The New England Maternal PKU Project: Identification of At-Risk Women

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Abstract: Young women with phenylketonuria (PKU) are at risk for bearing children with mental retardation, microcephaly, heart defects, and low birthweight. These effects may be prevented if a low phenylalanine diet is maintained prior to and throughout pregnancy. This report describes the procedures of the New England Regional Maternal PKU Project for identifying and locating this population of at-risk women. Newborn screening records, routine umbilical cord blood screening, and PKU Clinic records provided most of the identifying information. We identified 235 women with hyperphenylalaninemia, ages 12 to 44 years. Of these, 183 had PKU or atypical PKU while 52 had non-PKU mild hyperphenylalaninemia. The 235 women represent 88 per cent of the expected number of women with hyperphenylalaninemia in New England. We identified more than the expected number of those with PKU but only 57 per cent of the expected number with mild hyperphenylalaninemia. Developing a national registry, as well as screening women who utilize birth control clinics or prenatal clinics, may be helpful. Implementing routine umbilical cord blood screening programs may be beneficial in efforts to identify women with hyperphenylalaninemia who have had a child and may want more children in the future. (*Am J Public Health* 1988; 78:789–792.)

Introduction

Newborn screening and early dietary treatment have eliminated phenylketonuria (PKU) as a major cause of mental retardation. Maternal PKU is threatening to take its place, however. It is now well documented that women with phenylketonuria are at high risk for bearing children with mental retardation, microcephaly, congenital heart defects, and low birthweight.[1] These abnormalities seem to result from the effects of the mother's elevated blood phenylalanine or related abnormal metabolites on the developing fetus. Ironically, it is the success of the newborn screening for PKU that has converted maternal PKU from a rare medical occurrence into a public health problem. Before newborn screening, most women with PKU were mentally retarded and few bore children. Now phenylketonuric women have normal intelligence, are entering their childbearing years, and can be expected to have children.

Dietary therapy that reduces the maternal blood phenylalanine level and eliminates or reduces phenylalanine metabolite accumulation during pregnancy may protect the fetus. The diet probably needs to begin prior to conception and be maintained throughout pregnancy for maximum fetal protection.[2–4] Thus, careful planning of pregnancies is critical to the success of this treatment. The need to provide information about the risks of untreated pregnancy and the potential benefits of dietary treatment is urgent. The first step in this process is to locate adolescent girls and young women with PKU or any degree of hyperphenylalaninemia. While a few have been seen regularly in PKU clinics, most discontinued the phenylalanine restricted diet during childhood[5] and have not been followed for many years. In addition, those with atypical PKU or non-PKU hyperphenylalaninemia also need to be located since some may also be at risk for having affected children.[6–8]

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The New England Regional Maternal PKU Project was developed in 1979 as a collaboration of PKU programs in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont. The project, centered at the Children's Hospital in Boston, has as its goals to:

- identify women with PKU or any other degree of hyperphenylalaninemia in the region;
- provide information to the women and their families about the risks of maternal PKU and the need for dietary treatment;
- initiate and monitor the phenylalanine restricted diet before and during pregnancies when indicated; and
- evaluate the offspring from treated pregnancies as well as from pregnancies that were untreated.

At the very beginning of the project, we realized that identifying and locating young women with hyperphenylalaninemia would be a formidable task. We also understood, however, that our efforts to prevent the adverse effects of maternal PKU would only succeed to the extent that the young women at risk for maternal PKU were located. This paper describes the methods we used to identify women with PKU and the results of these tracking efforts in New England. The results of treatment for maternal PKU pregnancies in New England have been described elsewhere.[9]

Methods

Estimation of Population at Risk for Maternal PKU

A diagnosis of PKU is given to all individuals who have a blood phenylalanine level greater than 720 μM (12 mg/dl) when on a normal diet. Those with levels 1200 μM (20 mg/dl) or greater are defined as having classic PKU and those with 720 μM to less than 1200 μM are classified as having atypical PKU. Non-PKU mild hyperphenylalaninemia is characterized by blood levels of 120 μM (2 mg/dl) to less than 720 μM and is not usually treated with the phenylalanine restricted diet.

