ABSTRACT. Objective. The development of guidelines for phenylketonuria (PKU) management in the United Kingdom has resulted in much discussion in the community of parents and PKU clinics and parents have asked why the United States does not have such guidelines. The objective of this report is to discuss PKU management in the United States, the British guidelines on PKU management, and the feasibility, suitability, and mechanism of developing PKU management guidelines in the United States.

Methods. Members of the American Academy of Pediatrics (AAP) Committee on Genetics (COG) reviewed the literature and conducted surveys of parents of children with PKU, young adults with PKU, and directors of PKU clinics in the United States. A meeting was held at the National Institute of Child Health and Human Development to review the AAP/COG efforts at reviewing the status of PKU management and guideline development in the United States.

Results. The British guidelines are more stringent than the PKU management practices in many parts of the United States. Evidence exists that stricter management improves developmental outcome. The parents who responded to the surveys indicated willingness to comply with more stringent dietary management if that would improve outcome. They also identified problems that make such management difficult. The clinic directors supported the timeliness of the review. Some had begun a trend toward more stringent control of blood phenylalanine concentrations, at least in the first 4 years of life.

Conclusion. The AAP Committee on Genetics will complete its subject review of the management of PKU. Guidelines for care of PKU in the United States probably would look quite similar to the existing guidelines in other countries. The parents surveyed supported more stringent PKU management, but information from a broader distribution of parents would provide a more representative view. The status of the US health care system creates problems for improved PKU management in the United States that do not exist in the countries already following stricter guidelines. Pediatrics 1999;104(6). URL: http://www.pediatrics.org/cgi/content/full/104/6/e68; phenylketonuria, treatment, guidelines, phenylalanine, parents.

ABBREVIATIONS. PKU, phenylketonuria; phe, phenylalanine; IQ, intelligence quotient; AAP, American Academy of Pediatrics; COG, Committee on Genetics.

Phenylketonuria (PKU), an autosomal recessive disorder, occurs in one in 15,000 births and is most common among persons of Western European background. The disorder is associated with deficient activity of phenylalanine (phe) hydroxylase, which results in elevated concentrations of phe and phe metabolites (phenylketones) in the body fluids of affected individuals. Untreated, affected individuals develop severe to profound mental disabilities, behavioral difficulties, seizures, rashes, pigment dilution, and an unusual body odor.

The condition was originally described in 1934 by Folling. Over the next two decades, PKU was defined as a disorder in phe metabolism and deficiency in phe hydroxylase activity was demonstrated. In 1953, Bicket and colleagues reported the use of a phe-restricted diet for treatment and found that all features of untreated PKU were reversible except mental retardation. These observations established the need for early diagnosis and treatment. The development of the Bacterial Inhibition Assay by Guthrie in the 1960s provided the method for large scale newborn screening. In the 1980s, Woo and colleagues mapped and isolated the gene for phe hydroxylase. The identification of the mutations that cause PKU allowed the development of carrier detection and prenatal diagnosis by DNA studies for at-risk families.

Since the 1960s, detection through newborn screening and the resultant early dietary treatment of PKU have allowed vast improvements in the psychological and behavioral outcomes of PKU. With early institution of dietary therapy, individuals with PKU often have intellectual abilities that fall within 5 intelligence quotient (IQ) points of their unaffected siblings at school entrance. However, as a group, even well-treated patients have a mean IQ that is slightly lower than population-matched normal individuals. Behavioral and psychological problems remain in some children and adults. Many treated individuals with PKU have significant learning disabilities, especially in mathematics, language, visual perception, visual-motor skills, abstract thinking, and problem solving. The outcome for individual patients may be related to the control of their disease during the early years of life, especially before 4 years of age. Performance on testing also seems to be related inversely to the phe level at the time of testing.

Dietary control of PKU requires the use of special dietary products and the restricted intake of natural foods, especially those that are high in protein. Considerable time and effort must be made by the pa-
tient and family to achieve dietary control and acceptable blood phe levels. Many reports have shown that optimum outcome occurs when dietary therapy is started early and continued indefinitely. As with other chronic illnesses, decreased compliance and poor dietary control increase with age, especially after 6 years of age. Older individuals who have discontinued dietary therapy are at risk for developing loss of intelligence, magnetic resonance imaging findings consistent with white matter dysfunc-
tion, and occasionally acute demyelinating neuropathies. No variables currently predict which persons with PKU can discontinue therapy safely. Without strict control during pregnancy, infants born to women with PKU are at risk for the birth defects and psychomotor disabilities noted in the Maternal PKU syndrome.

Members of the American Academy of Pediatrics (AAP) Committee on Genetics (COG) undertook a subject review, reviewing the status of PKU management and guideline development in the United States. The review included a literature review, a survey of parents of children with PKU and of young adults with PKU, and a survey of directors of PKU clinics in the United States. The purpose of this report is to present the status of that review.

