)

Summary of Initial Hospital Course

In the NICU, the infant required 2 additional doses of surfactant at 16 and 24 hours of age with high ventilator settings. In the first few months of age, he was switched between high-frequency oscillatory ventilation and conventional ventilation multiple times because of intermittent periods of inadequate ventilation and oxygenation. On the 6th day of age, he required antibiotic therapy for methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia. At that time, the tracheal aspirate culture was negative. The patient's peripherally inserted central catheter (PICC) was removed on day 10 after birth as a result of persistently positive cultures. On the 10th day after birth, an ovoid, air-filled mass overlying the

AUTHOR DISCLOSURE Drs Yuhas, Bowens, Van Nostrand, Kelleher, Yohannan, and Yohannan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. The views expressed herein are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or US Government.

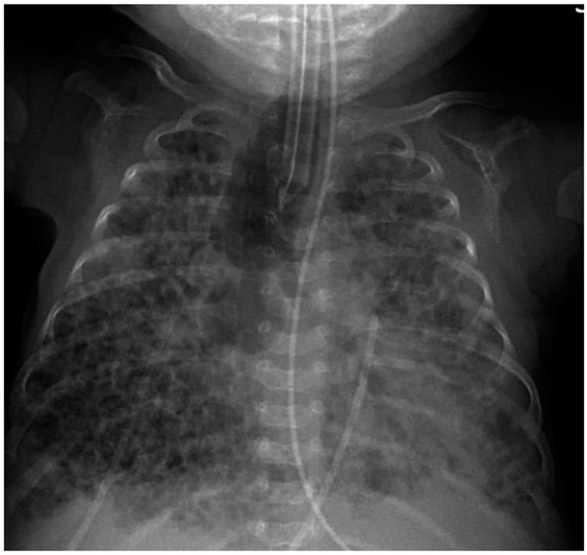

Figure 1. Chest radiograph demonstrates a lobular hyperlucent lesion overlying the superior mediastinum and right medial thorax as well as diffuse coarsened lung markings consistent with chronic lung disease of prematurity. At the time, this lucent lesion was suspected to be a pneumatocele.

upper right mediastinum was seen on chest radiography and thought to represent a large pneumatocele. After negative cultures, the PICC was again replaced on the 37th day of age. No vegetations were identified on echocardiography. Other imaging included head ultrasonography without evidence of intraventricular hemorrhage, and normal findings on abdominal ultrasonography and renal ultrasonography with Doppler flow. The infant received antibiotic therapy for 40 days for persistent MSSA bacteremia. Two courses of low-dose dexamethasone therapy were administered per the Dexamethasone: A Randomized Trial protocol at 30 and 52 days of age secondary to persistently high fraction of inspired oxygen (FIO_2) requirements. He underwent extubation briefly at 73 days of age but required reintubation the following day because of hypercarbia.

PRESENTATION

At 81 days of age, the patient arrived at our facility in critical condition. He was transitioned to the high-frequency oscillator and in the following days, was treated with nitric oxide and sildenafil for moderate pulmonary hypertension (seen on repeat echocardiography) and chlorothiazide for the management of bronchopulmonary dysplasia. He also required antibiotic treatment for presumed *Enterobacter cloacae* pneumonia after a positive tracheal aspirate culture.

Vital Signs (81 days of age)

- Heart rate: 126–152 beats/min
- Respiratory rate: 35 breaths/min
- Temperature: 98.6°F (37°C)
- Blood pressure: 68/30 mm Hg
- Oxygen saturation=93% on high-frequency oscillator with amplitude 36, mean airway pressure 20 cm H_2O, hertz 8, FIO_2 0.9 with 3.0 uncuffed endotracheal tube

Physical Examination

- General: Patient was awake and irritable with cares
- Head, eyes, ears, nose, and throat examination: Anterior fontanelle open, soft, and flat; sutures approximated
- Cardiovascular: Normal S1 and S2 with II/VI murmur, +2/4 pulses that are equal in extremities
- Lungs: Mechanically ventilated, lung sounds coarse with diminished breath sounds, an audible air leak was appreciated
- Abdomen: Soft, nondistended, normal bowel sounds
- Genitourinary: Normal male genitalia for age; patent anus
- Neurologic: Tone and strength normal for age

Laboratory Studies

Serial complete blood cell counts, metabolic profiles, and venous capillary blood gases were followed. Complete blood cell counts and metabolic profiles were unremarkable. Most recent venous capillary blood gas showed pH 7.33, $PaCO_2$ 61 mm Hg (8.1 kPa), PO_2 38 mm Hg (5.0 kPa), bicarbonate 30 mEq/L (30 mmol/L), base excess +2.8 mEq/L. Most recent tracheal aspirate culture showed no growth.

CASE PROGRESSION

Once the patient was stabilized, pediatric otolaryngology and pulmonology services were consulted for further investigation of the suspected pneumatocele that was noted on serial chest radiography (Fig 1).

Differential Diagnosis

This infant presents with an air-filled collection over the mediastinum in the setting of respiratory failure and prolonged ventilator-dependence. The differential diagnosis includes:

- Pneumatocele
- Congenital pulmonary airway malformation
- Bronchogenic cyst
- Pulmonary sequestration syndrome
- Congenital lobar emphysema

Actual Diagnosis

Tracheobronchomegaly. A computed tomography (CT) scan of the chest with and without contrast with 3-dimensional

(3D) reconstruction was obtained at 97 days of age, which demonstrated abnormal dilation of the trachea that extended into the bronchus intermedius on the right (Figs 2–6). The tracheal diameter measured up to 1.4 cm in anterioposterior (AP) dimension, with a dilated right main bronchus; the bronchus intermedius (distal to the right main bronchus and proximal to the branches of the right middle and lower lobar bronchi) measured up to 1.0 cm in AP dimension. Bronchi in the remainder of the right lung appeared normal. After discussion with the consulting services, the decision was made to follow the patient expectantly with potential for a tracheostomy in the future.

What the Experts Say

In this case, the chest CT scan is most consistent with a diagnosis of tracheobronchomegaly. Tracheobronchomegaly is an uncommon finding and is rarely reported in neonates or children. The first clinic description of an adult appeared in 1932 by Mounier-Kuhn; however, the etiology and pathogenesis of this abnormality remains poorly understood. (1) Tracheobronchomegaly could be congenital or acquired. Congenital tracheobronchomegaly or Mounier-Kuhn syndrome is typically discovered on radiography during adulthood and is characterized by atrophy of elastic fibers and predisposition for recurrent pulmonary infections and bronchiectasis. Data on Mounier-Kuhn syndrome are limited, with an estimation of only about 400 case reports published thus far. (2) Other cases of acquired tracheobronchomegaly have been associated with fetoscopic tracheal occlusion for congenital diaphragmatic hernias, prolonged intubation, and recurrent pulmonary infections. (3)

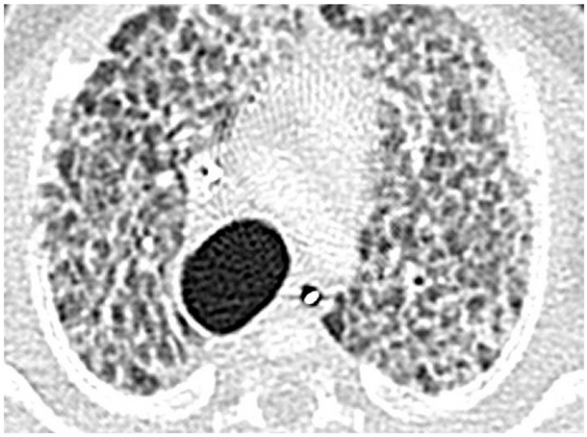

Figure 2. Axial computed tomography image at the level of the aortic arch demonstrates massive dilation of the trachea. Diffuse thickening of the interlobular septae and ground glass opacities are visualized within the lungs.

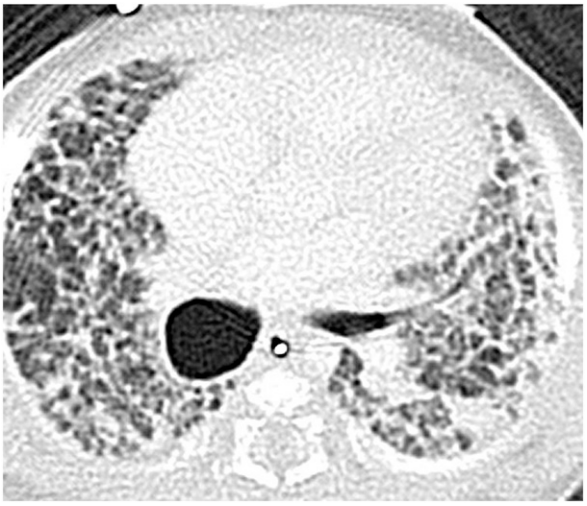

Figure 3. Axial computed tomography image at the level of the mainstem bronchi demonstrating massive dilation of the right mainstem bronchus and mild dilation of the left mainstem bronchus. Diffuse thickening of the interlobular septae and ground glass opacities are again visualized throughout the lungs.

Based on our literature review, pediatric cases of tracheobronchomegaly are mostly acquired, and limited to 23 reported cases, with only 3 individual cases with CT imaging of premature neonates. (4)(5)(6) To our knowledge, this is the first 3D CT reconstruction of tracheobronchomegaly in a neonate. In our case, there was no evidence of tracheobronchial abnormalities until the 10th day after birth, making it more likely to be an acquired than a congenital disorder. It is reasonable to postulate that this infant's

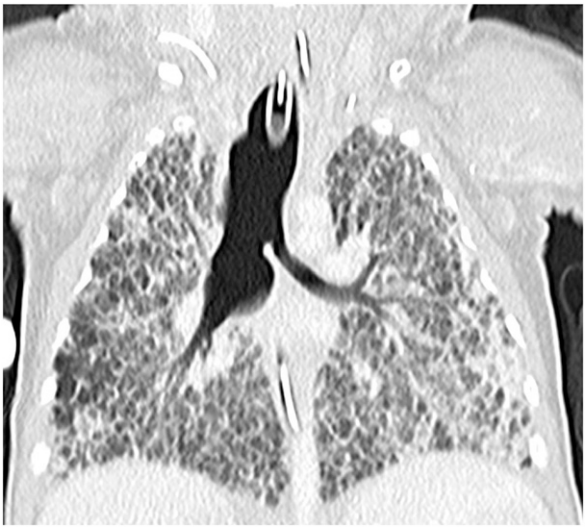

Figure 4. Coronal reconstructions from the same computed tomography study show massive dilation of the trachea and right mainstem bronchus correlating well with the lucent lesion visualized on prior imaging.

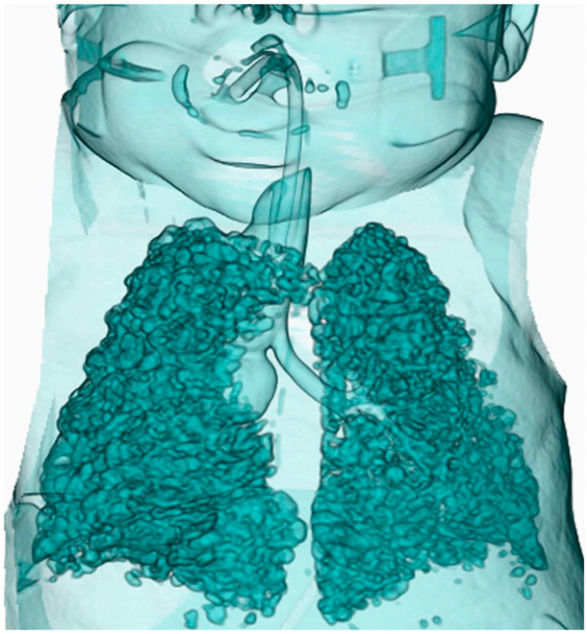

Figure 5. Coronal reconstructions from the same computed tomography study show massive dilation of trachea and right mainstem bronchus correlating well with the lucent lesion visualized on prior imaging. Three-dimensional surface rendering of the trachea and airway demonstrates massive dilation of the trachea and right mainstem bronchus.

tracheobronchomegaly was secondary to a combination of repeated barotrauma of prolonged positive pressure ventilation, prematurity, and MSSA bacteremia. It is important to note, however, that a congenital defect cannot be excluded as a possible predisposing factor. In adults, case reports have shown airway stenting or tracheobronchoplasty to improve respiratory symptoms and quality of life. (2) Similar interventions in children have not been reported. Our patient might require a tracheostomy for prolonged ventilation; at the time of this writing, no corrective surgery is planned.

Before the CT imaging, the diagnosis of a pneumatocele was strongly considered. A pneumatocele is a thin-walled, air-filled cyst that develops in the lung parenchyma. This can have a congenital, traumatic, postinfectious, or ventilator-induced etiology. Pneumatoceles are rare, with a reported incidence of 1.8% in preterm infants born at before 30 weeks of gestation, with an overall incidence in neonates that has decreased significantly in the postsurfactant era. (7) Our infant had prolonged positive pressure ventilation and developed the lesion after birth; however, CT imaging was not consistent with a walled-off cyst.

Other initial considerations for the air-filled collection found on this infant's radiograph are not consistent with the CT findings or history. Congenital bronchopulmonary anomalies such as congenital pulmonary airway malformation, bronchogenic cysts, bronchopulmonary sequestration, and congenital lobar emphysema have findings that would typically be noted on prenatal ultrasonography. (8) No such lesion was seen on antenatal ultrasonography and the infant's first radiograph did not show any pulmonary lesions.

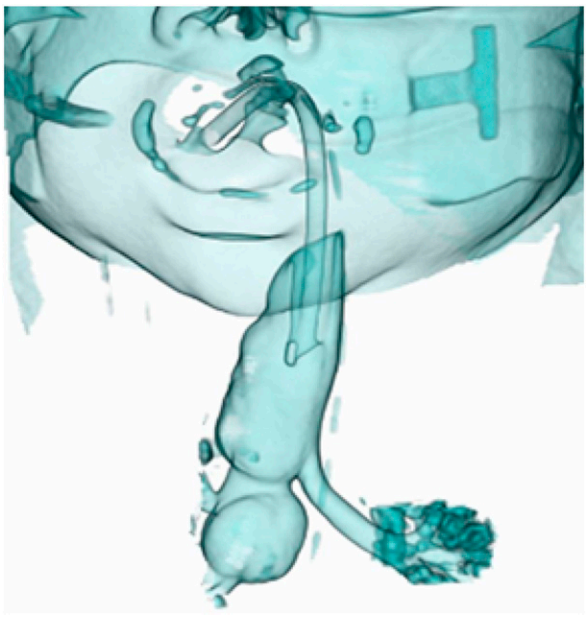

Figure 6. Coronal reconstructions from the same computed tomography study show massive dilation of trachea and right mainstem bronchus correlating well with the lucent lesion visualized on prior imaging. Three-dimensional surface rendering of the trachea and airway demonstrates massive dilation of the trachea and right mainstem bronchus.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical, laboratory, and imaging features of air leaks.
- Recognize the clinical and imaging features of congenital malformations of the lung, including congenital pulmonary lymphangiectasia, the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors.

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Vein of Galen Malformation

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CASE PRESENTATION

A 37-year-old gravida 3, para 1 pregnant woman was referred to the Maternal Fetal Care Center (MFCC) at Boston Children's Hospital at 36 weeks' gestation for the finding of vein of Galen malformation (VOGM).

