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A Few Words about Newborn Screening

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Abstract:

The newborn should be examined in detail within 24 hours. Performing a physical examination in the presence of the mother and family members allows them to ask questions, and the clinician to highlight the physical findings and provide advice. Growth and development are the most important indicators by which a child's health is assessed, and they are monitored on periodic systematic examinations. All the necessary measurements are then made, which are compared with the normal for age and sex, and also with earlier values in order to monitor the growth rate of the child. The child is also examined for all organ systems (head and neck, respiratory system, heart, abdomen, genitals, skin, bone and joint system). An important part of each examination is the assessment of the child's psychomotor development, ie whether he achieves at a certain age those skills that were expected for that age. It is extremely important to monitor the child's communication with the environment and speech development from an early age. By noticing the lag in time and intervening early, great progress can be made, which is better the earlier the child has started stimulation.

Keywords: baby; newborn screening; genetics; disorders; health

Introduction

Newborn screening programs are designed to identify neonates at risk for catastrophic outcomes from treatable illnesses [1]. Technologic advances in the past 50 to 60 years, such as tandem mass spectrometry, have made it possible to test for more than 50 metabolic disorders from a single blood spot. New techniques in molecular biology, including high-throughput DNA sequencing, allow for rapid diagnostic testing of conditions such as cystic fibrosis.

Since 2015, development of federal recommendations for newborn screening has been the responsibility of the Advisory Committee on Heritable Disorders in Newborns and Children (under the US Department of Health and Human Services). The conditions on the Recommended Uniform Screening Panel include metabolic disorders, hemoglobinopathies and thalassemias, congenital hypothyroidism, SCID, hearing screening, and critical congenital heart disease. Advances in treatment (eg, enzyme replacement therapy) have resulted in recent expansion of the panel. As of July 2018, the latest additions to the Core Conditions list were disease type II (ie, Pompe disease), mucopolysaccharidosis type I (ie, Hurler syndrome), X-linked adrenoleukodystrophy, and spinal muscular atrophy (caused by homozygous deletion of exon 7 in SMN1). The Recommended Uniform Screening Panel also has a list of Secondary Conditions, based on the earlier recommendations.

Primary care physicians have 3 crucial roles in newborn screening. First, they provide education to parents about the newborn screening process. Second, they ensure that specimens are drawn under proper circumstances and that the results are promptly followed up. Finally, they provide medical follow-up and referral in cases of positive test results. All physicians must have contact information for state newborn screening programs and local pediatric subspecialists.

Risk Assesment

It is important to review the mother's pregnancy, delivery, and postpartum notes to identify important risk factors [2]. For example, breech position during pregnancy,

especially in young girls, may require a follow-up ultrasound at 6 to 8 weeks to evaluate for developmental dysplasia of the hip. A shoulder dystocia during delivery will require a more detailed physical exam to evaluate for a brachial plexus injury. Failure to pass the screening hearing exam in the newborn nursery will require further evaluation. If not done during prenatal care, clinicians should obtain a detailed family history to identify increased risks for genetically linked conditions such as sickle cell disease/trait, thalassemia, cystic fibrosis, muscular dystrophy, fragile X syndrome, and Down syndrome. Many of these conditions are also screened for on routine state-mandated newborn screens at birth.

Finally, an in-depth social history can provide important information to guide care for the infant and the family. Clinicians should explore social, environmental, and financial stressors to identify families in need of additional community resources, ask mothers about postpartum depressive symptoms and inquire about contraceptive intentions.

Inadequate growth may be the presenting feature of a variety of disorders, such as endocrinopathies, cardiac diseases, and renal dysfunction but is more commonly a result of social stressors, poor bonding, and inadequate nutrition. Height, weight, and head circumference should be measured during all routine office visits during the first 2 years of life and plotted on a standardized growth chart. The growth rate may be more meaningful than individual measurements alone. After age 2, only height and weight need to be plotted and expressed as a BMI centile.

