Phenylketonuria

Experience at One Center in the First Year of Screening in California

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■ *One year's experience with phenylketonuria during the calendar year 1966, the first year for compulsory newborn screening in California, was reviewed. The over-all prevalence rate from reported cases in California during this period was one case per 19,500 persons tested. Fifty-seven persons suspected of having* PKU *were evaluated, and 25 of them were determined to be phenylketonuric. Eleven of the 25 were infants in whom the abnormality was detected through the newborn screening program or because it was detected in a sibling through a screening program. All the newborn phenylketonuric patients were developing normally at the time of last report (although the follow-up periods were short).*

In nine of the other children, PKU *was detected because they were retarded. Five retarded children who were diagnosed as phenylketonuric at another clinic were given dietary assistance.*

Five additional infants had elevated serum phenylalanines but did not have the classic biochemical findings of PKU *and are being evaluated further. Nine infants with positive screening tests exhibited biochemical and clinical findings consistent with transient tyrosinemia. Eighteen other children were evaluated and found to have no metabolic abnormality.*

The newborn screening program for PKU *is of decided benefit in early identification of a group of infants who have a high rate of potentially serious metabolic disease. Early identification permits treatment soon enough to prevent mental retardation. Newly identified patients should be evaluated in a medical setting capable of careful pediatric, biochemical and nutritional surveillance.*

ON 29 OCTOBER 1965 the California State Board of Health adopted regulations (Sec. 6500, Title 17) on testing for phenylketonuria (PKU) to conform with Assembly Bill 12 passed by the California Legislature in 1965. This regulation, which became effective 1 January 1966, requires physicians to order an approved test for PKU on all newborn infants and on infants of age 30 days or under when admitted to another hospital. The physician must also arrange for a repeat test within seven days of notification if the initial test is presumptively positive. The provisions of this section do not apply if the parent or legally appointed guardian objects to the test on the grounds that it conflicts with his religious beliefs or practices, or if it is determined by the patient's physician that there are medical contraindications to the procedure.

Tests approved for use by the State Health Department are the Bacterial Inhibition Assay[7] and the Fluorimetric Procedure,[14] which have both been found to be effective.[11] There are 202 approved public and private laboratories in California doing these studies (60 Fluorimetric, 113 Inhibition Assay and 29 both). California is unusual in that most other states require that the tests be performed in a centralized state laboratory.

In some areas of the country, routine blood testing has been performed since Guthrie[6] described a simplified method in 1961. Irwin[8] reported that a successful routine nursery screening program has been in operation at Sharp Memorial Community Hospital in San Diego since August of 1963. Mandatory testing laws in the United States first appeared in 1963 when Massachusetts passed such a law, and there are now 37 states with laws requiring testing.[17]

After one calendar year of testing newborns in California, it was thought fitting to review the results in light of the experience gained at the PKU Clinic, Childrens Hospital of Los Angeles. This is timely in the light of recent criticism regarding the value of routine testing.[2]

According to figures from the California State Board of Health,[4] 311,953 infants were tested in 1966 and 16 cases of PKU were discovered, for a prevalence rate of one case per 19,497 tested. Five additional infants with hyperphenylalaninemia were identified. If these are included, the prevalence rate would be one per 14,855. The reason for the variation in incidence in different series, such as reported in Massachusetts,[13] is unclear.

The PKU Clinic at Childrens Hospital of Los Angeles serves as one of the centers authorized by the Bureau of Crippled Children of the State Health Department for diagnosis and treatment for Southern California (See Appendix). Most children resided in Los Angeles County, but one-third were received from other Southern California counties, two from military installations located in Southern California, one from a bordering state and two from foreign countries (See Table 1). On four occasions individual parents without a family physician requested help and were assisted.