The patient's pregnancy was complicated by gestational diabetes. Her surgical history was notable for adenoidectomy, a previous cesarean section, and dilation and curettage following a spontaneous abortion. Maternal medications included prenatal vitamins and glyburide. Family history was noncontributory. This pregnancy was planned and naturally conceived. The woman received appropriate prenatal care. Noninvasive prenatal screening showed her to be at low risk and cell-free fetal DNA screening was negative. She had a normal anatomy scan at 20 weeks' gestation. Fetal ultrasonography performed at 36 weeks' gestation for evaluation of fetal growth demonstrated a prominent rounded vascular structure in the quadrigeminal cistern with turbulent flow consistent with a VOGM. Fetal echocardiography at that time revealed dilation of the right atrium and right ventricle with normal biventricular function. There was no evidence of hydrops.

Imaging at 37 weeks' gestation in the Boston Children's Hospital MFCC included repeat comprehensive fetal echocardiography, fetal ultrasonography, and fetal brain magnetic resonance imaging (MRI). Echocardiography revealed a markedly enlarged right atrium and right ventricle with mild right ventricular dysfunction. Moderate tricuspid regurgitation was noted, the innominate vein was markedly dilated, and the superior vena cava had increased flow. The interventricular septum was dyskinetic, suggesting increased pressure within the right ventricle. There was a patent foramen ovale and a patent ductus arteriosus with right-to-left shunting throughout the cardiac cycle. No evidence of pericardial effusion or hydrops fetalis was seen. Fetal ultrasonography showed a singleton male fetus with biometry measurements, including head circumference, corresponding to estimated gestational age. Amniotic fluid volume was normal. The fetal survey demonstrated a large midline intracranial vascular structure in the expected location of the median prosencephalic vein, with aneurysmal dilation, turbulent flow, and multiple bilateral feeding vessels (Fig 1A). The dilated prosencephalic vein drained into a persistent falcine sinus. The right jugular vein and the right common carotid artery were mildly prominent with

AUTHOR DISCLOSURE Drs Cordova, Levy, Kheir, Orbach, Barnewolt, and Estroff have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CPAP	continuous positive airway pressure
F_{IO_2}	fraction of inspired oxygen
MFCC	Maternal Fetal Care Clinic
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
PGE1	prostaglandin E1
VOGM	vein of Galen malformation

turbulent flow in the right jugular vein (Fig 1B). No evidence of ventriculomegaly or hydrocephalus was seen. The remainder of the fetal survey was notable for an enlarged heart but no other abnormalities. Fetal brain MRI demonstrated similar evidence of a VOGM, likely choroidal type. The prosencephalic varix measured approximately 1.7 cm in greatest cross-sectional diameter. The falcine sinus was large and dilated, and a straight sinus was present as well, with a markedly enlarged torcular (meeting point of 4 cranial venous sinuses) (Fig 2A). Multiple anomalous vessels were observed within the interhemispheric fissure in the pericallosal region, ambient cistern, and suprasellar cistern. The anterior and posterior arteries of the circle of Willis were enlarged, suggesting increased flow (Fig 2B). No hemorrhage or parenchymal injury was evident. The remainder of the brain structures were appropriately formed.

EXPERT OPINION

At the MFCC at Boston Children's Hospital, pregnant women carrying fetuses with suspected or confirmed congenital anomalies receive counseling and care from a multidisciplinary team of experts. In this case, the assembled multidisciplinary team included subspecialists in maternal-fetal medicine, neonatology, pediatric cardiology, pediatric neurology, interventional neuroradiology and pediatric neurosurgery, as well as nursing and social work staff from our medical-surgical intensive care unit. This team approach ensured the development of a comprehensive care plan that focused on confirming the prenatal diagnosis, antenatal monitoring, delivery planning, postnatal evaluation and possible intervention, and the long-term follow-up approach.

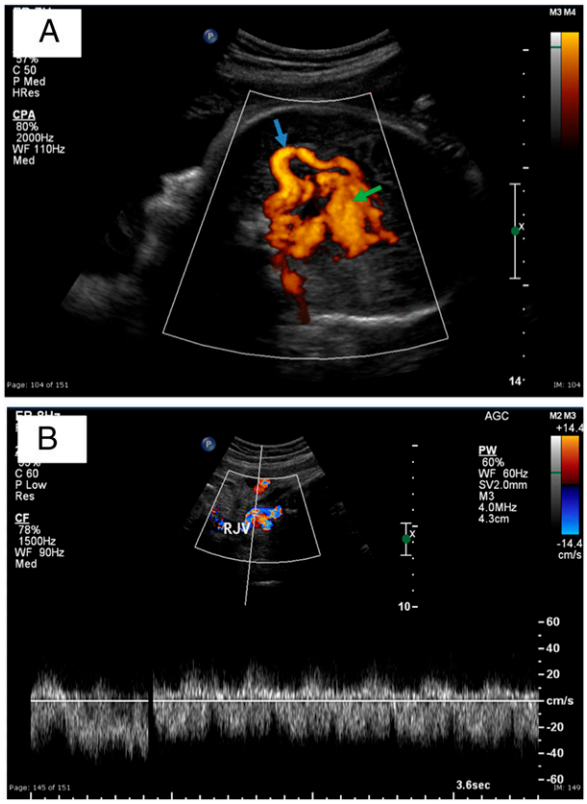


Figure 1. Fetal survey at 37 weeks' gestation. A. Vein of Galen malformation (VOGM) appears as a tangle of vessels confirmed on color Doppler ultrasonography as an arteriovenous shunt with multiple feeding arteries (blue arrow) that drain into the dilated venous sac (green arrow). B. VOGM causes dilation of blood returning to the right heart. Color Doppler ultrasonography shows dilated right jugular vein with turbulent flow.

The results of the MFCC diagnostic imaging studies confirmed the diagnosis of VOGM. Our team met with the family, explained the imaging findings, and discussed therapeutic options. We reviewed the cardiovascular dynamics of a VOGM and the potential problems it can cause.

Pediatric cardiology counseled the family about the impact of the VOGM on the developing heart and blood vessels in the lung. We explained that the relatively favorable findings on fetal echocardiography may not be predictive of the postnatal course, and we presented the cardiovascular course as a continuum, from relative stability at birth to potentially rapid decline caused by worsening high-output heart failure.

Pediatric neurosurgery described the possible neurologic impacts of the VOGM including brain injury from ischemia or hemorrhage and hydrocephalus. Fetal ultrasonography showed a normal head size with no evidence of hydrocephalus. We cautioned, however, that these initial favorable findings do not eliminate the possibility that after birth, the infant may develop subsequent neurologic dysfunction from ongoing brain blood flow disturbances.

We discussed potential postnatal treatments including the possibility of a neurointerventional procedure such as arterial embolization to diminish or occlude the arterial blood supply to the VOGM. In the context of the results of prenatal imaging, we explained to the family that if their newborn is stable from a cardiovascular standpoint, the strong preference is to wait until the infant is 3 to 5 months of age to perform embolization, because the procedural risk is markedly diminished as the infant gets older. Conversely, if their newborn is not stable, urgent embolization would be warranted.

The team emphasized the fact that the infant's prognosis will be influenced greatly by the events after birth. Depending on the postnatal complications, there is a wide range of developmental outcomes in VOGM: from normal development to moderate or severe deficits across motor and cognitive domains. Major postnatal complications include

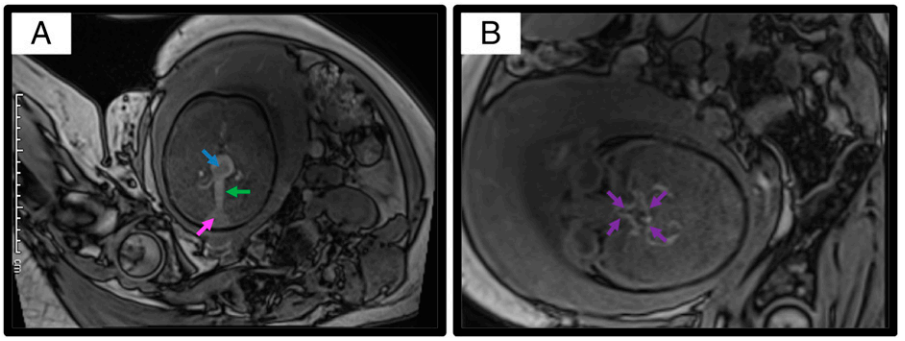


Figure 2. Axial T1 magnetic resonance imaging at 37 weeks' gestation showing the fetal brain. A. Choroidal type vein of Galen malformation (VOGM) demonstrating dilation of the persistent embryonic median prosencephalic vein (blue arrow), as well as dilation of the straight sinus (green arrow) and transverse/sagittal sinus confluence (pink arrow). B. Enlarged arteries in the circle of Willis (purple arrows) suggesting a high shunt flow.

ischemic or hemorrhagic injury to the brain or complications related to cardiac failure.

The multidisciplinary plan for this infant included delivery (timing and type to be determined by the obstetrician) followed by admission to a level III to IV NICU. In the NICU, central umbilical venous and arterial access would be obtained. The infant would be closely monitored clinically and postnatal diagnostic evaluation would include baseline head ultrasonography as well as MRI with angiography (MRA) and venography (MRV) from the aortic arch to the cranial vertex. These studies would further define the anatomy of the malformation, allowing for treatment planning, and assessment of subtle injuries to the brain parenchyma that might not have been visualized well on fetal imaging. The newborn would also be evaluated with serial postnatal echocardiography. Should there be a decline in cardiopulmonary status (eg, hypoxic respiratory failure from severe pulmonary hypertension or progressive heart failure), urgent embolization would be needed. If the infant remained stable for the first few days after birth, the plan would be to discharge from the NICU, with close follow-up by the pediatrician, pediatric cardiology, and pediatric neurology. Serial head ultrasonographic imaging would be performed and reviewed by the Cerebrovascular Surgery and Interventions Center at Boston Children's Hospital, who would also indicate the timing for repeat brain MRIs. The infant's developmental trajectory would be followed very closely for the first few years of age to determine the need for specialized services through early intervention.

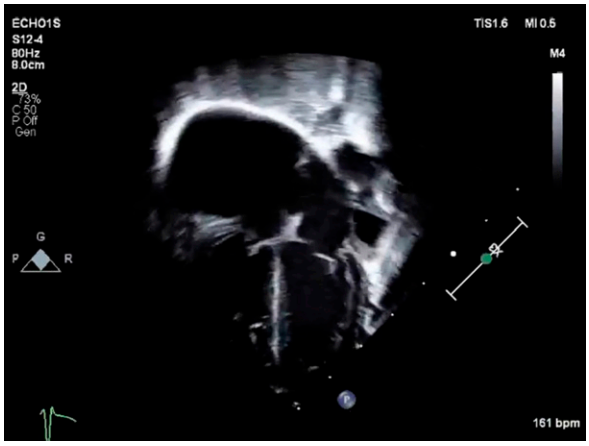
OUTCOME

After confirmation of the VOGM diagnosis and discussion with the family, the pregnant woman was monitored with weekly fetal nonstress tests and biophysical profiles. In consultation with maternal-fetal medicine and neonatology, she received a complete course of antenatal steroids at 35 weeks' gestation.

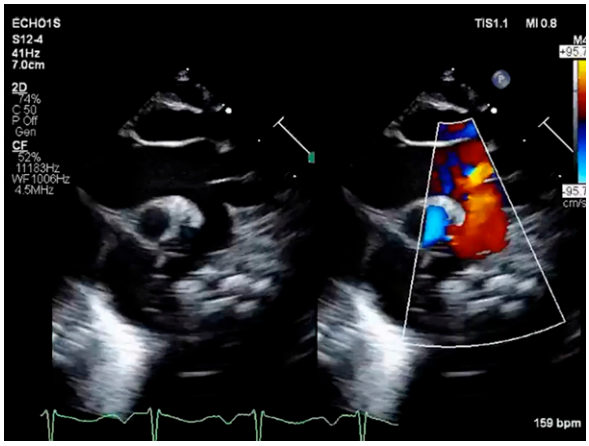
At 38 1/7 weeks' gestation, a 3,290-g male was delivered via repeat cesarean section. His Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The infant was admitted to the NICU and placed on continuous positive airway pressure (CPAP) of 6 cm H_2O shortly after birth because of tachypnea and oxygen requirement. The initial heart rate and blood pressure were normal for gestational age, with pre- and postductal saturations in the low 90s before the initiation of CPAP. The physical examination revealed a term infant with slightly decreased activity, in moderate respiratory distress with tachypnea and subcostal retractions. Breath sounds were symmetric and aeration was fair. There was a 2/6 systolic murmur, 2+ femoral pulses with cool extremities with a capillary refill of 3 seconds, and no hepatomegaly. The anterior fontanelle was open, soft, and full, and a cranial bruit was appreciated. The pupils were symmetric and reactive to light. Tone was appropriate for age, reflexes were 2+ and symmetric, and the infant had spontaneous movement in all 4 extremities.

Postnatal echocardiography (Video 1 and labeled still image) demonstrated right atrial and ventricular dilation with moderate systolic dysfunction, moderate tricuspid regurgitation, suprasystemic right ventricular pressure, and right-to-left shunting through the ductus arteriosus and foramen ovale. The transverse arch Doppler demonstrated holodiastolic flow reversal consistent with a hemodynamically significant shunt (Video 2 and labeled still image). Brain MRI/MRA/MRV confirmed a complex choroidal type of VOGM with bilateral anterior and posterior circulation contributions (Fig 3A). An interval increase was noted in size of the varix and feeding pedicles compared with the fetal imaging.

During the first 12 hours after birth, the infant became progressively more tachypneic, with increasing work of breathing and oxygen requirement. The infant's hemodynamics



Video 1 and Still Image. Postnatal echocardiogram. Apical 4-chamber view of the heart demonstrates a dilated right atrium. The arteriovenous shunt causes excess volume load from the superior vena cava into the right atrium. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle.



Video 2 and Still Image. Postnatal echocardiogram. High parasternal aortic arch view demonstrates retrograde flow (red). Ao=aortic arch; BV=brachiocephalic vein; Desc. Ao=descending aortic arch; RPA=right pulmonary artery.

worsened with tachycardia, narrowing pulse pressure, and evolving hypotension. The overall clinical picture was suggestive of progressive high-output heart failure from a large systemic shunt and pulmonary hypertension with hypoxemia from atrial and ductal level shunting.

Medical management included inotropic support (dobutamine with a maximum dose of 10 μg/kg per minute) to maintain goal mean arterial pressure, inhaled nitric oxide, and fraction of inspired oxygen (FIO_2) of 1.0 to decrease pulmonary vascular resistance and improve pulmonary blood flow. Despite these measures, the infant's clinical status deteriorated, requiring intubation, sedation, and muscle relaxation to optimize gas exchange and decrease metabolic demand. After intubation, the infant was placed on volume guarantee ventilation with a tidal volume of 4.5 mL/kg and positive end-expiratory pressure of 7 cm H_2O. An arterial blood gas measurement showed a pH of 7.36, PCO_2 of 34 mm Hg (4.5 kPa), PO_2 of 55 mm Hg (7.3 kPa), bicarbonate of 18 mEq/L (18 mmol/L), and base deficit −6.4 mEq/L with a lactate level of 4.7 mg/dL (0.5 mmol/L). The infant's urine output was 0.5 mL/kg per hour and serum creatinine was 1.2 mg/dL (106 μmol/L). Given these signs of impaired systemic circulation (hypotension, oliguria, elevated creatinine, and elevated lactate), a prostaglandin E1 (PGE1) infusion was initiated to maintain ductal patency and allow the right ventricle to support the systemic circulation. Because of the state of circulatory shock as a result of this hemodynamically significant VOGM, the decision was made to move toward urgent embolization by neurointerventional radiology.

