44. Screening for Phenylketonuria

RECOMMENDATION

Screening for phenylketonuria (PKU) by measurement of phenylalanine level on a dried-blood spot specimen is recommended for all newborns prior to discharge from the nursery. Infants who are tested before 24 hours of age should receive a repeat screening test by 2 weeks of age. There is insufficient evidence to recommend for or against routine prenatal screening for maternal PKU, but recommendations against such screening may be made on other grounds.

Burden of Suffering

PKU is an inborn error of phenylalanine metabolism that occurs in 1 of every 12,000 births in North America.[1,2] In the absence of treatment during infancy, nearly all persons with this disorder develop severe, irreversible mental retardation. Many also experience neurobehavioral symptoms such as seizures, tremors, gait disorders, athetoid movements, and psychotic episodes with behaviors resembling autism.[3] These clinical manifestations of PKU have rarely developed in children born after the mid-1960s, when routine screening was legislated and early treatment for PKU became common. This has resulted in a cohort of healthy phenylketonuric women who have entered childbearing age. If dietary restriction of phenylalanine is not maintained during pregnancy, these women are at increased risk of giving birth to a child with mental retardation, microcephaly, congenital heart disease, and low birth weight.[4] The incidence of this maternal PKU syndrome is 1 of every 30,000–40,000 pregnancies.[5] In the absence of dietary control in women with PKU who become pregnant, it is estimated that exposure of the fetus to the teratogenic effects of maternal hyperphenylalaninemia could result in an increase in the incidence of PKU-related mental retardation to the level seen before PKU screening was established.[6]

Accuracy of Screening Tests

Blood phenylalanine determination by the Guthrie test has been the principal screening test for PKU for three decades.[7] Although well-designed evaluations of the sensitivity and specificity of the Guthrie test have never been performed,[8] sensitivity estimates[9,10] and international experience with its use in millions of newborns suggest that false-negative results are rare. Fluorometric

assays, which can detect differences in blood phenylalanine levels as low as 0.1 mg/dL, are alternative forms of testing that also offer excellent sensitivity.[8] Most missed cases of PKU do not appear to be due to false-negative results of the screening tests, but to submission of an inadequate sample, clerical error involving the sample, or failure to follow up positive results.[9] Standards for adequate blood collection on filter paper for neonatal screening programs have been published.[10a]

False-positive as well as false-negative results can occur in PKU screening. In certain situations and population conditions, the ratio of false positives to true positives is as high as 32 to 1.[8] Although false positives have been viewed for many years as less important than false-negative results because they can be corrected easily by repeating the test, recalling patients for a second PKU test may generate considerable parental anxiety.[11,12]

The sensitivity of the Guthrie test is influenced by the age of the newborn when the sample is obtained. The current trend toward early discharge from the nursery (resulting in PKU screening being performed as early as 1 to 2 days of age) has raised concerns that test results obtained during this early period may have low sensitivity. This is because the blood level of phenylalanine is typically normal in affected neonates at birth and, with the initiation of protein feedings, increases progressively during the first days of life. Using the conventional cutoff of 4 mg/dL, diagnostic levels of phenylalanine may not be present in some phenylketonuric newborns tested in the first 24 hours of life. Prospective, longitudinal evaluations of serum phenylalanine levels in infants known to be at risk for PKU have demonstrated a variable rate of false-negative results when screening occurred within the first 24 hours of life.[13,14] The false-negative rates ranged from 2% to 31% for the first day of life, but decreased to 0.6% to 2% on the second day and to 0.3% by the third day.[8,13–16] Current rates may be lower due to the participation of many laboratories in a voluntary proficiency program run by the Centers for Disease Control and Prevention (CDC). The use of fluorometric assays, which offer more precise measurements of blood phenylalanine levels than the Guthrie test, result in lower false-negative rates as well.[8] Two additional solutions to improve sensitivity—repeat testing of all newborns after early discharge and lowering the cutoff value to reduce the false-negative rate—have encountered criticism for several reasons. Repeat testing would have low yield and reduced cost-effectiveness;[17,18] it has been estimated that detecting even one case of PKU in this manner would require performing an additional 600,000 to perhaps 6 million tests.[8,18] Lowering the cutoff value, on the other hand, improves sensitivity at the expense of specificity, thereby increasing the ratio of false positives to true positives.[8] As of 1991, nine of the 53 screening programs in the U.S. used a cutoff level of greater than 2 mg/dL to define abnormal.[19] The majority of labs continue to use

a cutoff of 4 mg/dL or greater.