When a request for assistance with the care of a patient suspected of having phenylketonuria was received, all team members were alerted. If the serum level was significantly elevated, above 12 to 15 mg per 100 ml (normal 2 to 4 mg), arrangements were made for admission to the hospital for complete diagnostic evaluation. However, if the serum phenylalanine level was only slightly elevated (6 to 12 mg per 100 ml), or if satisfactory laboratory studies had not been performed, a public health nurse was requested to obtain serum for phenylalanine and tyrosine determinations, and urine for amino-acid chromatography. The need for admission to hospital and follow-up evaluations was based upon the results of these initial studies. The diagnosis of PKU was considered confirmed when the serum phenylalanine was persistently greater than 20 mg per 100 ml, the serum tyrosine

TABLE 1.—*Source of Referrals for* PKU *Testing at Childrens Hospital, Los Angeles, by County*

Geographic, by county:	
Los Angeles	33
Santa Barbara	4
San Bernardino	4
Riverside	3
Orange	2
Ventura	2
San Diego	2
Kern	1
San Luis Obispo	1
Other	
Military	2
Vandenberg Air Force Base	
Morro Bay	
Arizona	1
India	1
Venezuela	1
TOTAL	57

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remained within normal limits and urine amino-acid chromatography revealed the classic metabolites consistent with PKU. After confirmation of diagnosis, the low-phenylalanine diet was instituted. In confirmed cases, serum phenylalanine levels were obtained on parents and siblings. In special cases, loading procedures were also performed on family members. Hospital discharge occurred when the serum phenylalanine approached normal, and the family was counseled regarding the disease and dietary treatment.

In case of any question regarding specific diagnosis, periodic tolerance tests were performed by increasing dietary protein. To ascertain that serum levels returned to normal but not to subnormal values, regular serum phenylalanine levels were obtained at weekly intervals, or in a few cases as often as every other day, by either the fluorimetric or inhibition methods. If the serum tyrosine was significantly elevated and transient tyrosinemia suspected, Vitamin C was prescribed, and the patient followed closely as an outpatient.

During the year 1966 there were 20 new confirmed cases of PKU identified by the clinic (Table 2). Eight infants were identified by routine newborn screening. Screening siblings of the eight newborn cases resulted in the identification of two older children. Another infant was identified during the first week of life because PKU had already been diagnosed in an older sibling. The condition in this child most likely would have been picked up by routine screening even had the known family history of PKU not resulted in special studies of this high risk patient.

In nine other children, ages six months to six and one-half years, PKU was initially diagnosed because the child was mentally retarded. Five other retarded children in whom PKU had previously been diagnosed elsewhere, were seen by the clinic staff for the first time in 1966 for assistance in management. Five children were tentatively identified as hyperphenylalaninemic. (These infants may later be identified as having PKU, or some other type of metabolic abnormality may be demonstrated.) There were five proven and four suspected cases of transient tyrosinemia. All of these presented with slightly elevated serum phenylalanine (6 to 12 mg per 100 ml) and elevated serum tyrosine levels (greater than 3 mg per 100 ml). Serum phenylalanine and tyrosine levels returned to normal within a few days or weeks after Vitamin C supplements were added to their diets. Five retarded children were evaluated because they were suspected of having PKU but subsequent tests did not confirm this. Thirteen other infants with slightly elevated serum phenylalanine levels initially, were found to be normal.

TABLE 2.—*Sources of Referral, by Physician or Other*

Pediatricians	20
General Practitioners	18
Public Health Department	8
PKU Clinic (Screening)	6
Self Referrals	4
Obstetrician-Gynecologist	1
TOTAL	57

Discussion

It is beyond the scope of this paper to discuss all aspects of the detection and diagnosis of phenylketonuria. However, such material is the subject of a recent review by Cunningham.[5] We are presenting the experience gained during the evaluation of 57 children referred to the PKU Clinic during the first calendar year in which compulsory testing of newborns was in effect in California.

While the exact cause of mental deterioration is not yet fully understood, studies from both institutional and non-institutional sources have shown that untreated PKU children frequently exhibit mental retardation. In our experience, and that of others, if the maximum benefit is to be derived from the low-phenylalanine diet, diagnosis must be made and therapy begun early in life.[3,9,10,12]

Widespread screening has shown that not all newborns with hyperphenylalaninemia are necessarily phenylketonuric. For this reason it is necessary to make certain that the diagnosis is well established before treatment is begun. We have