On postnatal day 2, the infant underwent partial transarterial embolization of the VOGM with coil occlusion of 5 right posterior cerebral artery distal feeding arteries at the arteriovenous junction, via umbilical artery catheter access (3.5F). The procedure finished when the maximal daily contrast dose for the patient's weight had been administered and was uncomplicated. After the procedure, ventilatory support and FIO_2 were weaned and markers of end-organ perfusion improved. On postnatal day 3, the infant returned to the interventional radiology suite for embolization of the left posterior cerebral artery feeders; after these 2 rounds of embolization it was estimated that a shunt reduction of approximately 50% had been achieved. This procedure was also uncomplicated, with the exception of a self-resolved episode of supraventricular tachycardia without hemodynamic compromise. Posttreatment echocardiography indicated that right ventricular pressure remained systemic but improved, with ductal flow now bidirectional and right ventricular function improved. At this point, treatment with PGE1 was discontinued to avoid compromising the systemic perfusion because of circular shunting: in the setting of right ventricular dysfunction, as pulmonary vascular resistance decreases, a large duct can result in flow reversal at the ductal level from left to right, stealing from the systemic circulation and increasing the pulmonary artery pressure; blood then regurgitates back into the dysfunctional right ventricle, from the right ventricle to the right atrium and from the right atrium to the left atrium via the foramen ovale without passing through the pulmonary capillary bed, which results in worsening hypoxemia.

After the initial improvement that lasted several days, the infant's clinical cardiopulmonary condition worsened, requiring nitric oxide and pressor support to be restarted. Consequently, at 11 days of age, the infant required additional embolization. The plan was to use a retrograde transvenous

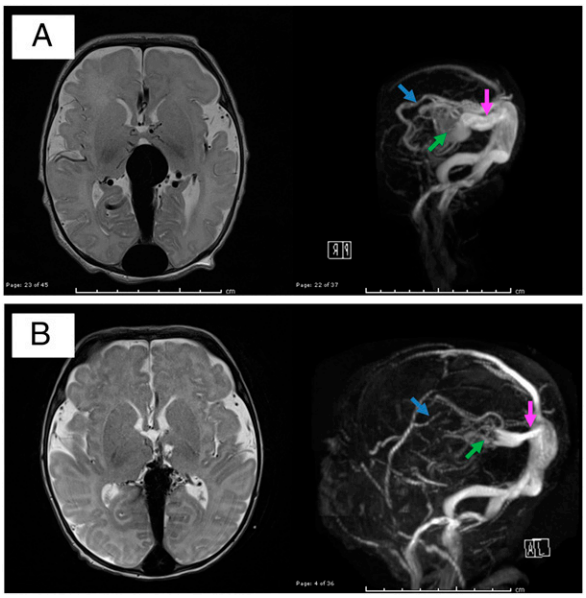


Figure 3. Postnatal magnetic resonance imaging (MRI) scans before and after embolization. Axial T2-weighted MRI scans showing vein of Galen malformation (VOGM) with corresponding 3D venography showing multiple feeding arteries (blue arrow), dilated median prosencephalic vein (green arrow) and prominent draining veins (pink arrow). A. Day 0 after birth before intervention. B. Day 43 after birth after 3 embolization procedures. Significant interval decrease of the arteriovenous shunt.

approach into the remaining arterial inflow points to definitively occlude or nearly occlude flow through the malformation. However, retrograde access to the target proved to be technically unfeasible, and as discussed with the parents before the procedure, the decision was made to directly embolize the varix itself. This was accomplished without complication, and with resultant clear angiographic diminution of flow (though without complete occlusion of the lesion). After the procedure, the infant's clinical status rapidly improved, allowing nitric oxide to be weaned the next day and pressor treatment to be discontinued the same day. The precordium was less hyperdynamic, though findings on echocardiography remained unchanged. By 3 days after this third embolization, the nitric oxide was discontinued, and the cranial bruit was no longer appreciated. Nine days after the last embolization (postnatal day 20), the infant underwent extubation to noninvasive positive pressure ventilation and was supported with diuretics. He continued to be monitored with serial echocardiography. Despite sustained clinical improvement, echocardiographic improvement in pulmonary hypertension lagged behind. Approximately 3 weeks after the last embolization, echocardiography showed only mild right ventricular dysfunction and mild pulmonary hypertension, though diastolic flow reversal persisted in the descending aorta.

Despite the overall improvement, the infant had difficulty in successfully initiating oral feedings because of persistent tachypnea and possible oral aversion from prolonged intubation. Four weeks after embolization, echocardiography showed continued right-sided improvement, with minimal pulmonary hypertension, but with possible new left ventricular depression. This clinical state persisted over the next 2 weeks, and repeat echocardiography showed evidence of sustained biventricular dilation and dysfunction. Brain MRA at that time showed overall diminution in caliber of the varix and general diminution of the caliber of the circle of Willis vessels. However, 3 individual arterial feeders remained, so the decision was made to target these vessels with transarterial embolization. This was done on day 43 with a liquid embolic agent. The infant was able to wean off noninvasive positive pressure ventilation to low-flow nasal cannula on day 31 and underwent only a brief reintubation for the procedure. He continued to receive supplemental oxygen and diuretics for the management of pulmonary hypertension. Follow-up echocardiography demonstrated resolution of biventricular dysfunction and pulmonary hypertension, and the infant weaned off supplemental oxygen on day 60. Brain MRI before discharge demonstrated significant interval decrease in the caliber of the dilated venous structures, as well as of the arteries in the circle of Willis, choroidal and pericallosal arteries (Fig 3B). The infant was discharged from the hospital at 2 months and 14 days of age breathing room air but still requiring some nasogastric tube feedings. Neurologic examination findings at discharge were normal for age.

The infant was monitored with monthly visits to his pediatrician and monthly head ultrasonographic imaging that was staggered so that he would be assessed clinically or radiographically every 2 weeks. Serial examinations showed a normal head growth trajectory and developmental milestones, including successful transition to full oral feedings. Serial scans demonstrated stable mild ventriculomegaly and no growth of the median prosencephalic vein. Follow-up MRIs at 6, 12, and 30 months of age (Fig 4) revealed stable embolization with similar caliber of feeding arteries and draining veins compared with the last inpatient study. There were no new brain injuries and no evidence of evolving hydrocephalus. A few residual feeding vessels were noted, though given the infant's normal neurologic findings and neurocognitive development, the consensus was to continue to monitor the patient clinically with serial follow-up MRIs. Further intervention would be considered only if the patient developed clinical deterioration or imaging exacerbations.

DISCUSSION

We present the case of an infant with antenatal diagnosis of VOGM who experienced early neonatal cardiovascular decompensation, underwent successful staged endovascular

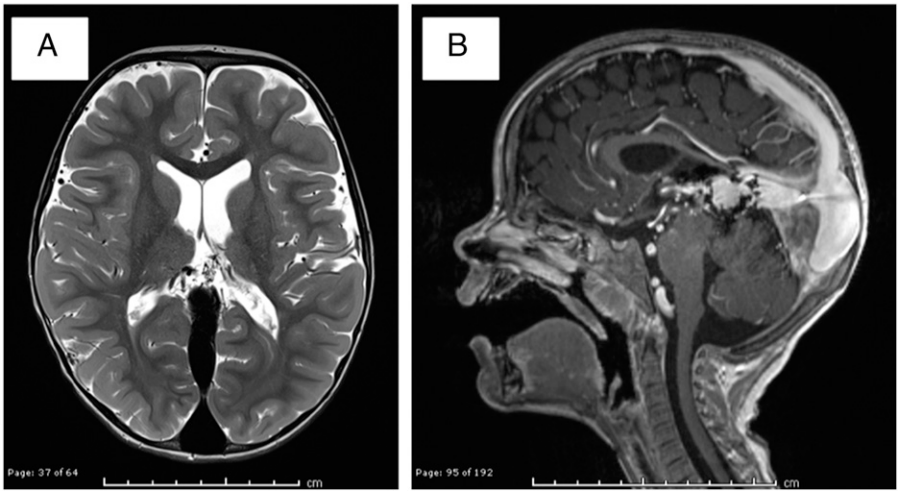


Figure 4. Magnetic resonance imaging (MRI) scan at follow-up. Axial and sagittal T1 MRI scans at 30 months of age. A. Stable size of vein of Galen malformation (VOGM). There is interval development of the brain with resolution of previously prominent extra-axial spaces. B. Susceptibility artifact from endovascular coils in the VOGM with little residual flow.

embolization, and had a good neurologic outcome at 3 years of age.

VOGM is a rare intracranial arteriovenous malformation with an estimated incidence of 1 in 25,000. (1) VOGM accounts for fewer than 1% of all cerebrovascular malformations, but represents nearly 30% of all pediatric cerebrovascular malformations. (2) It is characterized by the persistence of embryonic arteriovenous loops between the choroidal arteries and the median prosencephalic vein, which is an embryonic precursor of the mature vein of Galen. (3) Two morphologic subtypes are seen; in the choroidal subtype, as in this case, multiple choroidal arterial branches contribute to a complex plexiform network before draining into the median prosencephalic vein. The mural subtype exhibits either a single or a small number of direct arteriovenous fistulae connecting choroidal arterial feeders to defects in the wall of the persistent median prosencephalic vein. (4)

The neonatal presentation of VOGM is characterized by high-output cardiac failure and associated systemic hypoperfusion secondary to the effects of the large intracranial arteriovenous shunt. In utero overcirculation of the pulmonary vascular bed leads to the development of pulmonary hypertension. The increased pulmonary artery pressure imposes a pressure load on the right side of the heart and the large volume of the shunt imposes a volume overload, leading to right ventricular dilation and dysfunction. To avoid a shock state (insufficient oxygen delivery), the left ventricle must pump a normal cardiac output in addition to the shunt volume, which may lead to left ventricular dysfunction. In addition, intracranial steal from the VOGM during diastole may further contribute to cardiac dysfunction via coronary artery ischemia and is associated with retrograde descending flow in the aorta, which may worsen shock physiology with impaired end organ perfusion. (5) The neurologic effects of VOGM are the result of both arterial steal from the cerebral circulation and intracranial venous hypertension, leading to parenchymal ischemic/hemorrhagic injuries, encephalomalacia, seizures, and/or hydrocephalus. (4)

The medical management of VOGM is directed toward reducing the effects of the shunt by balancing pulmonary and systemic perfusion and supporting cardiac function. Invasive mechanical ventilation, sedation, and paralysis are used to lower the infant's cardiometabolic demand. Increasing FIO_2 to 1.0 and nitric oxide are used to manage pulmonary hypertension. Treatment with dobutamine serves to support ventricular dysfunction, and it is preferred over other pressors (eg, dopamine, epinephrine, norepinephrine) to avoid excessive systemic vasoconstriction that may further impair systemic perfusion. Milrinone should be used with caution because it may lower diastolic arterial pressure, compromising coronary and organ perfusion pressure. PGE1 plays a role in reducing right ventricular afterload and promoting postductal delivery of systemic blood flow. (6)

When diagnosed prenatally, fetal evaluation at an advanced maternal-fetal care center allows for extensive evaluation, counseling, and planning of delivery and treatment strategy after birth. When a VOGM is suspected prenatally, the objectives of the fetal evaluation are to confirm the diagnosis, to evaluate the extent of the malformation including identification of any injury to the surrounding brain or abnormal ventricular size, and to evaluate the fetal cardiac function. In this case, in utero imaging was favorable; however, the infant went on to develop high-output cardiac failure shortly after birth. This presentation illustrates the most common scenario, in which a fetus with a large VOGM

typically does not develop high-output cardiac failure in utero, likely because of low vascular resistance in the arteriovenous malformation being balanced by the low resistance of the uteroplacental unit. (7)

In relatively rare cases, antenatal manifestations are of significant prognostic value and should be incorporated in the counseling and decision making. Specifically, in utero cardiac failure (ie, severe tricuspid regurgitation) and major cerebral damage (ie, encephalomalacia) are prenatal findings associated with poor outcomes such as death, or severe global neurologic impairment. (8) Notably, the size of the prosencephalic varix itself does not necessarily predict the development of high-output failure or the severity of postnatal symptoms. For these already severely affected fetuses, when termination of pregnancy is not chosen or is not an option, a palliative approach is usually offered to families after birth. Although there is no currently approved fetal intervention, studies to assess the safety and efficacy of fetal intervention are being designed at our institution, with the goal of decreasing the incidence of aggressive neonatal cardiopulmonary presentation and the potential for parenchymal brain injury.

After delivery, the clinical presentation of neonates with a VOGM varies across a wide spectrum, in part because of the dynamic pathophysiologic changes of the cardiopulmonary and cerebral hemodynamics. A standardized approach to the assessment and therapeutic intervention is essential and requires careful physiologic characterization. Clinical decision tools such as the Bicêtre score (4) are available to assist in determining the appropriateness and timing of embolization. However, the clinical status of infants with VOGM can change rapidly and low scores at presentation are not necessarily predictive of poor outcome and should not preclude consideration to treat. (9) A strict score-based decision to treat is no longer adhered to rigorously at most high-volume centers, and an interdisciplinary assessment of the infant's evolving clinical status and radiologic findings is recommended instead. (10) Patients who require urgent neurointervention include those whose heart failure is severe. Critically ill newborns with VOGM and hemodynamic compromise require multidisciplinary care from a team of subspecialists in neonatology, cardiology, neurology, neurosurgery, and interventional neuroradiology who are experts in VOGM management. Historically, the outcome of infants with VOGM was almost universally grim, with mortality rates as high as 80% to 100%. (11) The advances in neonatal critical care, along with the advent of endovascular treatment techniques, have reversed this former poor prognosis. Consequently, timely referral of infants with this diagnosis to specialized centers with expertise in VOGM, including neurointerventional procedures, is imperative.