The development of a cloned phenylalanine hydroxylase gene probe has made possible the prenatal diagnosis of PKU in families with previously affected children by analyzing DNA isolated from cultured amniotic cells or samples of chorionic villi.[20–22] Through the use of polymerase chain reaction, 31 alleles of the phenylalanine hydroxylase gene have been identified.[1] This may eventually permit the screening of the general population for carriers of these alleles, thereby detecting at-risk families prior to the birth of an affected child.[21–23]

Routine screening of pregnant women for maternal PKU has been recommended as a means of preventing fetal complications.[2,5,24] This disorder is rare in the general population, however, and as a result of screening programs, many women with PKU are aware of their diagnosis. As the cohort of women born before implementation of routine newborn screening move out of their childbearing years, the yield from screening all pregnant women should be very low. In Massachusetts, routine screening of cord blood for 10 years detected only 22 mothers with previously undiagnosed hyperphenylalaninemia.[2,25]

Effectiveness of Early Detection

Before treatment with dietary phenylalanine restriction was recommended in the early 1960s, severe mental retardation was a common outcome in children with PKU. A review in 1953 reported that 85% of patients had an intelligence quotient (IQ) less than 40, and 37% had IQ scores below 10; less than 1% had scores above 70.[3] Since dietary phenylalanine restriction was introduced, however, over 95% of children with PKU have developed normal or near-normal intelligence.[26–29] A large longitudinal study reports a mean IQ of 100 in children who have been followed to 12 years of age,[30] and other reports show adolescent and young adult patients are functioning well in society.[31] Although the efficacy of dietary treatment has never been proven in a properly designed controlled trial, the contrast between children receiving dietary treatment and historical controls is compelling evidence of its effectiveness. Recognition of this prompted most Western governments to require routine neonatal screening as early as the late 1960s.

It is essential that phenylalanine restrictions be instituted shortly after birth to prevent the irreversible effects of PKU.[26,28,32,33] Traditionally, strict adherence to the diet was recommended for the first 4–8 years of life, after which liberalization of protein intake could occur without damage to the developed central nervous system.[26,28,32–34] Recent data, however, suggest that discontinuation of the diet may result in a deterioration of cognitive functioning, leading many to recommend continuation of the diet

through adolescence and into adulthood.[35–37] Even if these precautions are taken, dietary treatment may not offer full protection from subtle effects of PKU. Intelligence scores in treated persons with PKU, although often in the normal range for the general population, are lower, on average, than those of siblings and parents,[26] and mild psychological deficits, such as perceptual motor dysfunction and attentional and academic difficulties, have been reported.[38–40]

Early detection of hyperphenylalaninemia in pregnant women may also be beneficial. The incidence of maternal PKU syndrome is increasing with the growing number of healthy phenylketonuric females now of childbearing age. Maternal hyperphenylalaninemia can produce teratogenic effects, even on normal fetuses who have not inherited PKU. If the mother with classic PKU does not follow a restricted phenylalanine diet during pregnancy, there is an overwhelming risk of birth of an abnormal child. This risk appears to increase as the average maternal levels of phenylalanine maintained during pregnancy increase.[41,42] Over 90% of these children will have mental retardation, 75% microcephaly, 40–50% intrauterine growth retardation, and 10–25% other birth defects.[4,5] Uncertainties exist, however, as to the extent these outcomes can be prevented by instituting treatment with dietary phenylalanine restriction during pregnancy.[4,43] Although some pregnant women under treatment have given birth to normal children, a number of investigators have found that dietary intervention during pregnancy fails to prevent fetal damage.[40,43–47] Preliminary evidence from the North American Collaborative Study of Maternal Phenylketonuria, on the other hand, suggests improved outcome if metabolic control is achieved by the 10th week of pregnancy.[48] Many believe dietary restrictions must be instituted prior to conception for them to be effective.[2,4,45,49] There are concerns, however, that the low-phenylalanine diet may produce deficiencies in calories, protein, and other nutrients that are needed for proper fetal growth.[5,43]