TABLE 3.—*Data on Diagnosis in 57 Patients Referred for PKU Testing*

PKU (New)		20
Newborn Screening	8	
Sibling Screening After Newborn Detected	2	
Newborn Sibling of Known PKU	1	
Screened Because of Mental Retardation	9	
PKU (Known)		5
Referral for Assistance in Care		
Hyperphenylalaninemia		5
Transient Tyrosinemia		9
Proven	5	
Suspected	4	
Retarded Children (Not PKU)		5
Newborn suspected (Normal)		13
TOTAL		57

arbitrarily divided the patients evaluated during 1966 into six groups: (1) PKU (New), (2) PKU (Known), (3) hyperphenylalaninemia of undetermined cause, (4) transient tyrosinemia, (5) mentally retarded: not PKU, and (6) a group of normal newborns in whom no evident metabolic abnormality was detected. Other specific metabolic abnormalities have been reported to cause false positive reaction to PKU screening tests, but we did not encounter any such cases. The children whom we have classified as hyperphenylalaninemic may eventually be determined to have PKU or metabolic disorder of some other type.

Children with biochemical evidence of phenylketonuria, (significantly protracted elevated serum phenylalanine, a normal serum tyrosine and urine showing significant amounts of phenylalanine, phenylpyruvic acid and its metabolites to include orthohydroxyphenylacetic acid) should receive a low-phenylalanine diet as soon as the diagnosis is confirmed. Those with only slightly elevated serum phenylalanine levels, normal serum tyrosine and normal or slightly elevated urinary phenylalanine and its metabolites (hyperphenylalaninemia) should be on a modified diet containing limited amounts of protein, with periodic protein challenges and close observation. Transient tyrosinemia is considered to produce no consistent clinical syndrome,[1] and in general can be considered benign. Infants with this finding should be allowed to continue on a normal diet with supplementary ascorbic acid (Vitamin C) in the range of 100 mg per day until serum phenylalanine and tyrosine levels reach normal. Obviously those with no demonstrated metabolic defect should be allowed to continue a normal diet.

Diets deficient in protein or in specific essential amino acids should not be given unless a metabolic defect is present in which excess of either the substance itself or of its metabolites is detrimental to the functioning or development of the patient. Decreased growth,[16] severe anemia,[15] and skin rash have been described in patients who did not receive adequate dietary phenylalanine. Since phenylalanine is an essential amino acid to life, even death could occur with severe prolonged deprivation. It is imperative, therefore, that the diagnosis of PKU be confirmed, and that when the diet is instituted it be properly monitored. The commercially available low-phenylalanine formula, Lofenalac,* is effective in reducing serum levels of phenylalanine in phenylketonuric patients, but it should never be prescribed without supplemental phenylalanine, for even a phenylketonuric person requires exogenous phenylalanine.

Several patients in our series were started on Lofenalac before adequate diagnosis was made, and two of these, who later were determined to have PKU, had dangerously subnormal serum phenylalanine levels when initially evaluated. One patient was started on Lofenalac without additional protein when the physician misinterpreted the results of a normal screening test.

Because of the need for accurate diagnosis, the prescription of proper diet, monitoring of serum phenylalanine and counseling over a long term, it is recommended that these functions be performed by a multi-disciplinary team which includes a pediatrician, a nutritionist, a biochemist, a public health nurse and a psychologist. The routine medical care should be provided by the family physician. Accordingly, patients that we dealt with were cared for in conjunction with their family physician. However, the clinic personnel continued to follow all infants with confirmed PKU to study their nutritional needs and development.

*Produced by Mead, Johnson Incorporated, Evansville, Indiana.

REFERENCES

1. Avery, M. E., Clow, C. L., Menkes, J. H., Ramos, A., Schriver, C. R., Stern, L., and Wasserman, B. P.: Transient tyrosinemia of the newborn: Dietary and clinical aspects, Pediatrics, 39:378-384, Mar. 1967.

2. Bessman, S. P.: Legislation and advances in medical knowledge—Acceleration or inhibition? J. Pediat., 69: 334, Aug. 1966.

3. Bickel, H., and Gruter, W. P.: Prophylaxe und Behandlung der Phenylketonurie (Prophylaxis and Treatment of Phenylketonuria), Deutch Med. Wschr., 86:39-43, Jan. 1961.