Prognosticating outcome in VOGM cohorts has been challenging because of the widely variable inclusion criteria and management protocols. In infants presenting with symptoms during the newborn period, early mortality reported in the literature is between 20% and 50%. (12) Even after treatment, neonates remain at high risk. Postembolization mortality rates range between 10% and 15% across all age groups. In contrast, postembolization mortality rates in neonates with cardiac failure can be as high as 36% and possibly even higher. (13) Nonetheless, as shown in 2 recent meta-analyses, with treatment, the outcome has been noted to be good (defined as neurologically normal or mild developmental delay) in up to 68% of surviving patients with VOGM, (14)(15) with the caveat that these are cohorts selected as "treatable" by the local teams, with exclusion of more than 20% of the most critically ill neonates with VOGM. (3) Recent national population data from the United Kingdom, the first large unselected cohort, paints a somewhat grimmer picture: despite expert care at specialized centers, severely affected newborns with VOGM who develop cardiopulmonary symptoms early and who require urgent embolization (approximately two-thirds of all newborns with VOGM), continue to have a high mortality rate (~40%) and a high rate of severe neurodevelopmental morbidity among survivors (~50% of survivors). (16) Other patients with VOGM who do not have physiologic decompensation and do not require cardiac or respiratory support typically have an elective embolization at several months of age. This group has a mortality rate of ~10%, though this group still has a 30% risk of moderate to severe neurocognitive morbidity. (17) Robust data on postnatal predictors of outcome are lacking. However, severe neonatal congestive heart failure (18) and suprasystemic pulmonary hypertension (19) have been associated with postnatal death. Choroidal lesions have been reported to have worse outcomes, albeit not consistently. (20) Recently, middle cerebral artery pseudofeeders seen on MRI have been described as a risk factor for the occurrence of encephalomalacia. (21)

In eligible infants, transarterial endovascular embolization is the therapeutic standard of care. This neurointerventional procedure has markedly lowered mortality and reduced neurologic morbidity in survivors. The goal of early and aggressive medical management of cardiac failure is to achieve hemodynamic stability to allow for endovascular intervention. Embolization aims to occlude the arterial feeders to the malformation to reduce the shunt fraction. The anatomic target of embolization is the distalmost aspect of the arterial pedicles, ideally the arteriovenous junction or the proximal site of the venous collector. The embolic implant can be either detachable coils or a liquid embolic agent, such as cyanoacrylate glue. Although

direct embolization of the prosencephalic varix itself was one of the first embolization techniques developed, (22) this is rarely used as the first-line approach because of the risk of severe intracranial hemorrhage from deep venous occlusion. (23) Cases in which this approach is considered, such as the case presented here, have persistent severe cardiopulmonary decompensation despite significant transarterial embolization. Thus, in our patient, when it became apparent that further significant hemodynamic improvement could no longer be achieved via a transarterial approach, embolization of the venous varix was performed during the third round of treatment, at day 11 after birth.

When cardiovascular stability allows (ie, cardiac failure controlled with diuretics), embolization treatment is deferred until approximately 3 to 5 months of age to balance the risk of embolization with the risk of delayed cerebral maturation. (24) A staged embolization approach is recommended to avoid the massive hemodynamic shifts associated with the instant flow reversal after occlusion of a VOGM. After embolization, it is important to monitor for the development of hydrocephalus with serial neurologic assessments, including tracking of the child's head circumference, developmental milestones, and serial ultrasonographic measurement of ventricular size. Direct treatment of symptomatic or progressive hydrocephalus should be undertaken only after embolization, to minimize the well-documented risk of intracranial hemorrhage after the placement of ventricular drains in untreated infants with VOGM. (25)

The overall rate of moderate to severe neurodevelopmental delay associated with VOGM varies from 17% to 26% (15) with higher rates among neonates compared with infants. It is important to recognize that neurocognitive difficulties with higher-level functions that are not apparent in infancy can emerge at a later age. (26) A recent large single-institution series that evaluated neurodevelopmental outcomes at school age of children with a diagnosis of VOGM reported that only about half of the surviving patients had a favorable outcome, and a large proportion of them had neuropsychological alterations that may have repercussions on learning. (19)

Until recently, our understanding of the genetics and molecular mechanisms of VOGMs has been limited, which has represented an obstacle to the development of novel targets for VOGM screening, diagnosis, prognostic prediction, and treatment. However, recent demonstration of mutations in HHT-related genes, (27) *RASA1* (28) and coding for Ephrin B4, (29) have definitively demonstrated that the malformation has a genetic etiology, rather than a random embryonic maldevelopment. Whole exome sequencing on a large cohort of patients with VOGM has identified novel mutations in chromatin, as well as the previously described mutations. (30) Large inter-institutional registries and next-generation genetic sequencing are likely to enable further much needed VOGM genetic phenotyping. (31) Such tools may prove invaluable in counseling families and caring for infants with VOGM.

SUMMARY

- The severe form of VOGM presents in 65% of cases during the neonatal period with signs of high-output heart failure.
- Prenatal multidisciplinary counseling should be based on manifestations of major cerebral damage and in utero cardiac failure, while acknowledging that even in the absence of poor antenatal prognostic factors, the postnatal course and ultimate outcome will be influenced to a large extent by postnatal events and complications.
- Transarterial endovascular postnatal embolization in experienced hands has dramatically improved survival rates and reduced neurologic morbidity in eligible infants. Yet, neonatal presentation is associated with persistently high rates of mortality and long-term neurodevelopmental morbidity among survivors.
- The decision to treat and the timing of intervention for VOGM is best determined using an interdisciplinary diagnostic and therapeutic strategy that incorporates clinical, echocardiographic, and MRI data with input from subspecialists in neonatal intensive care, cardiology, neurosurgery, and interventional neuroradiology.
- It is critically important to have judicious patient selection and clarity of therapeutic goals for the medical team and the family. Emphasis is placed on frequent, open, interdisciplinary communication among the care team and with the family from prenatal consultation and delivery planning to postnatal care and follow-up.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the role and risks of magnetic resonance imaging, as well as other non-ultrasonographic imaging techniques in assessing fetal anatomy.
- Know the indications, application, and complications of the use of prostaglandin E1 to maintain patency of the ductus arteriosus in neonates.
- Recognize the clinical features and differential diagnosis of persistent pulmonary hypertension.
- Know the clinical features and evaluation, management, complications of management, and outcome of intracranial arteriovenous malformations.

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ANSWER KEY FOR OCTOBER 2020 NEOREVIEWS

Neonatal Presentations of Metabolic Disorders: 1. C; 2. D; 3. B; 4. A; 5. E.

Genetic Etiologies of Neonatal Seizures: 1. E; 2. D; 3. C; 4. B; 5. A.

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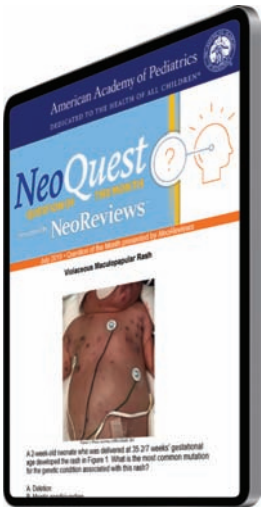

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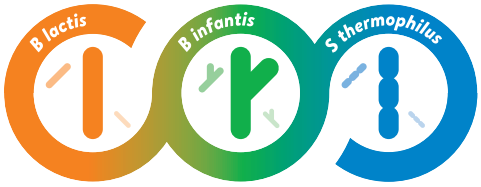

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Index of Suspicion in the Nursery

1 Rapidly Rising Bilirubin Level in a 3-day-old Term Infant

Christina G. Tise, MD, PhD,*† Neha S. Joshi, MD,* Alma D. Erice-Taganas, MD,* Elizabeth M. Blecharczyk, MD*

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PRESENTATION

A female infant is delivered at 38 weeks and 6 days' gestation, after induction of labor for preeclampsia, to an otherwise healthy 37-year-old, gravida 1, para 0 woman via vacuum-assisted vaginal delivery with 4 pulls and no pop-offs. The vacuum was used secondary to fetal heart rate decelerations. The mother was colonized with group B *Streptococcus* and received adequate intrapartum antibiotic prophylaxis. The infant is floppy at birth with a weak cry and heart rate greater than 100 beats/min. Continuous positive airway pressure is administered at 5 minutes of age because of respiratory distress, which resolves by 20 minutes of age. The infant's Apgar scores are 4 and 7 at 1 and 5 minutes, respectively. She has a birthweight of 3.15 kg (43rd percentile). The mother and infant both have O+ blood type and screen negative for antibodies. The infant's total bilirubin (TB) levels at 25 and 31 hours after birth are 9.1 mg/dL (155.6 μmol/L) and 11.5 mg/dL (196.7 μmol/L), respectively (Fig 1); direct bilirubin is not measured. Triple bank phototherapy (bili blanket and 2 bank overhead bili light) is initiated at 31 hours of age, because of a rapid rise in TB at a rate of 0.4 mg/dL per hour (6.8 μmol/L per hour). (Fig 1) The infant continues to receive phototherapy for 18 hours, with a subsequent TB level of 10.4 mg/dL (177.8 μmol/L). Phototherapy is stopped, and the infant is discharged from the hospital.

At 78 hours of age, the infant is readmitted because of a TB level of 18.9 mg/dL (323.2 μmol/L), with a phototherapy TB threshold of 18.3 mg/dL (312.9 μmol/L) and 0.30 mg/dL per hour (5.1 μmol/L per hour) rate of rise (1); direct bilirubin level is 0.63 mg/dL (10.8 μmol/L; normal <6.8 μmol/L). The infant's weight is 11.7% below birthweight and triple-bank phototherapy is initiated. The parents report frequent breastfeeding and adequate urine output. Clinical examination reveals a sleeping but arousable infant who has jaundice from the face to the thighs; her neurologic examination findings are normal and there is no hepatosplenomegaly, cephalohematoma, or bruising. There is no known family history of hematologic disease in either parent. Laboratory results at 82 hours of age are summarized in the Table.

Phototherapy is increased to quintuple-bank by adding a second 2-bank overhead bili light. The infant receives intravenous fluids in addition to oral ad lib feeding. After 22 hours of quintuple-bank phototherapy, the TB level is 10.0 mg/dL (171 μmol/L) and phototherapy is discontinued. She is discharged the next day after a rebound TB level of 11.8 mg/dL (201.8 μmol/L). At the pediatrician's office the day after discharge, the infant's TB level is 16.3 mg/dL (278.7 μmol/L). Supplemental formula feeding is initiated. The next day, the infant's TB level is

AUTHOR DISCLOSURE Drs Tise, Joshi, Erice-Taganas, and Blecharczyk have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

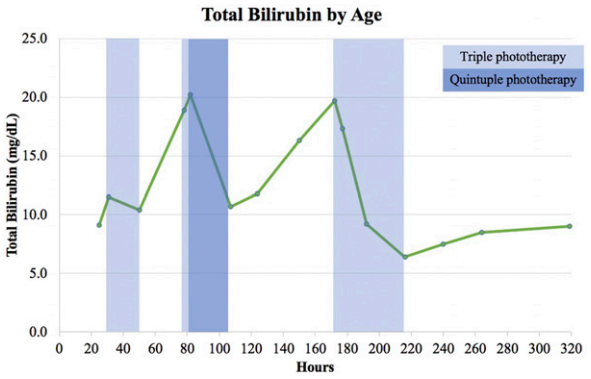

Figure 1. Total bilirubin by age. Results displayed in conventional units.

19.7 mg/dL (336.9 μmol/L) and she is readmitted for triple-bank phototherapy. Laboratory results at the time of the second admission are summarized in the Table. Hematology is consulted. Multiple laboratory tests are ordered, including lactate dehydrogenase, reticulocyte count, erythrocyte indices, smear review, erythrocyte enzyme tests, osmotic fragility test, and eosin-5-maleimide (EMA) binding test. The difference in EMA binding is 28.47% (normal ≤10%) and the peripheral blood smear reveals spherocytes and polychromasia (representative smear shown in Fig 2). The infant continues to receive triple-bank phototherapy for 40 hours. Subsequently, her TB level remains stable without phototherapy. She starts treatment with iron and folic acid and is discharged with a hematology follow-up appointment scheduled. Other test results are obtained at a later date revealing normal newborn state screen and erythrocyte enzyme tests (eg. glucose-6-phosphate dehydrogenase deficiency) showing no evidence of enzyme abnormality; however, osmotic fragility test is increased.

DIAGNOSIS

In a newborn with indirect hyperbilirubinemia, anemia, and reticulocytosis, hemolytic disease of the newborn is the most likely diagnosis. Most often, it is immune-mediated hemolysis or ABO incompatibility, but in this case, the Coombs test result was negative. The differential diagnosis for non-immune hemolytic disease can be categorized into 3 main groups:

- Red cell enzyme deficiencies (eg, glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency)
- Red cell membrane defects (eg, hereditary spherocytosis, elliptocytosis, and stomatocytosis)
- Abnormalities of hemoglobin (eg, thalassemias and sickle cell disease)

The increased EMA binding test and peripheral blood smear in this infant is suggestive of hereditary spherocytosis (HS) (Fig 2). After discharge, results of increased erythrocyte osmotic fragility, without evidence of erythrocyte enzyme deficiency, further suggested this diagnosis.

THE CONDITION

HS is the most common red blood cell (RBC) membrane defect, with an estimated prevalence of 1 in 5,000 in the United States, (2) and an increased prevalence of 1 in 2,000 among individuals of Northern European ancestry. HS is a genetic condition resulting from pathogenic variants in 1 of 5 genes (*ANK1*, *SLC4A1*, *SPTA1*, *SPTB*, and *EPB42*) encoding an essential RBC membrane protein. Approximately 75% of cases exhibit an autosomal dominant inheritance pattern, with 25% exhibiting an autosomal recessive or de novo pattern. (2) In addition, genotype-phenotype correlations are present with regard to age at onset and severity. (3)

The RBC membrane protein defects in HS cause RBC membrane instability, increasing RBC fragility and allowing RBCs to develop an abnormal spherical shape, which leads to splenic sequestration and further hemolysis. (2)(4) In some infants, jaundice will appear within 24 hours, with significant indirect hyperbilirubinemia and anemia. Laboratory evaluation may reveal a high reticulocyte count, elevated mean corpuscular hemoglobin concentration (MCHC) as a result of mild cellular dehydration, (5) elevated lactate dehydrogenase, and low haptoglobin. Spherocytes can be seen on peripheral blood smear; (2) however, this is not diagnostic because this can also be found in patients with hemolysis secondary to ABO incompatibility. In our case, the newborn also had reactive thrombocytosis in response to the hemolytic anemia. Further diagnostic evaluation includes the EMA binding test and osmotic fragility test (the latter is infrequently used in neonates because of its low sensitivity). (6) The EMA binding test uses flow cytometry to measure the relative amount of EMA bound to a specific RBC membrane protein (band 3 protein), which is reduced in patients with HS; thus, the fluorescence intensity is lower and the difference in EMA binding is higher in patients with HS compared with controls. The osmotic fragility test measures erythrocyte susceptibility to hemolysis when exposed to increasingly hypotonic saline solutions; the sooner hemolysis occurs, the greater the osmotic fragility of the cells, as is the case in HS. Although a long-term hallmark of HS is splenomegaly, this is uncommon in newborns and was not present in this case.

