Committee on Genetics

New Issues in Newborn Screening for Phenylketonuria and Congenital Hypothyroidism

Screening for phenylketonuria (PKU) and congenital hypothyroidism (CH) is of concern to parents, physicians, and public health professionals. Parents have an abiding interest in a predictive activity that can prevent disease in their offspring. Physicians and their consultants must counsel parents and interpret a positive screening test. Public health personnel are concerned with the specificity and sensitivity, efficacy, and effectiveness of newborn screening.

The Committee on Genetics has previously published recommendations on newborn screening for PKU and CH. Further recommendations are required because PKU and CH screening are widely practiced joint procedures in the newborn and because most full-term newborn infants are now being discharged from North American nurseries within the first three days after birth. This new practice is likely to have an effect on the validity of newborn screening and on screening for PKU, in particular.

A recent statement from the Committee on Fetus and Newborn (Pediatrics 65:651, 1980) addressed the problem of so-called “in and out deliveries.” However, the statement was ambiguous on the issue of whether such infants should be screened routinely on the initial discharge from the nursery. The Committee on Genetics believes that all infants, regardless of age, should be screened for PKU and CH at discharge from the nursery.

The Committee believes that screening is not the equivalent of diagnosis; some cases of PKU and CH will inevitably be missed by screening. Whereas an important reason for missed cases may be the biology of the target disorders, none should slip through the screening mesh because of flaws in the program and its components. Accordingly, we have examined the allied problems of initial screening and rescreening at a later age, in relation to early discharge from the nursery and our previous recommendations. The new statement emphasizes four issues: (1) organization of newborn screening programs for PKU and CH; (2) biologic adequacy of the blood sample and how it may influence the rate of false-negative results, and the need for routine rescreening; (3) performance of the screening method and how it may influence the frequency of false-negative test results; and (4) disorders of tetrahydrobiopterin homeostasis and their significance for diagnosis and treatment of infants with positive PKU tests.

RECOMMENDATIONS

1. An adequate screening PROGRAM for the persistent hyperphenylalaninemas (PHP), including phenylketonuria (PKU) and for congenital hypothyroidism (CH) (in its various forms) should assure: (a) total participation by the eligible population; (b) notification of parents about newborn screening and their participation in this activity; (c) reliable and prompt performance of the screening test; (d) prompt follow-up of subjects with positive tests; (e) accurate diagnosis of subjects with confirmed positive tests; (f) appropriate counseling and treatment of patients.

2. A blood SAMPLE should be obtained from every infant before he/she leaves the nursery, regardless of age.* Siblings of children with PKU/PHP and CH deserve special priority for collection of the sample. An adequate sample is defined as follows: (a) for PKU/PHP, it is heel blood obtained as close as possible to time of discharge from the nursery in a full-term infant; (cord blood is not sufficient); (b) for CH, it is cord blood at birth or heel blood at discharge; (c) in a premature infant, any infant receiving parenteral feeding, or any

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* This recommendation pertains to North American perinatal practices. In countries where there is a systematic home visit following early discharge or home delivery, it is appropriate to screen all babies on a sample drawn at home in the first week by the health visitor.
newborn infant being treated for illness, it is a blood sample obtained at or near the seventh day of age.

3. Infants initially screened before 24 hours of age should be rescreened for PKU/PHP because the probability of missing cases by the initial screening test is greatly increased. The repeat screening test should be completed before the third week of life.

4. Accurate ANALYSIS requires meticulous standardization of the screening method. Accuracy is improved when the cutoff level delineating an abnormal result is defined and specificity of the test is monitored regularly; to do so requires a high volume of samples per unit time. The analytical component in the program should be centralized to enhance ongoing evaluation of efficiency, accuracy, participation, and adequacy of samples.

5. All patients with persistent hyperphenylalaninemia should be investigated to rule out the tetrahydrobiopterin-deficient forms of phenylketonuria.

6. Systematic follow-up of infants with positive CH screening tests is necessary to evaluate the efficacy of CH prevention.

COMMENTS

1. Phenylketonuria and Other Forms of Persistent Hyperphenylalaninemia Associated with Disease

Early diagnosis and treatment largely prevent the mental retardation associated with untreated PKU and a properly executed program is clearly cost effective. PREVENTION requires an adequate PROGRAM, a satisfactory SAMPLE for the screening test, and reliable ANALYSIS of the sample.

1.1. The Program. Programs that reach every infant, perform the test reliably, provide timely follow-up of subjects with positive tests, assure accurate diagnosis, and provide appropriate counseling and treatment conform to published guidelines. Programs lacking any of these components cannot be recommended. Missed cases of PKU/PHP in screening programs may reflect faults of program organization, in particular, failure to obtain the blood sample or to perform a reliable analysis. On the other hand, cases can be missed because of biologic variation in the expression of hyperphenylalaninemia and are not necessarily the result of negligence in screening.