Recommendations of Other Groups

Every state has mandated that screening for PKU be provided to all newborns, but participation is not required by statute in Delaware, Maryland, North Carolina, or Vermont.[19] Testing for blood phenylalanine level after 24 hours of life and before 7 days is recommended by the American Academy of Pediatrics (AAP),[50] the American Academy of Family Physicians,[51] the American College of Obstetricians and Gynecologists (ACOG),[52] Bright Futures,[53] and the Canadian Task Force on the Periodic Health Examination.[54] All of these organizations recommend that infants who are not screened in the nursery should be screened by a physician by 3 weeks of age. As earlier hospital discharges (i.e., <24 hours) become the norm,

eight states have mandated a second screening of all newborns between 1 and 6 weeks of age, and most other states recommend repeat specimens if first collected before 24–48 hours of age.[19] The AAP endorses a second test for those infants who were screened before 24 hours of age.[50]

No major organization recommends routine prenatal screening for maternal PKU. ACOG recommends taking a history for known inborn errors of metabolism at the initial evaluation of the pregnant woman.[55] The AAP recommends that female patients known to have hyperphenylalaninemia be referred to appropriate treatment centers prior to conceiving.[56]

Discussion

There is good evidence that early detection of PKU by neonatal screening substantially improves neurodevelopmental outcomes for affected persons. The evidence is less clear for a benefit from screening pregnant women for PKU. Available evidence has not proven that dietary restrictions during pregnancy occur early enough to prevent fetal damage, and such restrictions may have other adverse effects. In addition, the incidence of previously undiagnosed maternal hyperphenylalaninemia is low, since many women who are currently of childbearing age were born after the introduction of widespread PKU screening in the mid-1960s and are likely to have been detected as newborns. The cost-effectiveness of screening during pregnancy has not been established.

CLINICAL INTERVENTION

Screening for phenylketonuria by measurement of phenylalanine level on a dried-blood spot specimen, collected by heelstick and adsorbed onto filter paper,[10a] is recommended for all newborns before discharge from the nursery ("A" recommendation). Infants who are tested in the first 24 hours of age should receive a repeat screening test by 2 weeks of age. Premature infants and those with illnesses optimally should be tested at or near 7 days of age, but in all cases before newborn nursery discharge. All parents should be adequately informed regarding the indications for testing and the interpretation of PKU test results, including the probabilities of false-positive and false-negative findings.

There is insufficient evidence to recommend for or against routine prenatal screening for maternal PKU ("C" recommendation), but recommendations against such screening may be made on other grounds, including the rarity of previously undiagnosed maternal hyperphenylalaninemia, cost, and the potential adverse effects of dietary restriction.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Robert Baldwin, MD, and Modena Wilson, MD, MPH.

REFERENCES

1. O'Flynn ME. Newborn screening for phenylketonuria: thirty years of progress. Curr Probl Pediatr 1992;22:159–165.
2. Waisbren SE, Doherty LB, Bailey IV, et al. The New England Maternal PKU Project: identification of at-risk women. Am J Public Health 1988;78:789–792.
3. Jervis GA. Phenylpyruvic oligophrenia (phenylketonuria). Res Publ Assoc Res Nerv Ment Dis 1953;33: 259–282.
4. Lenke RR, Levy HL. Maternal phenylketonuria and hyperphenylalaninemia: an international survey of the outcome of untreated and treated pregnancies. N Engl J Med 1980;303:1202–1208.
5. Hanley WB, Clarke JTR, Schoonheyt W. Maternal phenylketonuria (PKU): a review. Clin Biochem 1987;20:149–156.
6. Kirkman HN. Projections of a rebound in frequency of mental retardation from phenylketonuria. Appl Res Ment Retard 1982;3:319–328.
7. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. Pediatrics 1963;32:338–343.
8. Kirkman HN, Carroll CL, Moore EG, et al. Fifteen-year experience with screening for phenylketonuria with an automated fluorometric method. Am J Hum Genet 1982;34:743–752.
9. Holtzman C, Slazyk WE, Cordero JF, et al. Descriptive epidemiology of missed cases of phenylketonuria and congenital hypothyroidism. Pediatrics 1986;78:553–558.
10. Holtzman NA, Meek AG, Mellits ED. Neonatal screening for phenylketonuria. JAMA 1974;229:667–670.