MANAGEMENT

The initial management of HS is focused on treatment of the indirect hyperbilirubinemia with aggressive

TABLE. **Laboratory Results at First and Second Readmission after Discharge from Newborn Nursery**

LABORATORY TEST	1ST READMISSION AT 82 HOURS	2ND READMISSION AT 176 HOURS
Total bilirubin	20.2 mg/dL (345.4 μmol/L)	17.3 mg/dL (295.8 μmol/L)
Direct bilirubin	0.63 mg/dL (10.8 μmol/L)	0.64 mg/dL (10.9 μmol/L)
Sodium	156 mEq/L (156 mmol/L)	142 mEq/L (142 mmol/L)
Potassium	4.7 mEq/L 94.7 mmol/L)	4.7 mEq/L (4.7 mmol/L)
Chloride	113 mEq/L (113 mmol/L)	103 mEq/L (103 mmol/L)
Blood urea nitrogen	25 mg/dL (8.9 mmol/L)	8 mg/dL (3 mmol/L)
Creatinine	0.82 mg/dL (72 μmol/L)	0.49 mg/dL (43 μmol/L)
Albumin	3.9 g/dL (39 g/L)	3.7 g/dL (37 g/L)
Hemoglobin	11.0 g/dL (110 g/L)	9.7 g/dL (97 g/L)
Hematocrit	32.7%	27.3%
Platelet count	481×10^3/mL (481×10^9/L)	731×10^3/μL (731×10^9/L)
Mean corpuscular volume	97.3 fL (97.3×10^{-15} L)	93.5 fL (93.5×10^{-15} L)
Red blood cell distribution	19.3%	16.5%
Mean corpuscular hemoglobin	32.7 pg (32.7×10^{-9} mg)	33.2 pg (33.2×10^{-9} mg)
Mean corpuscular hemoglobin concentration	33.6 g/dL (336 g/L)	35.5 g/dL (355 g/L)
Reticulocytes	10.2%	4.35%
Lactate dehydrogenase	824 U/L	N/A
Haptoglobin	<8 mg/dL (80 mg/L)	N/A
Blood smear	Abnormal red blood cell morphology with presence of acanthocytes (1+), polychromasia (3+), spherocytes (2+), Howell-Jolly bodies, and Pappenheimer bodies	Abnormal red blood cell morphology with presence of polychromasia (1+), spherocytes (3+), and Pappenheimer bodies

Results displayed in conventional units, followed by SI units in parentheses, if applicable. N/A=not available.

phototherapy or, if necessary, an exchange transfusion. (1) Secondary management includes initiation of iron and folic acid for anemia. Individuals with HS require close follow-up during infancy and may need blood transfusions during the first 6 months of age. The need for transfusions in an affected infant does not prognosticate HS, because severe hemolysis can be transient while hemoglobin F (HbF) levels are elevated. This is thought to occur because of the inability of HbF to bind free 2,3-diphosphoglycerate, which further destabilizes RBC membrane proteins. (4)(7) Some patients will also require splenectomy as they progress into childhood and early adulthood, with partial splenectomy now recommended to decrease long-term infection risk. (8) All children who undergo a splenectomy need vaccination pre- and postoperatively for *Pneumococcus*, *Meningococcus*, and *Haemophilus influenza* type b in addition to prophylactic antibiotics for at least 2 years after the splenectomy or until 5 years of age. (7)

Lessons for the Clinician

1. HS is the most common inherited erythrocyte membrane disorder in Northern Europe and North America, (9) causing nonimmune hemolytic anemia and resulting in mild to severe neonatal jaundice.
2. Jaundice is the most common presenting feature of HS in neonates. HS should be considered in the differential diagnosis in a neonate who is being readmitted for direct antiglobulin test–negative jaundice, especially when the infant's MCHC is elevated (≥36.0 g/dL or ≥360 g/L) (82% sensitivity and 98% specificity). (10)(11) Increased

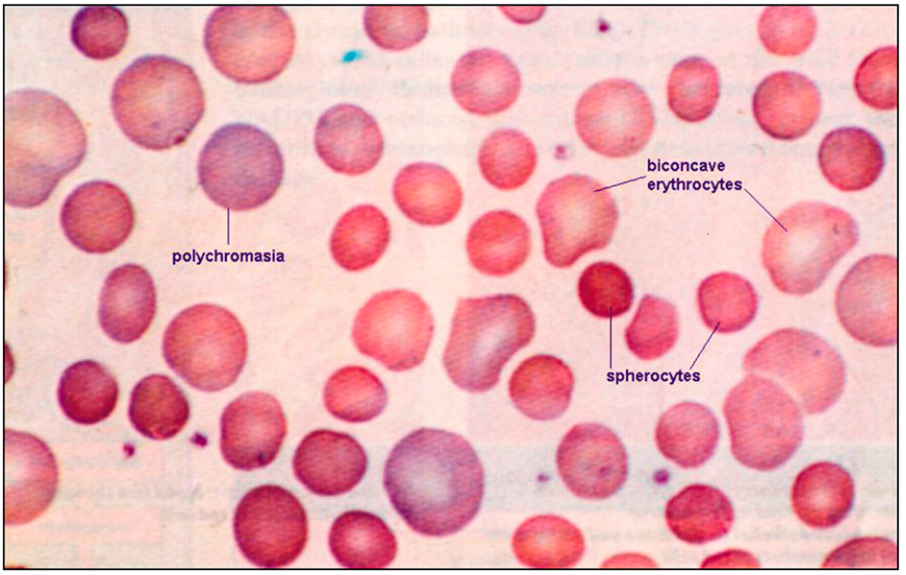

Figure 2. Characteristic findings on peripheral blood smear in a patient with hereditary spherocytosis. Reprinted with permission from Shah S, Vega R. Hereditary spherocytosis. *Pediatr Rev.* 2004;25(5):168–172.

osmotic fragility and elevated EMA binding are suggestive of HS. (6)

3. Approximately 75% of HS cases exhibit an autosomal dominant inheritance pattern, with 25% exhibiting an autosomal recessive or de novo pattern. (5) Despite a negative family history, a close review of red cell indices with high MCHC, reticulocytosis, and presence of spherocytes should prompt a clinician to consider HS.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology and pathophysiology of hemolytic anemias in the neonate.
- Know the clinical and laboratory features of hemolytic anemia in the neonate.
- Know the management of hemolytic anemia in the neonate.

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2 A Salty Baby

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PRESENTATION

A male term neonate is born to a 25-year-old, gravida 3 woman in a third-degree consanguineous marriage with 2 previous term neonatal deaths. Her first child was male and had an unexplained death at 14 days of age at home. Her second child was female and also had an unexplained death at 11 days of age.

The antenatal period during this current pregnancy is uneventful except for a diagnosis of gestational diabetes mellitus, which required treatment with insulin during the third trimester. The woman's blood glucose values were maintained in the normal range in the antepartum and intrapartum periods. Her antenatal scans are normal.

This neonate is delivered at 38 weeks of gestation via a planned lower-segment cesarean section (LSCS) in view of a previous LSCS and a history of 2 unexplained neonatal deaths. The neonate cries immediately after birth and does not require any resuscitation. His Apgar scores are 8, 8, and 9 at 1, 5, and 10 minutes after birth, respectively. The placenta weighs 380 g and is normal on gross examination. The infant's birthweight, length, and head circumference are 3,650 g (86th percentile), 51 cm (77th percentile), and 35.5 cm (86th percentile), respectively. The initial examination findings are normal and show that the infant does not have any obvious external anomalies, edema, or facial dysmorphisms; no skin lesions, limb abnormalities, or genital abnormalities are noted. Blood glucose monitoring performed as per protocol and all test results are normal. Because of the history of 2 previous neonatal deaths, electrocardiography, echocardiography, and cranial ultrasonography are performed before discharge, results of which are all normal. The expanded newborn screening panel is sent before discharge. The neonate is discharged from the hospital on day 4 after birth and the family is advised to follow-up closely with the pediatrician.

On the 7th day after birth, the neonate is noted to have neonatal jaundice, with a total bilirubin of 17.4 mg/dL (297.6 μmol/L) and direct bilirubin of 0.2 mg/dL (3.4 μmol/L) and significant weight loss, prompting admission to the hospital on the pediatric floor initially for phototherapy and intravenous fluids. The neonate's admission weight is 3,000 g, an 18% weight loss from birthweight. The parents report that the neonate has not had any fever, altered sensorium, abnormal movements, fast breathing, feeding issues, loose stools, or polyuria. At the time of admission, the neonate has a heart rate of 168 beats/min, respiratory rate of 45 breaths/min, temperature of 97.7°F (36.5°C), and oxygen saturation of 98% in room air. His blood pressure is 74/48 mm Hg, with a mean of 50 mm Hg, and his capillary refill time is 3 seconds. On examination, the neonate appears dehydrated, with decreased activity with icteric sclera. His skin is notable for a rash that looks

AUTHOR DISCLOSURE Drs Kallem, Vardhelli, and Murki have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

similar to miliaria crystallina (Fig 1). He also has cold extremities and tachycardia. Based on concerns for dehydration and significant jaundice, he is transferred to the NICU and maintenance intravenous fluids and phototherapy are started.

EVALUATION

The infant's initial laboratory test results are as follows:

- Complete blood count: Normal
- C-reactive protein: Negative (0.4 mg/dL [4 mg/L])
- Serum sodium 129 mEq/L (129 mmol/L), serum potassium 7.8 mEq/L (7.8 mmol/L), chloride 98 mEq/L (98 mmol/L), bicarbonate 20 mEq/L (20 mmol/L)
- Arterial blood gas: pH 7.37, P_{CO_2} 38.2 mm Hg (5.0 kPa), P_{AO_2} 72 mm Hg (9.5 kPa), and base excess −4 mmol/L
- Blood urea nitrogen 40.7 mg/dL (14.5 mmol/L), serum creatinine 0.8 mg/dL (70.7 μmol/L)
- Newborn screening (sent before initial discharge from hospital) result is normal
- Blood culture (sent later) shows no growth
- Urine electrolytes: Pending
- Urine culture (obtained by catheter, sent later) shows no growth

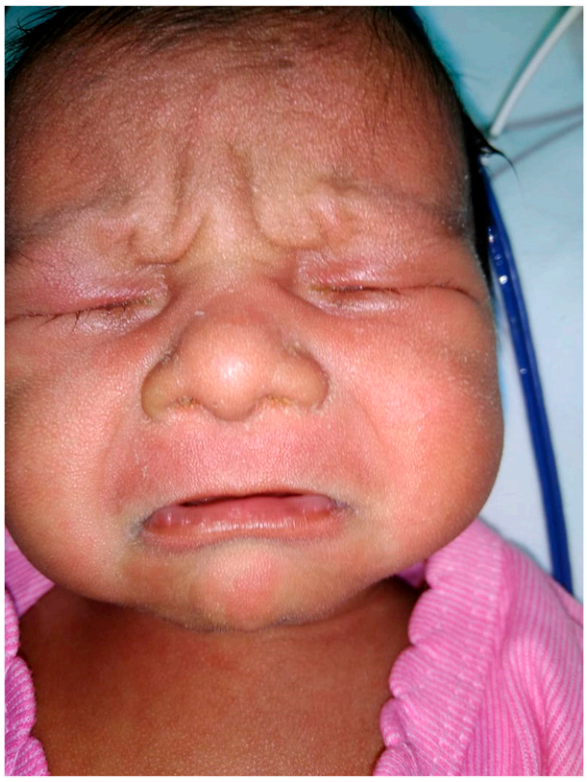

Figure 1. Skin rash on the face similar to miliaria crystallina.

- Repeat total bilirubin 12 hours after phototherapy: 15.2 mg/dL (260 μmol/L)

Abdominal (to assess for adrenal hemorrhage) and renal ultrasonography findings are normal. His blood pressures continue to be normal and his urine output (3 ml/kg/hour) is also normal.

His electrolytes are repeated after 4 hours to rule out spurious hyperkalemia. Repeat testing reveals a serum sodium of 127 mEq/L (127 mmol/L) and a serum potassium of 9.7 mEq/L (9.7 mmol/L). The team considers a possible diagnosis of congenital adrenal hyperplasia (CAH), and before starting intravenous hydrocortisone and oral fludrocortisone, performs additional tests including serum cortisol, 17-hydroxyprogesterone, aldosterone, and renin levels. The team places the infant on continuous cardiorespiratory monitoring and initiates supportive measures for hyperkalemia including an intravenous calcium gluconate bolus, intravenous insulin and glucose infusions, rectal potassium exchange resins, intravenous sodium bicarbonate, and salbutamol nebulization.

PROGRESSION

Six hours later, after the intravenous fluid, hydrocortisone, and supportive measures for hyperkalemia are initiated, the neonate's repeat electrolytes are not significantly improved (serum sodium 127 mEq/L [127 mmol/L], serum potassium 8.8 mEq/L [8.8 mmol/L]). The neonate's serum cortisol (26.57 μg/dL [733 nmol/L]) and 17-hydroxyprogesterone (4.25 nmol/L) are normal. The other 2 laboratory tests (serum aldosterone and serum renin) confirm the diagnosis.

DIAGNOSIS

In patients with severe hyperkalemia with hyponatremia, the clinician needs to assess for CAH. Because our patient's blood pressures, serum glucose levels, renal function tests, and genitalia were all normal as were his serum cortisol and 17-hydroxyprogesterone levels, his glucocorticoid axis appeared intact. However, his abnormal sodium and potassium values suggested that the neonate had an abnormality in the mineralocorticoid pathway, such as aldosterone synthase deficiency or pseudohypoaldosteronism type 1. The neonate's serum renin activity was greater than 250 ng/mL per hour (normal values 2.4–37 ng/mL per hour), and his serum aldosterone was greater than 1,000 ng/dL (27,740 pmol/L; normal values 5–90 ng/dL [138.7–2496.6 pmol/L]). The patient's urinary electrolytes are suggestive of salt

wasting, with urine sodium of 55 mEq/L, urine potassium 2.5 mEq/L, and urine chloride 40.9 mEq/L. In contrast to this infant, patients with aldosterone synthase deficiency have low normal or low aldosterone levels because the conversion of corticosterone to aldosterone is inhibited. In this infant, the markedly elevated aldosterone levels, along with elevated serum renin, suggest a diagnosis of pseudohypoaldosteronism (PHA) type 1. Affected infants have physical features of coarse skin with a salty appearance, as seen in our patient, with a rash that appears similar to miliaria crystallina because of salt losses from the skin.

DISCUSSION

PHA type 1 is a rare monogenic disease that was first described by Cheek and Perry in 1958. (1) It is caused by resistance of the mineralocorticoid receptors to aldosterone, leading to salt wasting; aldosterone and renin levels increase to try to compensate for this resistance. Two forms have been identified. The autosomal dominant form is caused by mutations in the *NR3C2* gene encoding mineralocorticoid receptor. Affected patients usually have isolated renal involvement without systemic involvement, have mild clinical symptoms, respond to salt supplementation, and generally improve clinically with age. (2) The autosomal recessive form is a severe form of PHA type 1 that is usually caused by homozygous mutations in the α (SCNN1A), β (SCNN1B), or γ (SCNN1G) subunits of the epithelial sodium channel (ENaC). Affected patients have systemic involvement, with salt wasting from multiple organs including the kidneys, skin, intestines, salivary glands, and lungs. In this systemic PHA type 1, defects in ENaC lead to decreased sodium-dependent liquid absorption, which leads to excessive fluid in the airway lumen, causing narrowing of the airway and predisposing to wheezing and recurrent pulmonary infections. Patients with the autosomal recessive type require close monitoring, have frequent hospitalizations (for respiratory infections or dehydration associated with salt-wasting episodes), and require lifelong treatment. Patients with either type of PHA type 1 can develop life-threatening hyperkalemia, severe metabolic acidosis, and hyponatremia as a result of deficient aldosterone activity leading to salt wasting. (2)(3)(4) It is theorized that the death of the other 2 children resulted from 1 of these complications. Patients with autosomal recessive PHA type 1 with systemic involvement can have skin manifestations such as miliaria rubra or crystallina, a salty taste to their skin, and sometimes pulmonary symptoms similar to patients with cystic fibrosis. (5)

In our patient, mutational analysis with clinical exome sequencing revealed a homozygous nonsense variation in exon 8 of the *SCNN1B* gene (chr16:23387118C>A; Depth: 74x), which results in a stop codon and premature truncation of the protein at codon 404 (p.Tyr404Ter; ENST00000343070.2).