We estimated that there are 267 girls and young women ages 12 through 44 years in New England who have PKU or mild hyperphenylalaninemia. This number represents the sum of estimates for each of the six New England states. We derived these estimates by extrapolating from the 1983 census the number of women ages 12 through 44 years, determining the expected numbers with PKU and mild hyperphenylalaninemia based on a frequency of 1:12,000 for

TABLE 1—Hyperphenylalaninemia in New England: Comparison of Expected vs Actual Number of Women Identified, Ages 12 to 44 Years

State	Expected Number	Number Identified	Type of PKU: Classic or Atypical, Number Expected	Classic or Atypical, Number Identified	Mild Hyperphenylalaninemia, Number Expected	Mild Hyperphenylalaninemia, Number Identified
Connecticut	71	56	47	46	24	10
Massachusetts	129	129	86	90	43	39
Maine	24	14	16	14	8	0
New Hampshire	22	21	14	19	8	2
Rhode Island	21	15	13	14	8	1
Total	267	235	176	183	91	52

PKU and 1:18,000 for mild hyperphenylalaninemia.* Based on these calculations, we anticipated that among the 267 girls and young women, 176 would have PKU and 91 would have non-PKU mild hyperphenylalaninemia (Table 1). The 0.3 per cent frequency of tetrahydrobiopterin-dependent hyperphenylalaninemia (BH_4deficiency) in New England indicates that one of these 267 individuals might have a pterin disorder rather than phenylalanine hydroxylase deficiency.[10]

Resources Used for Identification

The following sources were used in New England to identify and locate women with hyperphenylalaninemia:

PKU Clinics—On several occasions, the core team of the project, including the physician, psychologist, nutritionist, nurse, and social worker visited the six PKU programs in the region to introduce the project, discuss methods for identifying clients, and coordinate tracking efforts.

Newborn Screening Records—Records from newborn screening retained by the state newborn screening programs were consulted. These records contained information regarding the initial and follow-up blood phenylalanine levels, names of physicians, addresses, phone numbers and, in some cases, information on other family members discovered to have PKU.

Cord Blood Screening—Between 1971 and 1981 screening of filter paper specimens of umbilical cord blood was routinely conducted in Massachusetts to identify women with maternal hyperphenylalaninemia.[6] Information from this screening was available at the newborn screening program in Massachusetts.

State Institutions—Ten state institutions for individuals with mental retardation were contacted. A letter was sent to the superintendents or directors of these institutions informing them of maternal PKU and requesting that either they or their medical directors contact the families and provide us with information regarding the number of women known to them with hyperphenylalaninemia.

Departments of Mental Health—Forty mental health coordinators were contacted to identify women with PKU who were receiving or had received mental health or mental retardation services. This was particularly directed at women with PKU who had formerly lived in institutions but were now living in community residences.

Departments of Public Health—Connecticut maintains a comprehensive list of individuals identified by screening programs. Vermont (which does not have a PKU clinic) follows children and adults with metabolic disorders through state nutritionists. Examination of Crippled Children's Services' records served to double check the newborn screening records. Sometimes the provision of the special formula to a family was the only record confirming PKU.

Maternal and Child Health Network—Public health nutritionists and nurses in the region were contacted because of their personal knowledge of clients with PKU.

Publicity—Articles appeared in magazines and newspapers. In addition, talks about maternal PKU were given at local, regional, and national professional meetings.

Identifying the women with hyperphenylalaninemia was only the first step. Locating them and meeting with them proved equally difficult and time-consuming. When addresses were missing or outdated, physicians whose names were on newborn screening records were contacted. Sometimes, the pediatricians were able to provide forwarding addresses for families that had moved. Phone directories and telephone information operators proved helpful in some cases. Old medical records were reviewed for clues regarding the most recent address. In some cases, a forwarding address to a relative was found. In cases involving military families, the Armed Forces Directory was used.