Development can be monitored by documenting achievement of age-appropriate milestones for intellectual, motor, and social skills. Early identification of developmental delays allows timely implementation of appropriate interventions and identification of available community resources. Unfortunately, clinical assessment alone detects 30% of children with developmental disabilities. Standardized developmental screening instruments such as Denver II screening test, Battelle Developmental Inventory, and others, are more sensitive. Parent report instruments, such as the Parents' Evaluation of Developmental Status and Child Development Inventories, can be similarly effective and require much less physician time. Clinicians generally begin using standardized developmental screening around 6 months of age.

IEM

Screening for Inborn Errors of Metabolism (IEM) has a relatively low yield (0%–5%) in children who present with developmental delay or ID [3]. Most patients with IEM will be identified by newborn screening or present with specific indications for more focused testing, such as failure to thrive, recurrent unexplained illnesses, plateauing or loss of developmental skills, coarse facial features, cataracts, recurrent coma, abnormal sexual differentiation, arachnodactyly, hepatosplenomegaly, deafness, structural hair abnormalities, muscle tone changes, and skin abnormalities. However, treatable forms of IEMs may present later or without regression or plateau. There are currently 89 "treatable" types of IEM. Treatments may target improvement in symptoms, slowing progression of the disease, or providing support during an illness. Tier 1 tests/"nontargeted screening tests" include blood tests for lactate, ammonia, plasma amino acids, total homocysteine, acylcarnitine profile, copper, ceruloplasmin; and urine tests for organic acids, purines and pyrimidines, creatine metabolism, oligosaccharides, and glycosaminoglycans. Testing for 7- and 8-dehydrocholesterol to screen for Smith-Lemli Opitz syndrome and screening for congenital disorders of glycosylation may also be included in first-tier testing. Second-tier testing usually comprises tests that are the only tests for one disease or are more invasive such as tests of cerebrospinal fluid. AAP guidelines for tier 1 tests are somewhat different and include blood tests for plasma amino acids, total homocysteine, acylcarnitine profile; and urine tests for organic acids, purines and pyrimidines, creatine metabolism, oligosaccharides, and mucopolysaccharides. An app has been developed, which is helpful for identifying appropriate tests for treatable etiologies of ID/GDD.

Disorders

Most neonates with disorders detected on newborn screening are clinically asymptomatic in the first 2 weeks after birth, but others may have significant signs and symptoms [1]. The presence of such features may require a more urgent work-up or even hospitalization. Unfortunately, severe forms of some metabolic disorders may cause coma and encephalopathy by 48 hours of age. In these cases, newborn screening results are critical, because they will suggest a probable diagnosis and allow early optimization of therapy.

Although newborn screening techniques are continually improved, false-positive and false-negative results may occur. Mislabeled specimens, technical errors, and reporting errors can occur in any laboratory. Any specimen collected before 12 hours of age is at risk for a false-negative metabolic result or a false-positive hypothyroidism result. Preterm newborns have a reduced metabolic capacity and therefore may exhibit higher metabolite levels compared with levels in full-term infants, which can produce false-positive results. Anemia or polycythemia can affect the amount of plasma per blood spot, which may lead to false-negative results. Transfusion may alter galactosemia and hemoglobinopathy testing. Neonates receiving hyperalimentation may have increased amino acid and lipid levels, especially if the newborn screen is drawn from a central line (rather than a heel stick). To ensure accurate and uniform testing and interpretation, it is imperative that relevant clinical information be included when the newborn specimen is submitted.

Criteria for screening newborns for a disorder include its frequency, its consequences if untreated, the ability of therapy to mitigate consequences, the cost of testing, and the cost of treatment [4]. With the availability of tandem mass spectrometry, newborn screening has expanded greatly to now include 25 core conditions and multiple secondary conditions screened by most states. In general, amino acidopathies, organic acidurias, and disorders of fatty acid oxidation are the disorders for which screening now occurs. Most states also screen for hypothyroidism, congenital adrenal hyperplasia, hemoglobinopathies, biotinidase deficiency, galactosemia, and cystic fibrosis. Screening for severe combined immune deficiency and congenital heart disease has been recently added. A few states have begun screening for some of the lysosomal and peroxisomal disorders. Screening should occur for all infants between 24 and 72 hours of life or before hospital discharge.