Management

The infant described in this vignette had a complicated clinical course. As noted earlier, he was initially started on intravenous fluids, along with supportive measures for hyperkalemia. He was allowed to feed orally, and his total fluid intake was 250 to 300 mL/kg per day. After the diagnosis was confirmed, the supplemental steroids were discontinued. In the setting of excessive skin and urine sodium losses, hypertonic saline (3%) was added to the intravenous fluids to provide sodium of 20 mEq/kg per day. With a change made to oral feedings, the supplemental sodium and potassium resins were provided orally. (6) His serum potassium levels decreased but were persistently slightly elevated (5.7–6.8 mEq/L [5.7–6.8 mmol/L]). Later, he required an increase in oral sodium supplementation to 40 to 50 mEq/kg per day by adding table salt to the oral feedings (1 g of table salt gives 17 mEq of sodium) with the plan of stopping intravenous fluid support. (7) The infant did not have consistent weight gain and could not tolerate the high oral sodium supplementation because of emesis associated with the hypertonicity, so he was transitioned to hourly oral feedings along with intravenous fluid support. After a prolonged period of 2 to 3 weeks, when he demonstrated some weight gain, intravenous fluid support was stopped. Because of recurrence of intolerance to high oral sodium supplementation demonstrated by vomiting and severe dehydration within 1

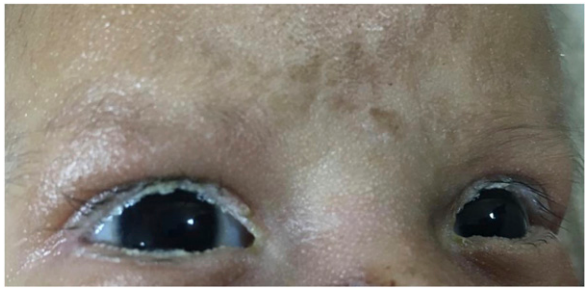

Figure 2. Dry salty skin with salty crystals over eyelids.

day, intravenous fluid support was restarted through a central intravenous access. Because the infant continued to have excessive salt wasting and was unable to wean off intravenous fluids, a trial of oral indomethacin was given at a dose of 2 mg/kg per day for 2 days. After 2 days, he developed acute renal injury (serum creatinine 2.4 mg/dL [212.1 μmol/L] and decreased urine output of 0.4 mL/kg per hour) with excessive weight gain; this prompted the team to stop indomethacin and restrict his total fluid volume. Slowly, his renal function and urine output improved. The neonate continued to have dry salty skin with salty crystals over the eyelids (Fig 2), (8) with fluctuations in weight. He was unable to return to his birthweight during his hospital stay. Because of his continued intolerance of feedings, a button gastrostomy was performed, and the parents were trained in feeding through gastrostomy a preparation of 3% saline, table salt, and potassium resins with his feedings. He was discharged from the hospital at 82 days of age receiving gastrostomy feedings 250 to 300 mL/kg per day, sodium supplementation of 40 mEq/kg per day, and oral potassium resins 1 g/kg every 6 hours, with close follow-up with the pediatrician.

Lessons for the Clinician

- Aldosterone and renin levels should be obtained in neonates who present with clinical features suggestive of congenital adrenal hyperplasia.
- Pseudohypoaldosteronism, though rare, is an important cause of salt wasting in neonates.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical manifestations and laboratory features of the various types of congenital adrenal hyperplasia.

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3 Term Infant with Apnea

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PRESENTATION

A male infant is born at 39 weeks' gestational age via repeat cesarean delivery to a 36-year-old (gravida 3, para 2, term 2, living 2) woman. The prenatal history is notable for group B *Streptococcus*–positive maternal status; the prenatal course is otherwise benign and there is no known family history of medical disorders. The infant is vigorous at birth, with spontaneous respirations and a heart rate greater than 100 beats/min; his Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. He weighs 3,460 g (59th percentile), his head circumference is 34.5 cm (51st percentile), and length is 48.9 cm (30th percentile). The rest of his physical examination findings are normal.

The infant initially remains with his mother; however, at approximately 15 minutes of age during skin-to-skin contact with his mother, the infant is noted to be pale, with a preductal pulse oximetry oxygen saturation of 50% in room air. He is provided continuous positive airway pressure via mask for 5 minutes, then placed on blow-by oxygen supplementation and monitored in the nursery. He has no signs of respiratory distress and is able to wean to room air after 45 minutes, maintaining pulse oximetry saturations over 90% without supplemental oxygen. Within the next hour, however, he again has desaturations on pulse oximetry and requires 1 L/min supplemental oxygen via nasal cannula. Chest radiography demonstrates mild hazy opacification of the lungs bilaterally, suspected to be retained fluid in the setting of cesarean section. His complete blood cell count and immature-to-total neutrophil ratio are normal; a blood culture specimen is obtained. At that time, the decision is made to transfer the infant from the newborn nursery to the NICU.

Over the subsequent several hours, he has a decrease in muscle tone, intermittent apnea, and shallow and slow respiratory effort (respiratory rate 10–30 breaths/min). He undergoes intubation and is started on treatment with dextrose-containing intravenous fluids as well as ampicillin and gentamicin for presumed sepsis. His ventilatory requirements are minimal (tidal volume of 4 mL/kg, fraction of inspired oxygen of 0.21) and improvement in tone is noted, so he undergoes extubation to noninvasive support. Because of the recurrent apnea with noninvasive support, however, he undergoes reintubation within several hours. A trial of caffeine was started, but without improvement in apnea.

The ventilator mode is set for neurally adjusted ventilatory assist (NAVA) at level 0.5 and positive end expiratory pressure of 5 cm H_2O, with a set backup rate of 30 breaths/min. Figure 1 demonstrates the findings: intermittent episodes with none or minimal Edi peaks recorded, indicating no electrical signal from the

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patient for respiratory effort. Invasive NAVA ventilator summary data show that the neonate requires pressure control backup support 50% to 90% of the time. Pediatric pulmonology is consulted at 1 day of age because of the presence of central apnea in a term infant; pulmonology has a suspicion of a diagnosis and requests confirmatory testing.

The neonate does not have any bowel movement by 2 days of age and distended loops of bowel are visible on abdominal radiography (Fig 2). After the onset of bilious emesis, he undergoes a barium enema that demonstrates a complete microcolon (Fig 3). Rectal biopsy is performed at 2 days of age, which shows absence of ganglion cells and no evidence of nerve hyperplasia. Multiple laparoscopic mapping biopsy specimens are obtained and no ganglion cells are reported until 70 cm above the ileocecal valve, confirming long-segment Hirschsprung disease.

Brain magnetic resonance imaging (MRI) is performed at 6 days of age, which does not show any structural or brainstem abnormalities.

DISCUSSION

Apnea in a term infant may be secondary to a broad range of causes, including infectious processes, upper airway anatomic obstructions, neuromuscular weaknesses, brainstem anomalies, genetic disorders, and seizures. The infant in this case had central apnea as seen on invasive NAVA, reassuring infectious evaluations, an MRI without brainstem abnormalities, and no other physical abnormalities

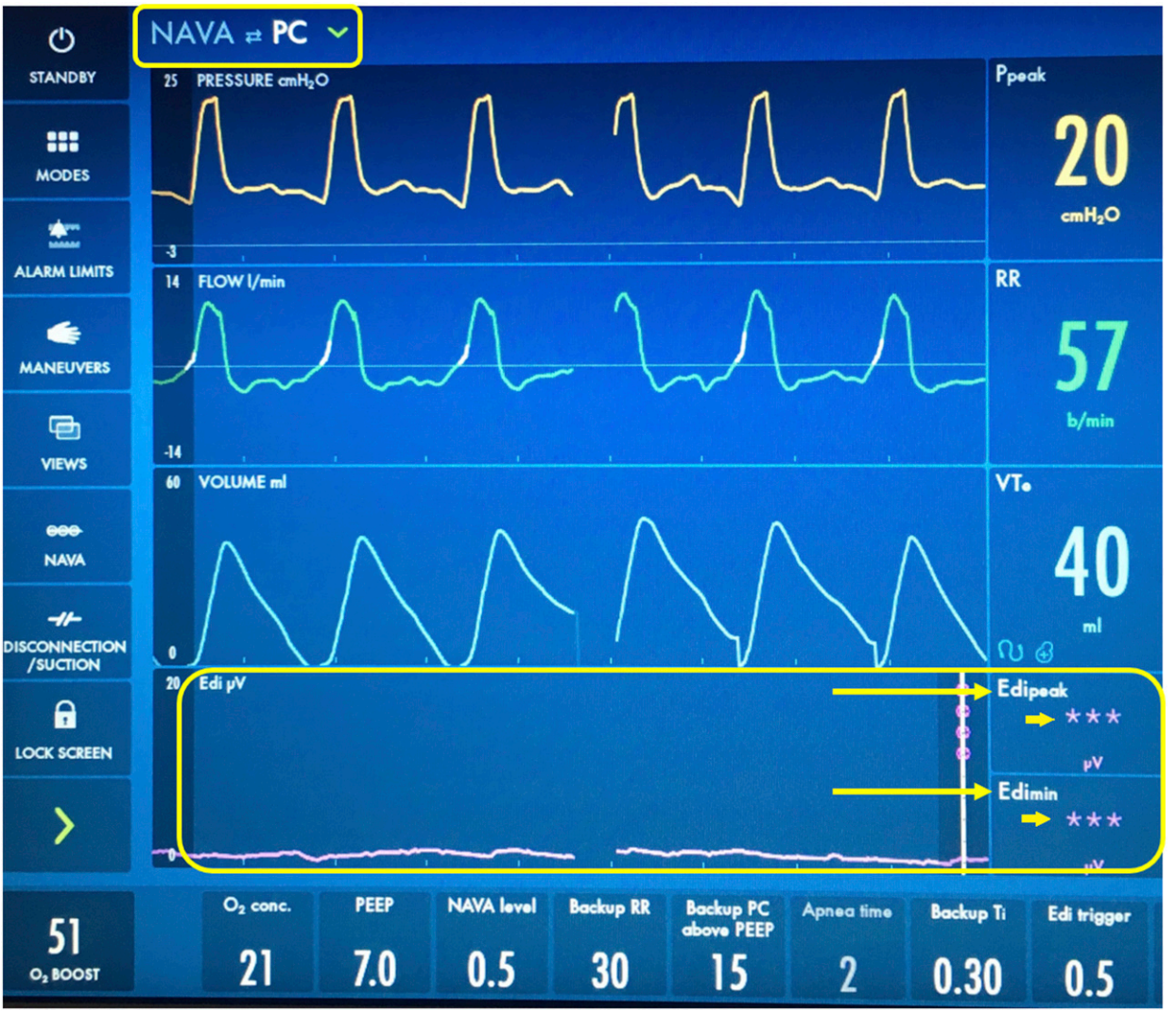

Figure 1. Invasive neurally adjusted ventilatory assist (NAVA) ventilator screen. No Edi peak or Edi minimum readings are recorded at this time, demonstrating no patient electrical signal with which the ventilatory system can synchronize. As a result, the ventilator pressure control backup is providing ventilator set rate breaths.

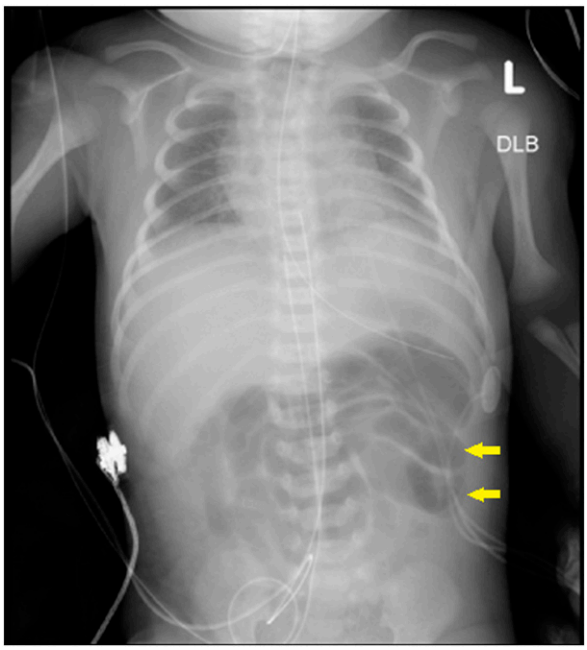

Figure 2. Abdominal radiograph demonstrating distended loops of bowel (yellow arrows).

except Hirschsprung disease. The pulmonary service recommended genetic testing for central congenital hypoventilation syndrome (CCHS) within several days after birth, which confirmed the diagnosis (p. Ala241[32] pathogenic mutation in *PHOX2B* gene, 32 polyalanine repeat expansion).

CCHS is an autosomal dominant disorder that occurs as a result of mutations in the *PHOX2B* gene; the majority of cases result from de novo germline mutations; however, mosaicism has been noted in 5% to 10% of parents. (1) The *PHOX2B* gene encodes a transcription factor known to be involved in the development of the autonomic nervous system, and it was discovered to be the "disease-defining gene" for CCHS in the early 2000s. (2)(3) Among patients with CCHS, 90% are heterozygous for polyalanine expansion repeat mutations (PARM) and 10% are heterozygous for a frameshift, missense, or nonsense mutation (non-PARM). (3) *PHOX2B* contains a 20-alanine repeat sequence on exon 3 in both alleles; in patients with CCHS with PARM, the number of repeats range from 24 to 33, such as the patient described here with PARM 32. (1) The genotype and phenotype correlations demonstrate that patients with longer PARMs and non-PARMs have a higher likelihood of needing continuous ventilatory support than those with PARMs of 24 to 25. (3) CCHS results in an inability to change ventilation to meet the demands of severe hypoventilation during sleep; as a result, infants with CCHS require tracheostomy with mechanical ventilation during sleep and variably while awake. (1) For older children, other options for ventilatory support including diaphragmatic pacing are now available. (3)

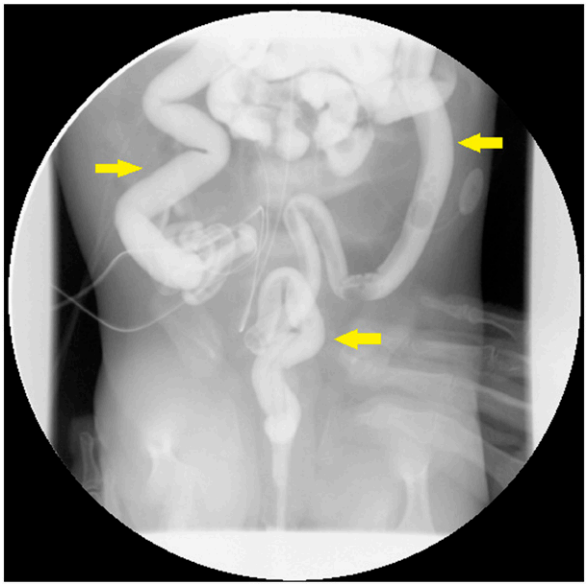

Figure 3. Contrast barium enema with complete microcolon (yellow arrows).