1.2. The Sample. Cases of PKU have been missed because the level of blood phenylalanine was not elevated above normal, even after the third day of life (B. Wilcken et al, personal communications, 1981. In general, however, the chance of a false-negative test result for PKU and other forms of PHP is greater when the blood sample is obtained before 72 hours of age. This statement is based on the following evidence: (1) Serial measurements in PKU infants during the first 3 days of life show that blood phenylalanine concentrations less than 4 mg/100 ml are more likely to occur in this period than after 72 hours of age; (2) The incidence of false-negative test results in PKU (either actual or predicted on statistical grounds) is higher in the first 3 days of life than in older infants.

Extrapolations from available data suggest that 16.1% of PKU cases could be missed on the first day (1 to 24 hours) of life because the screened blood sample contained less than 4 mg of phenylalanine per 100 ml; 2.2% of cases could be missed when screening is done on the second day (25 to 48 hours); and 0.3% on the third day (49 to 72 hours) of life. However, these are only statistical estimates of the frequency of missed cases. They are based on the distribution of blood phenylalanine in the PKU and non-PKU populations during the first three days of life where skewness and other factors in the variance contribute to the probability statements. An evaluation of routine repeat blood screening indicated that routine follow-up blood testing of infants for PKU was not productive.

It is now firmly established that cord blood cannot be used for PKU/PHP screening. Whether or not feeding practices influence the accuracy of screening in the first three days of life remains uncertain; it is the opinion of the Committee that this factor is of only minor importance, and the Recommendations should be followed regardless of the feeding protocol.

1.3. The Analytical Method. Accurate analysis of the sample is a critical facet of prevention. The Guthrie test is a threshold (cutoff) method that estimates phenylalanine concentration above a certain level in the blood sample. Quantitative methods permit the age-specific distribution of phenylalanine to be described and the corresponding cutoff level to be defined statistically. In practice, either method has predictive validity for PKU screening.

1.4. Tetrahydrobiopterin-deficient PKU. Infants with disorders of tetrahydrobiopterin homeostasis are likely to experience progressive neurologic deterioration when treated with low-phenylalanine diet alone. Current estimates indicate that 0.5% to 3% of infants with persistent hyperphenylalaninemia have a disorder of tetrahydrobiopterin metabolism. Their prognosis is quite different from that for infants with benign PHP or typical PKU.
treated and counseled in the conventional manner. Accordingly, prognosis for any patient with persistent hyperphenylalaninemia must be guarded, until experience with early diagnosis and treatment of tetrahydrobiopterin-deficient hyperphenylalaninemia has been accumulated and evaluated. Prompt consultation with the appropriate regional center for further investigation is recommended for all cases of PKU with persistent hyperphenylalaninemia.

1.5. Rescreening. Whereas the ideal screening program achieves perfect specificity (no false-positive tests) and perfect sensitivity (no false-negative tests), in practice this is seldom attained. Errors of classification do occur in the real world. It is our belief that errors should not occur because of organizational and technical flaws in the screening program. Yet, the Committee recognizes the fact of biologic variability when PKU/PHP screening is done before 24 hours of age; accordingly, routine rescreening of these infants is recommended.

1.6. Maternal PKU and PHP. Exposure to unmodified maternal PHP, in any of its forms, constitutes a risk to the fetus. Current screening programs for PKU/PHP should consider their responsibility for long-term follow-up of female patients so that physicians can initiate appropriate counseling in due course.

2. Congenital Hypothyroidism

All foregoing statements about adequacy of PROGRAM, SAMPLE, and ANALYSIS pertain equally to CH screening. The Committee cannot document other issues of CH screening with an authority comparable to that associated with PKU screening because the former is still an ongoing development. Proceedings of an international conference on CH screening are available for guidance.

Effective approaches to CH screening include thyroxine (T4) and thyroid-stimulating hormone (TSH) measurements on all samples, TSH measurements alone, and T4 with supplemental TSH measurement. Cord blood and heel blood have both been used effectively. Rapidly changing technology makes overcommitment to any particular sample protocol or laboratory analysis unwise at present. Two general comments are pertinent to programs utilizing a primary T4 measurement: (1) The risk of a false-negative test result in CH screening is increased when infants with incomplete absence of thyroid tissue are screened by the T4 assay alone; (2) Rescreening with combined T4 and TSH measurements is always recommended when the initial T4 value is abnormally low.

All infants classified as CH should be treated and systematically reevaluated to determine whether the initial condition was transient.

Committee on Genetics, 1980–1981
Charles R. Scriver, MD, Chairman
Neil A. Holtzman, MD
R. Rodney Howell, MD
Peter Mamunes, MD
Henry L. Nadler, MD
Liaison Representatives
Audrey F. Manley, MD
Godfrey Oakley, MD
Joe Leigh Simpson, MD

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Charles R. Scriver, Neil A. Holtzman, R. Rodney Howell, Peter Mamunes, Henry L. Nadler, Audrey F. Manley, Godfrey Oakley and Joe Leigh Simpson

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