Some screening tests measure a metabolite (eg, phenylalanine) that becomes abnormal with time and exposure to diet. In such instances, the disease cannot be detected reliably until intake of the substrate is established. Other tests measure enzyme activity and can be performed at any time (eg, biotinidase deficiency). Transfusions may cause false-negative results in this instance, and exposure of the sample to heat may cause false-positive results. False-positives also result from prematurity, parenteral nutrition, hyperbilirubinemia, and liver or renal disease. Technologic advances have extended the power of newborn screening but have brought additional challenges. For example, although tandem mass spectrometry can detect many more disorders in the newborn period, consensus on diagnosis and treatment for some conditions is still under development.

Screening tests are not diagnostic, and diagnostic tests must be undertaken when an abnormal screening result is obtained. Because false-negative results occur, a normal newborn screening test does not rule out a condition, and some common disorders (eg, ornithine transcarbamylase deficiency) are not detectable in the screening tests performed in every state.

The appropriate response to an abnormal screening test depends on the condition in question and the predictive value of the test. For example, when screening for galactosemia by enzyme assay, complete absence of enzyme activity is highly predictive of classic galactosemia. Failure to treat may rapidly lead to death. In this case, treatment must be initiated immediately while diagnostic studies are pending. In phenylketonuria, however, a diet restricted in phenylalanine is harmful to the infant whose screening test is a false-positive, while diet therapy produces an excellent outcome in the truly affected infant if treatment is established within the first weeks of life. Therefore, treatment for phenylketonuria should only be instituted when the diagnosis is confirmed. Physicians should review American College of Medical Genetics recommendations, state laws and regulations, and consult with their local metabolic center to arrive at appropriate strategies for each hospital and practice.

The first step in the detection of amino acid and organic acid disorders is newborn screening of blood spots using tandem mass spectroscopy [5]. A diagnosis can be established by detecting characteristic organic acid profiles in urine by gas chromatography/mass spectroscopy. The results may trigger additional reflex testing, such as amino acid analysis or enzyme assays in cultured fibroblasts and other cells. Prenatal diagnosis can be accomplished by detection of abnormal metabolites in amniotic fluid and by measuring enzyme activity in cultured amniocytes or chorionic villus samples. When the actual mutation is known, DNA analysis can be used for prenatal diagnosis and carrier detection.

Every birthing facility should establish routines to ensure that all newborns are screened in accordance with state law [6]. States test newborns primarily through blood samples collected from heel pricks that are placed on a special filter paper. Umbilical cord blood is never an appropriate specimen because it will be inaccurate for detection of disorders in which metabolite accumulation occurs after birth and after the initiation of feeding. Newborn screening blood specimens are ideally collected between 24 hours and 48 hours of age and sent to the designated state newborn screening laboratory as soon as possible. In most states if the initial specimen is obtained before the infant is 24 hours old, it is recommended that a second specimen be obtained to decrease the probability that disorders with metabolite accumulation (eg, phenylketonuria) will be missed as a consequence of early testing. Some states also mandate, or strongly recommend, that an additional newborn screening blood specimen be collected on all infants at 10–14 days of age in order to reduce the chance of missed identification of infants with clinically significant disorders because of early testing. Diagnostic testing should be performed if clinically indicated, regardless of the initial screening results. Some newborns with disorders included in the newborn screening panel will not be identified even with a properly conducted screening test because of individual or biologic variations, very early discharge, or administrative or laboratory error.

Genetics

Universal newborn screening is the practice of screening every newborn for genetic testing [7]. Through early identification and treatment, newborn screening improves care. Primary intervention provides an opportunity for reduction in infant morbidity and mortality.

Expanded newborn screening using tandem mass spectrometry (MS/MS) can detect many genetic diseases. Every year, approximately 4 million infants are screened. Of these screened infants, 12,500 are diagnosed with one of the 29 core conditions of the uniform screening panel. Hearing loss, primary congenital hypothyroidism, cystic fibrosis, sickle cell disease, and medium-chain acyl-CoA dehydrogenase deficiency are the most common genetic entities detected in the United States.

Many of the diseases of the expanded newborn screen in the past were not diagnosed until after the child was very ill or died. Diagnosing disease early from the newborn screen can result in treatment before mortality or morbidity occurs. In the case of the twin infants with MMA, they had liver transplants to prevent the devastating effects of the disease.