CCHS is also associated with other abnormalities in the autonomic nervous system, including Hirschsprung disease, neural crest tumors, and differences in pupillary responses, basal body temperature, and pain perception. (1) The American Thoracic Society (ATS) guidelines recommend that patients with CCHS be screened with chest and abdominal imaging for neural crest tumors (for non-PARMs and longer PARMs), with barium enema for Hirschsprung disease (if constipation is present), with 72-hour Holter monitoring for cardiac dysrhythmias, and with complete ophthalmologic evaluations for eye abnormalities. (3) Per the ATS guidelines, if CCHS is considered as a possible diagnosis, it is recommended that *PHOX2B* screening should be performed without delay because of its high sensitivity and specificity for CCHS. (3) While awaiting the genetic results, other potential diagnoses should be ruled out, including brainstem lesions and infectious etiologies.

The current patient was noted to have central apnea while receiving NAVA, without the need for polysomnography, which expedited the decision to proceed with diagnostic genetic testing for CCHS. He underwent tracheostomy placement after genetic confirmation of the diagnosis of CCHS, because of the expectation of his requirement for long-term ventilation. He had surgical bowel resection and ostomy formation for his long-segment Hirschsprung disease, and is currently in the NICU to increase feedings.

Genetics was consulted and parental testing for mosaicism was recommended.

Lessons for the Clinician

- Identification of central apnea in a term infant may be assisted with use of invasive NAVA
- A high index of suspicion is required for diagnosis of CCHS
- Early genetic testing for CCHS is recommended in a term infant with central apnea (4)

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.
- Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis, and how to interpret test results.
- Identify the developmental pattern for motility of various segments of the alimentary canal.
- Recognize the association of major congenital anomalies involving the GI tract and abdominal wall with those involving other organs.

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Established and Emerging Treatments for Patients with Inborn Errors of Metabolism

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See Bonus Wall Chart Accompanying This Issue!

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ABBREVIATIONS

BH4	tetrahydrobiopterin
CoA	coenzyme A
CPS	carbamoyl phosphate synthetase
ERT	enzyme replacement therapy
FAH	fumarylacetoacetate hydrolase
FDA	Food and Drug Administration
HPD	4-hydroxyphenylpyruvate dioxygenase
HSCT	hematopoietic stem cell transplantation
HT-1	hereditary tyrosinemia type 1
IEM	inborn error of metabolism
LCT	liver cell transplantation
MCT	medium-chain triglycerides
MMA	methylmalonic acidemia
MPS	mucopolysaccharidoses
NAG	N-acetylglutamate
NTBC	2-[2-nitro-4-(trifluoromethyl) benzoyl]cyclohexane-1,3-dione
OLT	orthotopic liver transplantation
PA	propionic acidemia
PAH	phenylalanine hydroxylase
PKU	phenylketonuria
TPN	total parenteral nutrition
UCD	urea cycle disorder
VLCAD	very-long-chain acyl-coenzyme A dehydrogenase

Education Gaps

Early recognition and treatment of inborn errors of metabolism is essential. Treatment regimens are often complex and may involve a combination of several therapies. Novel therapies are rapidly emerging and can be life-saving. This review serves to assist the neonatologist in keeping abreast of these developments.

Abstract

Inborn errors of metabolism (IEMs) are inherited defects in a metabolic pathway resulting in clinical disease. The overall goal of therapy is to restore metabolic homeostasis while minimizing the deleterious effects of the interruption. Conventional treatments focus on decreasing substrate, providing product, and replacing deficient enzyme or cofactor. We discuss examples of established, novel, and emerging therapies to provide a framework for understanding the principles of management for patients with IEMs.

Objectives After completing this article, readers should be able to:

1. Describe the principles of treatment for patients with inborn errors of metabolism
2. Apply these principles to selected conditions that are relevant to a neonatal population
3. Recognize the indication for use of emerging therapies, including organ transplantation, enzyme replacement therapy, and gene therapy

INTRODUCTION

Inborn errors of metabolism (IEMs) are a heterogenous group of disorders characterized by an interruption in the complex biochemical network of human metabolism. This network is composed of connected pathways that are responsible for vital processes, including the conversion of nutrients into usable energy,

recycling of waste products, and organelle functioning. IEMs are caused by an interruption or block in a key metabolic pathway because of insufficient or defective enzyme, cofactor, or transporter. Clinical manifestations often arise from the direct and downstream effects of substrate accumulation and/or product deficiency (Fig 1).

The management of IEMs aims to restore the balance between substrate and product on either side of the blockage. This traditionally involves a combination of 1) decreasing substrate and removing toxic metabolites, 2) providing deficient product, and 3) enhancing conversion of substrate to product via enzyme or cofactor replacement. In this review, we will systematically discuss each of these approaches to treatment, with examples of how they have been applied in human disease.

DECREASING SUBSTRATE

Enzymatic deficiency or dysfunction results in accumulation of substrate, which may then be converted into secondary, sometimes toxic, byproducts. Substrate accumulation and/or secondary byproducts are often directly responsible for disease manifestations. Limiting substrate accumulation is therefore an essential component of treating many metabolic conditions. This is achieved by regulating the intake of substrate in the diet, secondary reduction of substrate, and removal of secondary byproducts (Fig 2). (1) We will discuss each of these individually.

Dietary Substrate Restriction

Dietary management is the foundation of treatment for many IEMs and involves limiting disease-specific substrate in the diet. In disorders of protein metabolism, for example, natural protein is restricted, and residual protein needs are met with medical protein that lacks substrate amino acids. This is well exemplified in the management of classic phenylketonuria (PKU) resulting from phenylalanine hydroxylase (PAH) deficiency. PAH is responsible for the conversion of phenylalanine to tyrosine. In the untreated state, phenylalanine accumulates and is neurotoxic, resulting in severe cognitive impairment and psychiatric disability. (2) Dietary management of PKU involves a phenylalanine-restricted diet, attained by restricting natural forms of dietary protein with supplementation of phenylalanine-free and tyrosine-rich amino acid equivalent formula. With lifelong dietary therapy starting at birth, most patients with PKU are able to lead independent lives with normal or near-normal neurocognition. (3)

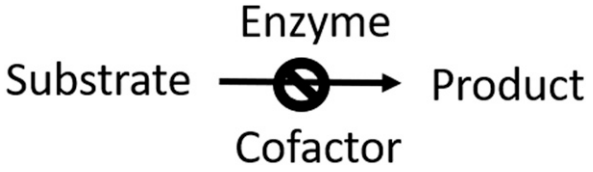

Figure 1. Interruption in an enzymatic pathway (denoted with a circle backslash) may result in decreased product distal to the block and increase in enzymatic substrate proximal to the block.

The success of dietary management in PKU has inspired the application of dietary treatment to many other IEMs. In fact, 16 of the core conditions on the Recommended Uniform Screening Panel for newborn screening are treated with nutritional management. (4) This includes other disorders of protein metabolism (amino acidopathies, urea cycle disorders, and organic acidurias) as well as disorders of fatty acid oxidation. For each condition, the paradigm of reducing the offending substrate is tailored to the enzymatic defect. In disorders of long-chain fatty acid oxidation, for example, long-chain fats (containing ≥14 carbons) are restricted in the diet. (5) In galactosemia, a disorder of galactose metabolism, the use of galactose-free formulas can be lifesaving. (6)

Despite the potential for success with strict dietary therapy alone, many factors limit adherence to such regimens. These include issues of palatability, cost, complexity of care, and caregiver burden. (7) In total parenteral nutrition (TPN)–dependent patients, specialty formulations of TPN lacking the offending amino acids may be considered. However, such preparations are not readily available at most institutions.

Substrate Reduction Therapy

Substrate reduction therapy is an alternative approach to decrease substrate intake. Unlike nutritional management, substrate reduction therapy acts upstream of the enzymatic block to decrease production of substrate. Hereditary tyrosinemia type 1 (HT-1) is a condition in which substrate reduction therapy is commonly used.

HT-1, also known as classic or hepatorenal tyrosinemia, is caused by fumarylacetoacetate hydrolase (FAH) deficiency. This enzyme is the fifth and final enzyme in tyrosine metabolism. In the untreated state, patients with HT-1 develop acute liver failure in infancy, followed by renal disease in early childhood. Dietary therapy alone, even when started in the first year of age, falls short of preventing these complications. (8) Substrate reduction therapy with 2-[2-nitro-4-(trifluoromethyl) benzoyl]cyclohexane-1,3-dione (NTBC) has changed the prognosis of this disease. NTBC acts as a potent inhibitor at the site of 4-hydroxyphenylpyruvate dioxygenase (HPD), the second enzyme in tyrosine metabolism (Fig 3). (9)

By blocking HPD activity, the substrate load delivered to the deficient FAH downstream is greatly decreased. This results in a block in production of the hepatotoxic metabolite succinylacetone. With the combination of NTBC and dietary therapy started in the newborn period, the major clinical manifestations of HT-1 can be prevented, and liver transplantation can be prevented. NTBC therapy is recommended to be started at the time of diagnosis of HT-1. (8)

Scavenger Therapy

For many IEMs, substrate accumulation leads to secondary production of a toxic byproduct. Scavenger therapies offer a sink for these toxic byproducts and are particularly relevant to the care of patients with urea cycle defects and organic acidemias.

The urea cycle disorders (UCDs) are a group of disorders characterized by an inherited defect in the urea cycle. This cycle is responsible for the conversion of waste nitrogen in the form of ammonia into urea, which can be excreted in the urine. Disruption of the urea cycle results in accumulation of nitrogen in the form of ammonia. Elevation of ammonia, known as hyperammonemia, results in cerebral edema and risk of irreversible neurologic injury and death. As such, tight ammonia control is an absolute priority in the care of patients with UCDs.

Ammonia accumulation results in secondary accumulation of nitrogen in the form of glutamine and, to a lesser extent, glycine. Ammonia scavengers conjugate to these secondary metabolites, allowing for urinary excretion of nitrogen (Fig 4). Sodium benzoate and sodium phenylbutyrate, 2 widely used ammonia scavengers, conjugate with glycine and glutamine, respectively, and allow for urinary nitrogen excretion. (10) This results in reduction of whole-body nitrogen stores, thereby decreasing ammonia levels while bypassing the urea cycle.

A new medication, glycerol phenylbutyrate, is a pre-prodrug of phenylbutyrate with superior palatability, which has been found to be not inferior to sodium phenylbutyrate. (11) It has been approved by the US Food and Drug Administration (FDA) for children aged 2 years and older, but recent studies have demonstrated tolerance in patients with UCD who are as young as 2 months. (12) In times of acute illness, sodium phenylbutyrate and sodium phenylacetate

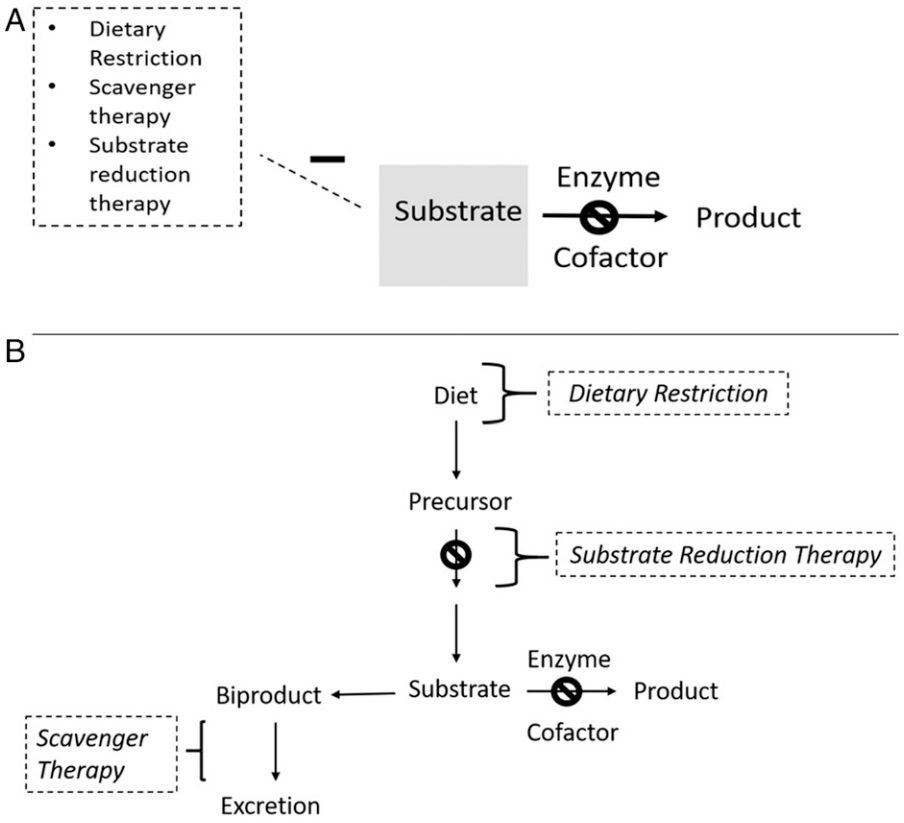

Figure 2. A. Substrate reduction (denoted with a minus [–] sign) can be achieved via dietary restriction, scavenger therapy, or substrate reduction therapy. B. The site of action of each of these approaches in more detail. Dietary restriction involves limiting disease-specific substrate in the diet. Substrate reduction therapy acts upstream of the enzymatic block. Scavenger therapy allows for excretion of toxic byproducts that resulted from substrate accumulation.