10a. National Committee for Clinical Laboratory Standards. Blood collection on filter paper for neonatal screening programs, 2nd ed; approved standard. Vol 12 no 13. Villanova, PA: NCCLS, 1992. (NCCLS document LA4-A2.)

11. Rothenberg MB, Sills EM. Iatrogenesis: the PKU anxiety syndrome. J Am Acad Child Psychiatry 1968;7:689–692.
12. Sorenson JR, Levy HL, Mangione TW, et al. Parental response to repeat testing of infants with false-positive results in a newborn screening program. Pediatrics 1984;73:183–187.
13. Meryash DL, Levy HL, Guthrie R, et al. Prospective study of early neonatal screening for phenylketonuria. N Engl J Med 1981;304:294–296.
14. Doherty LB, Rohr FJ, Levy HL. Detection of phenylketonuria in the very early newborn blood specimen. Pediatrics 1991;87:240–244.
15. Holtzman NA, McCabe ERB, Cunningham GC, et al. Screening for phenylketonuria [letter]. N Engl J Med 1981;304:1300–1301.
16. McCabe ERB, McCabe L, Mosher GA, et al. Newborn screening for phenylketonuria: predictive validity as a function of age. Pediatrics 1983;72:390–398.
17. Schneider AJ. Newborn phenylalanine/tyrosine metabolism: implications for screening for phenylketonuria. Am J Dis Child 1983;137:427–432.
18. Sepe SJ, Levy HL, Mount FW. An evaluation of routine follow-up blood screening of infants for phenylketonuria. N Engl J Med 1979;300:606–609.
19. Newborn Screening Committee, The Council of Regional Networks for Genetic Services (CORN). National Newborn Screening Report—1991. New York: CORN, July 1994.
20. Lidsky A, Guttler F, Woo S. Prenatal diagnosis of phenylketonuria by DNA analysis. Lancet 1985;1: 549–551.
21. Wulff K, Wehnert M, Schutz M, et al. Prenatal diagnosis of phenylketonuria by haplotype analysis. Prenat Diagn 1989;9:421–425.
22. Guttler F. Impact of medical genetics concerning phenylketonuria: accomplishments, status, and practical future possibilities. Clin Genet 1989;36:333–334.
23. Dockhorn-Dworniczak B, Dworniczak B, Brommelkamp L, et al. Non-isotopic detection of single strand conformation polymorphism (PCR-SSCP): a rapid and sensitive technique in the diagnosis of phenylketonuria. Nucleic Acids Res 1991;19:2500.
24. MacCready RA, Levy HL. The problem of maternal phenylketonuria. Am J Obstet Gynecol 1972;123:121–128.
25. Levy HL, Waisbren SE. Effects of untreated maternal phenylketonuria and hyperphenylalaninemia in the fetus. N Engl J Med 1983;309:1269–1274.