Ethical Considerations

A major challenge in maternal PKU is to maintain confidentiality while identifying and locating at-risk women to provide them with information. As part of our study protocol approved by the Committee on Clinical Investigation of the Children's Hospital, procedural safeguards were incorporated. Names were omitted on the information forms collected from the agencies and physicians unless explicit permission from a woman to include her name had been obtained. Equally important to us was the assurance that information about maternal PKU reached the women and their families once they had been "counted" in our survey. Since we often did not have access to names and addresses, we sent the information that included brochures, referral phone numbers, and fact sheets to each agency and each PKU program or contact person for transmittal to the women or their families. In this way, even families with institutionalized offspring would be provided information in the event that other relatives were at risk. Invitations to conferences on Maternal PKU were also extended in this manner to women with hyperphenylalaninemia. Many of the women or their families returned enclosed postcards indicating an interest in learning more about PKU, and over 50 women attended conferences. Every woman whom we were able to locate

*Levy HL, Simmons JR: (Unpublished data).

received information and was encouraged to contact a PKU clinic or program. In most cases, the clinics also provided outreach and made appointments for the women.

Results

During the five years of the New England Regional Maternal PKU Project, 235 women ages 12 through 44 years with hyperphenylalaninemia were identified (Table 1). Of these, 183 have classic or atypical PKU and 52 have non-PKU mild hyperphenylalaninemia. No one had the features of a pterin defect. An additional six females with PKU who would have been in this age group had died: three during infancy, two from car accidents, and one from a brain tumor. In 1986, the mean age of the living women was 23.3 ± 7.5 years. The majority had normal intelligence. However, 63 women (27 per cent of the total study population and 34 per cent of those with PKU) were known to have mental retardation as indicated by their residence in institutions for the mentally retarded (42 women) or by reports of low IQ scores (21 women). All but five of these women were born prior to newborn screening and did not receive early dietary therapy.

Forty-two women were not located, either because they were known to have moved from the New England area or because current addresses and phone numbers were missing. Among these women, 24 have PKU, 16 have mild hyperphenylalaninemia, and for two there are no records regarding blood phenalalanine levels.

Most of the women had been identified through newborn screening records but current information on them could usually be obtained only through records at the PKU clinics or programs. The clinics also maintained lists of individuals with PKU who were born prior to routine newborn screening and who came to attention because of developmental delay or family screening following the birth of a younger sibling with PKU identified through newborn screening. The state institutions for mental retardation provided a significant number of additional names. State departments of mental health and of public health and the maternal and child health network were beneficial primarily in locating individuals whose names were on our lists but whose whereabouts were unknown. Publicity elicited responses from many concerned women and resulted in the location of two women who had been identified on the PKU clinic lists but whose addresses were unknown.

Table 2 summarizes the "yield" from each method of ascertainment in Massachusetts (where this information was most readily available). Many individuals were named on more than one list. However, their identification is attributed to only one source in Table 2. We began with the newborn screening list since this was most up-to-date. Clinic lists were reviewed next. Other sources were contacted thereafter. The largest number of identifications (51 per cent) came from newborn screening records. The second most important source was routine umbilical cord blood screening[6] which accounted for 17 per cent of those identified. We included 20 women in whom hyperphenylalaninemia was discovered in this manner. Almost all of these women were functioning adequately in the community.[11] In addition, two female offspring of a hyperphenylalaninemia mother identified by cord blood testing were found to have mild hyperphenylalaninemia.[6,12] Nineteen phenylketonuric women of childbearing age living in institutions for mental retardation in Massachusetts were born prior to newborn screening. PKU clinics contributed 18 names that could not be found elsewhere. These records were indispensable for locating the women. Current addresses and phone numbers, names of physicians, records of health status, family situations, and results of psychological testing could only be obtained from this rich source of information.

TABLE 2—Hyperphenylalaninemia in Massachusetts: Ascertainment of Women Ages 12 to 44 Years

Source	Number Identified	Per Cent of Total Identified
Newborn Screening Program	66	51
Family screening after sibling identified by newborn screening	4	3
PKU Clinics	18	14
Institutions	19	15
Umbilical Cord Blood Screening	22	17
Total	129	100

Discussion

From this experience we learned that locating adolescent females and young women with PKU or other degrees of hyperphenylalaninemia for the purpose of providing them with information about maternal PKU is an arduous task. It requires almost fulltime commitment by one individual who must contact many other professionals in different programs, who must travel to many locations scattered over a state or a region in order to review records, and who must spend a great deal of time on the telephone obtaining information. In addition, many others in the New England Regional Maternal PKU Project devoted very substantial portions of time to this endeavor. Only by this combined effort that continued through the five years of the project could we locate what we believe to be essentially all of the women of childbearing age in New England who have PKU and many of those who have non-PKU hyperphenylalaninemia.