Cystic Fibrosis

CF (Cystic Fibrosis) affects over 30,000 individuals in the United States [8]. As an autosomal recessive genetic disorder, 1 in 25 Caucasians carry a genetic mutation for CF, and the incidence of CF among Caucasians is approximately 1 in 3000. The gene mutation responsible for CF encodes for the cystic fibrosis transmembrane regulator (CFTR), a protein that is trafficked to the apical portion of many epithelial cells and conducts chloride. This chloride channel defect is responsible for a multitude of problems in CF, but the most common and worrying is dried airway secretions in the lungs leading to mucous retention, chronic infection, and chronic inflammation. This triad of mucous retention, infection, and inflammation, if left untreated and even despite therapy, leads to bronchiectasis. Because the lung parenchyma is spared, the elastic forces of the lung tissue pull these damaged airways open and ektasis (Greek; stretching) of the bronchi (Greek; windpipe) occurs.

Clinically, CF lung disease and bronchiectasis present as chronic cough with purulent sputum production. Examination findings may include weight loss; lung crackles, wheezes, or rhonchi; and

digital clubbing. Examination of the sputum may reveal typical pathogens, with Pseudomonas aeruginosa being a common bacterium that causes chronic infection. PFT often displays characteristic findings consistent with airways obstruction.

The diagnosis of CF requires clinical suspicion plus a confirmatory test. In CF, clinical suspicion occurs when signs and symptoms are present, there is a sibling with CF, or newborn screening is positive. The confirmatory testing for CF includes sweat chloride testing, nasal potential difference measurements, or genetic testing for CFTR mutations. The most common confirmatory test, and still considered the gold standard, is the sweat chloride test in which sweat obtained by pilocarpine iontophoresis is obtained and analyzed for the chloride content. Chloride values <40 mmol/L are normal, 40–60 mmol/L are considered borderline, and >60 mmol/L are diagnostic of CF in the correct clinical setting. It should be noted that newborns and infants less than 6 months of age with sweat chloride values >30 mmol/L should still be considered to be at risk for CF because some babies have eventually been diagnosed with CF who had sweat chloride values 30–60 mmol/L.

Nasal potential difference testing directly evaluates chloride conductance across the respiratory epithelium at the level of the nasal turbinates. This testing takes advantage of the unified epithelium throughout the respiratory tract to measure chloride conductance at the nasal epithelium that represents chloride conductance in the lower airways. This is a highly specialized test that is offered at selected CF centers.

Genetic testing for CF allows for detection of CFTR gene mutations that can lead to CF. With over 1500 CFTR gene mutations discovered to date, genetic testing has the possibility of confirming the diagnosis. The downfall of genetic testing is that not all genetic mutations of CFTR have been proven to directly contribute to the pathophysiology of CF. In fact, only 23 genetic mutations of CFTR have been directly linked with CF. However, 85% of patients with CF carry 1 of those 23 genetic mutations, and the most common CFTR mutation, by far, is the DF508 mutation.

Newborn screening for CF involves obtaining a blood sample from the newborn and measuring immunoreactive trypsinogen (IRT), which is elevated in the blood of babies with CF. Some newborn screening programs employ only IRT with a repeat test, if elevated, and then referral to a CF center for further testing (sweat chloride testing). Other programs employ a two-tiered approach that evaluates IRT and, if elevated, further evaluates for CFTR gene mutations. The result of the two-tiered approach allows for the potential diagnosis of CF if two gene mutations are discovered. Most physicians will still perform sweat chloride testing to confirm the diagnosis of CF even with newborn screening that identifies two CFTR gene mutations. The advantages of newborn screening for CF include early identification and therapy to promote growth and prevent lung disease and infection.