4. California State Department of Public Health, Personal Communication, Mar. 1967.

5. Cunningham, G. C.: Phenylketonuria: Early detection, diagnosis and treatment, Calif. Med., 105:1, July 1966.

6. Guthrie, R.: Blood screening for phenylketonuria, JAMA, 178:863, Nov. 25, 1961.

7. Guthrie, R., and Susi, A.: A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants, Pediatrics, 32:338-343, Sept. 1963.

8. Irwin, H. R., Notrica, S., and Fleming, W.: Blood phenylalanine levels of newborn infants — A routine screening program for the hospital, Calif. Med., 101:331, Nov. 1964.

9. Kang, E. S., Kennedy, J. L., Jr., Gates, L., Burwash, I., and McKinnon, A.: Clinical observations in phenylketonuria, Pediatrics, 35:282, Aug. 1963.

10. Koch, R., Acosta, P., Fishler, K., Schaeffler, G., and Wohlers, A.: Clinical observations on phenylketonuria, Am. J. Dis. Child., 113:6, Jan. 1967.

11. Koch, R., Williamson, M. L., Donnell, G. N., Guthrie, R., Straus, R., Coffelt, R. W., and Fish, C. H.: A cooperative study of two methods for phenylalanine

determination: McCaman-Robins Fluorimetric and microbiological inhibition methods, J. Pediat., 68:905, June 1966.

12. Knox, W. E.: An evaluation of the treatment of phenylketonuria with diets low in phenylalanine, Pediatrics, 26:1, July 1960.

13. Massachusetts Department of Public Health: Screening program for phenylketonuria and other inborn errors of metabolism, New Eng. J. Med., 273:109, 8 July 1965.

14. McCaman, M. W., and Robins, E.: Fluorimetric method for the determination of phenylalanine in serum, J. of Lab. Clin. Med., 59:885, May 1962.

15. Royston, N. J. W., and Parry, T. E.: Megaloblastic anemia complicating dietary treatment of phenylketonuria in infancy, Arch. Dis. Child., 37:430, Aug. 1962.

16. Rouse, B. M.: Phenylalanine deficiency syndrome, J. Pediat., 69:246, Aug. 1966.

17. U.S. Department of Health, Education and Welfare, Welfare Administration, Children's Bureau—State laws pertaining to phenylketonuria as of Nov. 1966, 1967.

APPENDIX I

Medical centers approved by the Bureau to provide consultation and evaluation in phenylketonuria:

1. Peter Cohen, M.D., Neurological Diagnostic Center, U.C.-Moffitt Hospital, Third and Parnassus Streets, San Francisco, California 94122.

2. Richard Koch, M.D., Division of Child Development, Childrens Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles, California 90027.

3. Thomas Nelson, M.D., White Memorial Hospital, 1720 Brooklyn Avenue, Los Angeles, California 90033.

4. Edward Senz, M.D., Neurological Diagnostic Center, Children's Hospital Medical Center of Northern California, 51st and Dover Streets, Oakland, California 94609.

5. Richard Umansky, M.D., Child Development Center, Children's Hospital Medical Center of Northern California, 51st and Dover Streets, Oakland, California 94609.

6. Stanley Wright, M.D., University of California Medical Center, 405 Hilgard Avenue, Los Angeles, California 90024.

7. Bernard Rudis, M.D., Neurological Diagnostic Center, Valley Children's Hospital, 3151 North Millbrook Avenue, Fresno, California 93703.

8. Robert E. Greenberg, M.D., Stanford Medical Center, Palo Alto, California 94304.

9. Robert F. Chinnock, M.D., Loma Linda University Hospital, Loma Linda, California 92354.

CORRECTION

An error was made in a sentence in the article "Fractures of the Calcaneus" by Carl E. Horn, M.D., which appeared in the March issue of CALIFORNIA MEDICINE. The sentence which begins "Protruding bone," in the paragraph starting a little below mid-way of the right-hand column on page 213 is corrected as follows: "Protruding bone from the lateral border of the calcaneus was excised and subtalar arthrodesis performed. Films taken five months following operation showed clearly the residual shortening in length and height of the tuberosity with resultant poor structure of the hind-foot."