As anticipated, the majority of women were identified through newborn screening records. However, these records were or relatively little use in locating the women. Coordination between the newborn screening program and the PKU clinics was essential. Often the clinics had information "buried" in old records that would not have been discovered without a reminder from a newborn screening list.

A surprising result of this study is that more women with PKU were identified than we expected from the known frequency of this disorder in New England. It is disturbing that only 57 per cent of the expected number of women with mild hyperphenylalaninemia were identified. Although their degree of hyperphenylalaninemia may pose little or no risk to the fetus,[6] this is not certain and they also need to be located, counseled, and followed during pregnancy. There are several possible reasons for the limited identification of women with mild hyperphenylalaninemia in our follow-up efforts. First, women with mild hyperphenylalaninemia who were born before newborn screening are unlikely to be known as having a metabolic defect since they would not be mentally retarded.[11] Second, women who were identified with mild hyperphenylalaninemia by newborn screening would not have received dietary treatment; consequently, most would not have had contact with a PKU clinic after infancy and many might never have been seen at a clinic. In addition, they would not be known to a Crippled Children's Service or other maternal and child health agency because they never required

the dietary formula. Third, some girls with mild hyperphenylalaninemia might have been missed by newborn screening since it is known that a neonate with non-PKU hyperphenylalaninemia might not have an elevated blood phenylalanine level when the newborn blood specimen is collected.[13]

Six individuals with PKU had died, suggesting a 2.5 per cent mortality rate in our population. This is comparable to that in the general population[14] and confirms earlier reports that PKU does not substantially reduce longevity.[15] It is unlikely that we failed to identify a significant number of the older women since the mean age of the women was in the early twenties, suggesting that the distribution of women is fairly even throughout the age span represented.

Very few of the women born after newborn screening was instituted were reported to have mental retardation and none resided in institutions. This highlights the need for adequate outreach and education about maternal PKU. Given their normal intelligence, these women are likely to marry and have children.

Little documentation existed regarding those known to have moved from New England. Given the mobility of families in the United States, we believe that this is a major problem. Those who moved represented 9 per cent of the study population; an additional 9 per cent could not be located, suggesting that they also may have moved. This 18 per cent of our study population represents a significant failure in our efforts. We believe that a register for PKU and any degree of hyperphenylalaninemia updated annually and with proper design to maintain confidentiality, as is in operation in Canada,[16] should be developed for the United States.[17] A register of this type was developed on a very limited scale,[18] but is presently inactive.

In some parts of the country, screening the female population who utilize birth control clinics or who come in for prenatal care may be beneficial in identifying women born prior to the initiation of newborn screening and re-identifying those lost to follow-up. This was quite productive in Oregon.[19] Although most women who were born before newborn screening programs were initiated are mentally retarded and are less likely to bear children, some will become pregnant. In addition, a small number of women with untreated PKU are of normal intelligence but their children will not escape the effects of maternal PKU.[6] Moreover, women born outside of the United States may not have been screened.

The possible value of routine umbilical cord blood screening should be considered. This was a particularly productive method of ascertainment in Massachusetts. Although newborn screening with careful follow-up should eventually eliminate the need for this type of detection, it will continue to be a potentially valuable means of identification for at least 15 more years. Few women identified by newborn screening are older than 25 years of age and many more women are now having children in their late thirties and early forties. Not only is umbilical cord blood screening a relatively expedient method, but our experiences[6] suggest that it is likely to identify women with the milder phenylalanine elevations—precisely the women who are least likely to be identified through other methods. An obvious major disadvantage of umbilical cord blood screening, however, is that at least one child will already have been born before the woman is identified. The optimal system for identifying women with hyperphenylalaninemia has yet to be developed, but some screening may be necessary.

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