26. Berman PW, Waisman HA, Graham FK. Intelligence in treated phenylketonuric children: a developmental study. Child Dev 1966;37:731–747.
27. Hudson FP, Mordaunt VL, Leahy I. Evaluation of treatment begun in first three months of life in 184 cases of phenylketonuria. Arch Dis Child 1970;45:5–12.
28. Williamson ML, Koch R, Azen C, et al. Correlates of intelligence test results in treated phenylketonuric children. Pediatrics 1981;68:161–167.
29. Hsia DY. Phenylketonuria 1967. Dev Med Child Neurol 1967;9:531–540.
30. Azen CG, Koch R, Friedman EG, et al. Intellectual development in 12-year-old children treated for phenylketonuria. Am J Dis Child 1991;145:35–39.
31. Koch R, Yusin M, Fishler K. Successful adjustment to society by adults with phenylketonuria. J Inherit Metab Dis 1985;8:209–211.
32. Waisbren SE, Mahon BE, Schnell RR, et al. Predictors of intelligence quotient and intelligence quotient change in persons treated for phenylketonuria early in life. Pediatrics 1987;79:351–355.
33. Holtzman NA, Kronmal RA, van Doorninck W, et al. Effect of age at loss of dietary control on intellectual performance and behavior of children with phenylketonuria. N Engl J Med 1986;314:593–598.
34. Hackney IM, Hanley WB, Davidson W, et al. Phenylketonuria: mental development, behavior, and termination of low phenylalanine diet. J Pediatr 1968;72:646–655.
35. Seashore MR, Friedman E, Novelly R, et al. Loss of intellectual function in children with phenylketonuria after relaxation of dietary phenylalanine restriction. Pediatrics 1985;75:226–232.
36. Thompson AJ, Smith I, Brenton D, et al. Neurological deterioration in young adults with phenylketonuria. Lancet 1990;336:602–605.
37. Smith I, Beasley MG, Ades A. Effect on intelligence of relaxing the low phenylalanine diet in phenylketonuria. Arch Dis Child 1990;65:311–316.
38. Pennington BF, van Doorninck WJ, McCabe LL, et al. Neuropsychological deficits in early treated phenylketonuric children. Am J Ment Defic 1985;5:467–474.
39. Smith I, Beasley MG, Wolff OH, et al. Behavior disturbance in 8-year-old children with early treated phenylketonuria. Report from the MRC / DHHS Phenylketonuria Register. J Pediatr 1988;112: 403–408.
40. Faust D, Libon D, Pueschel S. Neuropsychological functioning in treated phenylketonuria. Int J Psych Med 1986–87;16:169–177.
41. Platt LD, Koch R, Azen C, et al. Maternal phenylketonuria collaborative study, obstetric aspects and outcome: the first six years. Am J Obstet Gynecol 1992;166:1150–1162.
42. Matalon R, Michals K, Azen C, et al. Maternal PKU collaborative study: the effect of nutrient intake on pregnancy outcome. J Inherit Metab Dis 1991;14:371–374.
43. Lenke RR, Levy HL. Maternal phenylketonuria: results of dietary therapy. Am J Obstet Gynecol 1982;142:548–553.
44. Murphy D, Saul I, Kirby M. Maternal PKU and phenylalanine-restricted diet: studies of seven pregnancies and of offspring produced. Ir J Med Sci 1985;154:66–70.
45. Scott TM, Fyfe WM, Hart DM. Maternal phenylketonuria: abnormal baby despite low phenylalanine diet during pregnancy. Arch Dis Child 1980;55:634–637.
46. Koch R, Hanley W, Levy H, et al. A preliminary report of the collaborative study of maternal phenylketonuria in the United States and Canada. J Inherit Metab Dis 1990;13:641–650.
47. Smith I, Glossop J, Beasley M. Fetal damage due to maternal phenylketonuria: effects of dietary treatment and maternal phenylalanine concentrations around the time of conception. J Inherit Metab Dis 1990;13:651–657.
48. Rohr FJ, Doherty LB, Waisbren SE, et al. The New England Maternal PKU Project: prospective study of untreated and treated pregnancies and their outcomes. J Pediatr 1987;110:391–398.
49. Koch R, Levy HL, Matalon R, et al. The North American Collaborative Study of Maternal Phenylketonuria. Status report 1993. Am J Dis Child 1993;147:1224–1230.
50. Committee on Genetics, American Academy of Pediatrics. Issues in newborn screening. Pediatrics 1992; 89:345–349.
51. American Academy of Family Physicians. Age charts for periodic health examination. Kansas City, MO: American Academy of Family Physicians, 1994. (Reprint no. 510.)
52. American Academy of Pediatrics and American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 3rd ed. Washington, DC: American College of Obstetricians and Gynecologists, 1992.
53. Green M, ed. Bright Futures: guidelines for health supervision of infants, children, and adolescents. Arlington, VA: National Center for Education in Maternal and Child Health, 1994.

54. Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Canada Communication Group, 1994:180–188.
55. The American College of Obstetricians and Gynecologists. Standards for obstetric-gynecologic services. 7th ed. Washington, DC: The American College of Obstetricians and Gynecologists, 1989.
56. Committee on Genetics, American Academy of Pediatrics. Maternal phenylketonuria. Pediatrics 1991;88: 1284–1285.