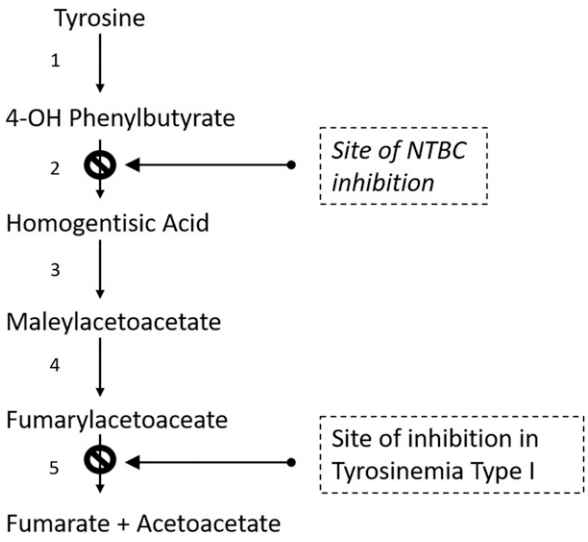

Figure 3. Substrate reduction therapy for hereditary tyrosinemia type 1 (HT-1) with 2-[2-nitro-4-(trifluoromethyl)benzoyl]cyclohexane-1,3-dione (NTBC). The enzymes in the tyrosine degradation pathway are labeled 1 through 5. 1: Tyrosine aminotransferase; 2: 4-OH hydroxyphenylpyruvate dioxygenase (HPD); 3: homogentisic acid dioxygenase; 4: maleylacetoacetate isomerase; 5: fumarylacetoacetate hydrolase (FAH). HPD (2) is the site of inhibition by NTBC. HT-1 is caused by FAH deficiency. (5)

can be given intravenously. If hyperammonemia is severe and nonresponsive to medical management, hemodialysis or continuous venovenous hemofiltration is used for emergent removal of ammonia. (10)

Scavenger therapy is also widely applied in the treatment of methylmalonic acidemia (MMA) and propionic acidemia (PA). These inherited disorders of amino acid metabolism result in significant morbidity and mortality, along with metabolic acidosis, failure to thrive, and varying degrees of cardiac dysfunction and renal disease. (13) MMA and PA result in accumulation of toxic short-chain acyl-coenzyme A (CoA) compounds. The administration of L-carnitine allows urinary excretion of these short-chain acylcarnitines and is an important component of treatment. (13)(14)

Short-chain CoA species also mediate secondary hyperammonemia in patients with MMA and PA, by reducing N-acetylglutamate (NAG) synthesis. NAG is a stimulator of

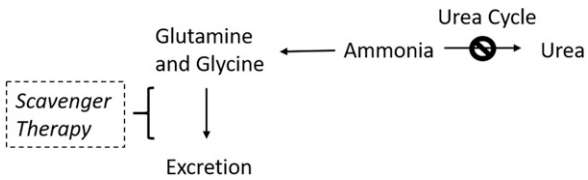

Figure 4. In urea cycle disorders, waste nitrogen accumulates in the form of ammonia, with secondary accumulation of glutamine and glycine. Ammonia scavengers facilitate excretion of nitrogen by conjugating with glutamine and glycine, which is then excreted in the urine.

carbamoyl phosphate synthetase (CPS), the first and rate-limiting step in the urea cycle. With insufficient NAG, CPS activity is decreased and hyperammonemia develops. (15) Currently, there are no treatments available in the United States for hyperammonemia in patients with organic acidemias. N-carbamylglutamate (carglumic acid) is a synthetic analog of NAG. (16) It is approved for the treatment of NAG synthetase deficiency; clinical trials are currently under way to evaluate the use of carglumic acid for the management of hyperammonemia in patients with PA and MMA. (17)

PROVIDING PRODUCT

Insufficient product distal to the biochemical block causes its own set of physiologic perturbations. For many disorders, administration of product is necessary to achieve metabolic control or restore homeostasis (Fig 5). This is well-illustrated by the practice of supplying tyrosine in the treatment of PKU. Tyrosine has various physiologic responsibilities, including the synthesis of epinephrine, norepinephrine, and dopamine, as well as melanin. In patients with PKU, phenylalanine is not converted to tyrosine because of PAH deficiency and tyrosine becomes conditionally essential. PKU-specific formulas are enriched with tyrosine to meet this need. (3) Similarly, in UCDs, arginine becomes an essential amino acid and it, or its precursor citrulline, is supplemented, provided the primary defect is not in arginine or citrulline metabolism. (10)

Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a disorder of very-long-chain fatty acid metabolism, characterized by varying degrees of hypoketotic hypoglycemia, cardiomyopathy, and myopathy. In this disorder, there is deficiency of the enzyme VLCAD, which catalyzes β-oxidation of fatty acids of 14 to 20 carbons in length. With each turn of the β-oxidation spiral, 2 carbons are cleaved. The relevant dehydrogenase changes based on carbon length, with chains of 10 to 14 fatty acyl-CoAs being processed by long-chain acyl-CoA dehydrogenase, 6 to 10 by medium-chain acyl-CoA dehydrogenase, and 4 to 6 by short-chain acyl-CoA dehydrogenase. (18) Patients with long-chain defects such as VLCAD deficiency are given a long-chain fat-restricted diet, with supplementation of medium-chain triglycerides (MCTs), which bypasses the enzymatic block in long-chain fatty acid oxidation disorders. (5) Triheptanoin is an investigational treatment for long-chain fatty acid oxidation disorders that also provides MCT as an energy source. However, unlike MCT, it also provides propionyl-CoA which serves to replace deficient tricarboxylic acid

intermediates by conversion to succinyl-CoA. This investigational drug is still under study, but a phase II open-label trial showed some benefits in exercise tolerance. (19)

ENHANCED CONVERSION OF SUBSTRATE TO PRODUCT

Treatments that enhance the conversion of substrate to product are desirable because they most directly address the underlying biochemical defect. This has historically been approached with cofactor therapies. However, with advances in medicine, we have begun to more precisely correct the biochemical perturbation with enzyme replacement and gene therapies (Fig 6).

Cofactor Therapy

Cofactors are compounds that assist in enzymatic activity. Some IEMs are caused by a primary cofactor deficiency; others are not caused by cofactor deficiency but show clinical improvement with cofactor supplementation. Some subtypes of MMA, for example, are B_{12} responsive. These subtypes have defects in the transport or synthesis of B_{12} and related cofactors and can be treated with hydroxocobalamin with favorable prognosis. For this reason, testing for B_{12} responsiveness is recommended as part of the evaluation for patients newly diagnosed with MMA. (20)

An example of cofactor supplementation without deficiency is sapropterin treatment in PKU. Tetrahydrobiopterin (BH4) is a cofactor for PAH, the enzyme deficient in PKU. In 2007, sapropterin dihydrochloride was approved by the FDA for the treatment of PKU. Sapropterin is an orally administered synthetic BH4. Despite normal BH4 levels, approximately 25% to 50% of PAH-deficient patients are sapropterin-responsive. (21)(22)(23)(24) Sapropterin is hypothesized to act as a chaperone for residual enzyme. Patients who are sapropterin-responsive may have a 2- to 3-fold increase in protein intolerance, and are found to have improved neuropsychiatric symptoms and positive impact on quality of life. (25)

Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) involves the periodic infusion of deficient enzyme to patients with eligible diseases. Lysosomal storage diseases have been the focus of ERT development because of the ability to target the drug to the lysosome with mannose-6-phosphate tagging. The first effective ERT was developed in the 1980s for Gaucher disease, when researchers demonstrated that weekly infusions of exogenous macrophage-targeted human placental glucocerebrosidase was of clinical benefit for type 1 Gaucher disease. (26) Since then, many more ERTs have become clinically available for the treatment of lysosomal storage diseases, including Fabry disease, Pompe disease, lysosomal acid lipase deficiency, mucopolysaccharidoses (MPS) type I, II, IV-A, VI, and VII. Clinical trials are currently under way for the use of ERT for acid sphingomyelinase deficiency (Niemann-Pick disease type B) and MPS IIIB. (27) Despite the overall success of ERT, there remain a few key challenges. These include the time commitment and financial burden inherent to lifelong infusion therapies. Safety concerns also exist, including the risk of an antidrug antibody response with hypersensitivity reactions. For diseases with neurologic symptoms, another major challenge is the inability of the drug to cross the blood-brain barrier. (28) Intraventricular ERT has been FDA approved for the treatment of neuronal ceroid lipofuscinosis type 2 disease. This lysosomal disorder causes neurodegeneration in early childhood, with loss of motor, language, and

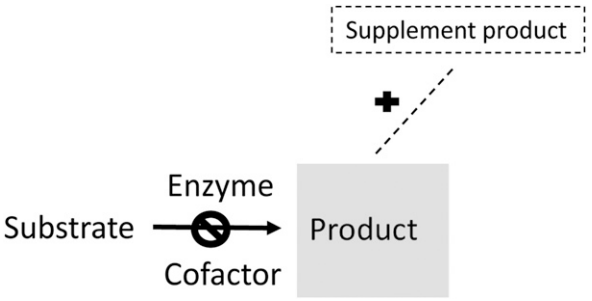

Figure 5. Insufficient conversion of substrate to product results in product deficiency. For many inborn errors of metabolism, supplementation of product (denoted with a plus (+) sign) is an important component of restoring homeostasis.

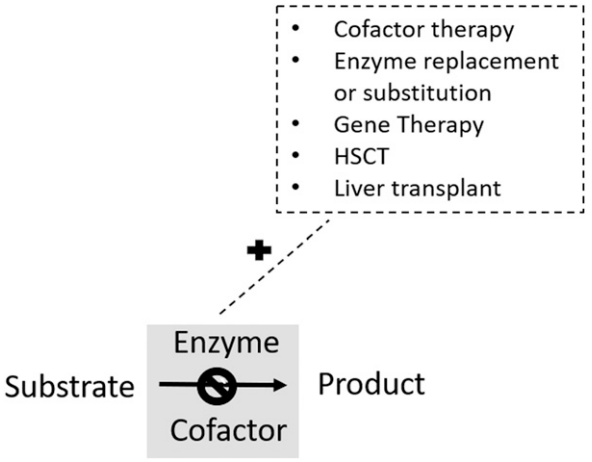

Figure 6. Treatments that enhance the conversion of substrate to product include cofactor therapy, enzyme replacement and substitution therapies, gene therapy, hematopoietic stem cell transplantation (HSCT), and liver transplantation.

TABLE. **Multipronged Approach to Treatment of Select IEMs**[a]

	DECREASE SUBSTRATE			PROVIDE PRODUCT	ENHANCE CONVERSION OF SUBSTRATE TO PRODUCT	
DISEASE	DIETARY RESTRICTION	SCAVENGER THERAPY	SUBSTRATE REDUCTION THERAPY	DIETARY SUPPLEMENT	COFACTORS	ENZYME REPLACEMENT
PKU	Phenylalanine-restricted diet			Tyrosine enriched formula	Sapropterin	Pegvaliase
MSUD	Branched chain amino acid–restricted diet				Thiamine	Liver transplant
HT-1	Phenylalanine- and tyrosine-restricted diet		NTBC			Liver transplant
MMA	Methionine-, threonine-, valine-, and isoleucine-restricted diet	Carnitine			B12	Liver transplant
PA	Methionine-, threonine-, valine-, and isoleucine-restricted diet	Carnitine			Biotin	Liver transplant
UCDs	Essential amino acid formulas	Nitrogen scavengers		Arginine or citrulline		Liver transplant, gene therapy

HT-1=hereditary tyrosinemia type 1; IEM=inborn error of metabolism; MMA=methylmalonic acidemia; MSUD=maple syrup urine disease; NTBC=2-[2-nitro-4-(trifluoromethyl)benzoyl]cyclohexane-1,3-dione; PA=propionic acidemia; PKU=phenylketonuria; UCDs=urea cycle disorders.
[a]Often treatments from each category (decreasing substrate, providing product, and enhancing conversion) are provided in concert to optimize metabolic control.

visual function. Intraventricular ERT has been shown to slow disease progression but requires an intraventricular device, which poses a risk for central nervous system infections and device malfunction. (29)

A novel enzyme substitution therapy, pegvaliase, was approved by the FDA in 2019 for the treatment of adults with PKU. Pegvaliase is a PEGylated form of phenylalanine ammonia lyase, a bacterial enzyme that converts phenylalanine to transcinnamic acid and ammonia, resulting in clinically significant reduction of phenylalanine levels. (30)(31)

HEMATOPOIETIC STEM CELL TRANSPLANTATION

When ERT is not available or desirable, hematopoietic stem cell transplantation (HSCT) can serve as an indirect method of enzyme delivery. Transplanted donor cells offer a continuous source of enzyme and may even deliver enzyme within the central nervous system by the passage of donor-derived cells across the blood-brain barrier to become microglia. (32) HSCT has been performed for inborn errors with neurologic manifestations, including X-linked adrenoleukodystrophy, metachromatic leukodystrophy, and Krabbe disease.

Despite the availability of ERT, HSCT remains the standard of care for children with severe MPS I who are younger than 2 years and have minimal cognitive impairment. (33)(34) Although ERT has not been shown to prevent neurocognitive decline, early treatment with HSCT may be neuroprotective. (35)(36)(37)(38)(39)(40)(41)(42) However, HSCT is not curative and has been shown to have limitations in preventing and treating other disease manifestations, including orthopedic and ophthalmologic symptoms. (32)(43) Any benefits must be carefully weighed against the morbidity and mortality of transplantation.

LIVER TRANSPLANTATION/HEPATOCYTE TRANSFER

Orthotopic liver transplantation (OLT) is used as a treatment for many IEMs with prevalent enzyme expression in the liver. For such diseases, the donor liver serves as a source of gene therapy in the recipient. IEMs now account for 19% of pediatric liver transplantations in the United States; a 6-fold increase in liver transplantation for IEMs was seen between 1987 and 2017. (44) Transplantation is now considered standard of care for children with ornithine transcarbomylase deficiency and other proximal urea cycle defects. (10) Transplantation before age 2 years is recommended for these conditions because of

the high risk for life-threatening metabolic decompensation before transplantation. After transplantation, patients are effectively cured, though they may require ongoing citrulline repletion. Maple syrup urine disease is also cured by liver transplantation. Many other conditions, including PA and MMA, have significant improvements in metabolic stability but require ongoing protein restriction; affected patients remain at risk for metabolic stroke. (45)

Despite the overall success of OLT for patients with hepatic IEMs, transplantation invites its own set of risks and complications. Data from the Scientific Registry for Transplant Recipients and United Network for Organ Sharing demonstrate that children younger than 2 years have a lower 5-year survival compared with children aged 2 to 9 years. (44)(46) Human heterologous liver cell transplantation (LCT) is a lower-risk procedure that has been proposed as a bridge to transplantation. (47) In LCT, cells from human donor organs are cryopreserved and infused through the portal vein. They then engraft into the recipient liver and compete for growth. (48) In a prospective clinical trial of 12 patients with severe UCDs, LCT was found to have a favorable safety profile. Hepatocyte transfer has the added advantage of sharing a single donor organ among several recipients. (49) However, metabolic stability from this procedure is transient. (47)

GENE THERAPY

Recent advances in gene replacement therapy and genome editing offer hope for nonsurgical cures for IEMs. Gene replacement therapy involves delivery of the therapeutic gene using a viral vector. Because of the safety and efficacy benefits, adeno-associated viral vectors are currently favored for liver-directed gene therapies. (48) Lentiviral and retroviral vectors are being explored for central nervous system disease. (50)

Adenoviral and lentiviral therapies are being evaluated in preclinical and clinical trials for a variety of disorders including several UCDs, metachromatic leukodystrophy, X-linked adrenoleukodystrophy, and MPS IIIa, to name a few. Ongoing research will need to continue to evaluate safety and efficacy of these treatments.

Genome editing encompasses a group of technologies that allow alteration of the DNA sequence in the recipient. Genome editing with the CRISPR-Cas9 system successfully corrected a mouse model of tyrosinemia type 1, and more recently a mouse model of PKU. (51)(52) This new technology is promising for the future of hepatic IEMs but will require rigorous study of safety and efficacy before clinical application.

CONCLUSION

Over the past several decades, the treatment of children with IEMs has been at the forefront of scientific progress. Medications like NTBC for HT-1, sapropterin dihydrochloride for PKU, and ERTs for children with lysosomal storage diseases have changed the course of previously devastating illnesses. Emerging gene therapy and editing technologies offer hope for a single, curative therapy for many IEMs. Nonetheless, the paradigm of restricting substrate, providing product, and enhancing conversion of substrate to product, remains the basis of present treatment for many of these diseases. These therapies are often provided in concert with one another, as illustrated in the Table. Titrating such interventions is complex and should be done in coordination with clinicians specializing in IEMs whenever possible.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids.
- Know the clinical manifestations, laboratory features, and treatment of organic acid disorders.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.

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