Hearring Loss

A veritable earth shift has occurred in the field since the advent of newborn screening for hearing loss and the accompanying advocacy toward extension of effective, early intervention services for families and their infants and toddlers diagnosed with hearing loss [9]. For decades, the issue of language deprivation was neglected, although that was the primary and often misunderstood issue associated with the condition of permanent hearing loss among children. Advancements in technology have made large-scale hearing screening procedures feasible, and definitive diagnosis of hearing loss is possible for infants at only a few weeks of age. Early identification of congenital hearing loss is not only feasible and promising, but it is now the norm. With early diagnosis, referral for and implementation of intervention can commence far earlier in the life of the child. With appropriate support and information, families can respond more effectively to the needs of their young baby affected by hearing loss.

Extension of effective intervention means infants and toddlers who are deaf or hard of hearing are able to access language stimulation and demonstrate trajectories of language development commensurate with age-level expectations. For decades, significant delays and deficits in language development, and concomitantly with social and cognitive and academic functioning, were documented among children with all degrees of hearing loss, mild to profound. A significant factor accounting for delays in language development among deaf and hard of hearing children was the age at diagnosis of hearing loss. Diagnostic procedures that are then integrally linked with meaningful habilitative interventions can now be commenced during the crucial period when access to language can optimize long-term outcomes for babies born with hearing loss. While the greatest risk of hearing loss is disruption or delay in acquiring effective means of communication, the greatest promise of early detection of hearing loss is that with vigorous and appropriate intervention, the likelihood of delay in language acquisition can be obviated.

FTT

Failure to thrive (FTT) is generally defined as a weight lower than the third or fifth percentile on a growth chart or a change in weight that has crossed down 2 major percentile lines over 3 to 6 months [10].

FTT is due to inadequate calorie intake, excessive calorie losses, or increased calorie requirements. The most common cause, found in 85% of cases in the United States, is inadequate calorie intake, which may be associated with significant psychosocial issues. However, this approach is too rigid, as often inadequate nutrition reflects a complex interaction among a child's medical, nutritional, and social issues. Therefore, a thorough psychosocial evaluation is an important part of patient assessment.

Indications for hospitalization include failure of outpatient therapies, severe FTT or malnutrition, serious infections, neglect or a concern for the patient's safety, or the need for a multidisciplinary team approach and/or services for parental education and coordination of care that are best performed in the inpatient setting.

A detailed history is critical to making the diagnosis. Take a thorough dietary history, including foods and formula (preparation, frequency), feeding/breastfeeding patterns, juice/water intake, and behaviors at mealtime. Quantify the daily caloric intake. It is best to do a 24-hour diet recall or to have the family keep a 3-day diet log. Inquire about gastrointestinal (GI)

symptoms (vomiting or spitting up, difficulty swallowing or eating), stooling (pattern, frequency, consistency, diarrhea, bloody, mucoid), respiratory issues (difficulty breathing, chronic cough, snoring), and recurrent infections. Pregnancy and birth history, including birth weight, as well as a complete medical history and review of symptoms are essential. Document the developmental milestones in infants, and confirm the newborn screen results.

The vital signs and general appearance (dysmorphic features, cachexia, general activity) are priorities. Examine the oropharynx for a cleft palate, poor suck or swallow, dental caries, and enlarged tonsils. Assess the work of breathing, auscultate for a murmur, and palpate the abdomen for hepatomegaly. Note any loose skin, edema, poor hygiene, rash, or bruises or evidence of trauma. Perform a neurologic examination for tone, reflexes, social interaction, and developmental milestones. One final, important part of the physical examination is an observation of the parent/child interaction and feeding routine.

Conclusion

After the examination by the neonatologist at the maternity hospital and the arrival of the child at home, the first examination by a pediatrician is performed at the age of one month, and earlier if necessary. This is the beginning of preventive programs for monitoring the growth and development of the child, which include systematic examinations, vaccinations and advice on the care and nutrition of the child. It is also an opportunity to meet the chosen pediatrician who will usually be the first contact doctor in case of a child's illness. The examination begins with taking anamnestic data on the course of childbirth and stay in the maternity hospital, possible diseases in the family and the current health and nutrition of the child. This part also includes a discussion about the adopted rhythm of feeding and sleeping and the possible occurrence of infant colic. The medical examination of the child begins with the observation of the child's behavior upon arrival at the office, and it is obligatory to take off the clothes and a general examination according to the systems. So-called somatic status and neurological status are assessed.

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