METHODS

Review of Current Guidelines for PKU Management

The Medical Research Council Working Party on PKU of the United Kingdom has published guidelines for the dietary management of phenylketonuria. These guidelines are part of an attempt to improve the outcome for individuals with PKU detected by newborn screening. These guidelines and their supporting literature were reviewed.

Survey of Parents

Sustained efforts were sent to parents and young adults with PKU. The surveys were distributed at PKU clinics and through the nonprofit organization, National PKU News. A total of 108 surveys were distributed to the PKU clinics, and some clinics made an unknown number of additional copies to distribute. National PKU News distributed 1,500 surveys. The information sought included demographic data, current diet practice, practices in serum phe monitoring, cost, and satisfaction with care. Data from the surveys were collated and analyzed.

Survey of PKU Clinic Directors

Sustained efforts were sent to all directors of PKU clinics identified in the directory of Treatment Programs for Inherited Metabolic Disease. Data from the surveys were collated and analyzed.

RESULTS

Review of British Guidelines for the Dietary Management of PKU

The Medical Research Council Working Party on PKU from the United Kingdom published guidelines for the dietary management of PKU in 1993. The recommendations were based on outcome data from >800 patients in the PKU Register of the United Kingdom. Smith et al provide compelling evidence for the importance of keeping the blood phe values between 380 μM (6.3 mg/dL) and 650 μM (10.7 mg/dL) in early childhood. Studying PKU individuals who were detected by newborn screening, they reported a gradual decrease in IQ, measured by standardized testing (Stanford Binet) that correlated with increasing increments of blood phe during the first 4 years of life. Increasing average blood phe correlated with increasingly lower IQ outcome, compared with normal population means. Average blood phe levels of 650 μM (10.7 mg/dL) resulted in a decrement of ~11 IQ points. The recommendations of the Working Party are summarized as follows.

- For infants with PKU, the diagnosis should be established and dietary treatment initiated by 20 days of age.
- Infants with blood phe levels >600 μM (9.9 mg/dL) and those with levels between 400 μM (6.6 mg/dL) and 600 μM (9.9 mg/dL) persisting for more than a few days should be started on dietary therapy.
- Infants with blood phe levels >900 μM (14.9 mg/dL) should have all natural sources of phe eliminated for a few days, with daily monitoring of blood phe levels, to allow a rapid decrease of blood phe into the control range.
- Blood phe levels should be maintained in the 120 μM to 360 μM range (2.0–6.0 mg/dL) for all infants and young children. An upper limit of 480 μM (7.9 mg/dL) may be allowed in school-aged children and 700 μM (11.6 mg/dL) in older children. Patients and families should be cautioned, however, that interference with performance and in decision making might be noted at the higher levels. Dietary treatment and control of blood phe levels should continue into adult life. However, maintaining this level of control is difficult in adolescents and young adults with PKU. Patients in these age groups will have to make choices concerning their phe intakes.
- Blood phe levels should be monitored at least weekly during infancy through 4 years of age, every 2 weeks until 10 years of age, and monthly after that. Samples for blood phe levels should be taken in early morning at the time of natural peak levels.
- Blood phe levels should be determined by accurate micromethods, such as those employing fluorometry or high performance liquid chromatography. Ion-exchange chromatography is also acceptable but expensive.
- Dietary phe intake of natural foods should be adjusted based on blood phe levels and on requirements for the individual patient. Long-term, serial monitoring of individual patient intakes should be kept and referred to in adjusting the diet.
- Special dietary formulas or protein substitutes, reduced or devoid of phe, should supply ≥3 g/Kg body weight/day protein intake to children <2 years of age, 2 g/Kg/day protein intake to children >2 years of age, and 100–120 mg/Kg/day of tyrosine. Special dietary formulas or protein substitutes should be taken as evenly as possible throughout the day.
- Patient assessments, to include an evaluation of growth, nutrient intake, and general health needs should be done every 2 to 3 months during in-
fancy, every 3 to 4 months to school age, and every 6 months thereafter.

- A protocol should be established for the management of PKU during intercurrent illnesses, such as the sick day management for patients with other inborn errors and diabetes mellitus.
- In patients with mild PKU (hyperphenylalaninemia), special dietary supplements should be stopped only if their phe blood levels remain <400 μM (6.6 mg/dL) while on an adequate natural protein intake. Lowered natural protein diets and protein-loading tests are to be avoided.
- All PKU patients, including adults, should be followed by specialists in PKU management. Patients and families should receive counseling concerning dietary management, prognosis, and genetics by specialists familiar with PKU. School-aged children should be encouraged to become responsible for dietary management and obtaining samples (finger stick) for blood phe measurement.
- Women with PKU should be counseled regarding the risks of Maternal PKU syndrome and return to strict control before conception. Blood phe levels should be monitored twice a week and range between 60–250 μM (1.0 mg/dL-4.1 mg/dL) in the period before conception and during pregnancy for optimum outcome. Women with PKU who conceive with blood phe concentrations more than 700 μM (11.6 mg/dL) should be offered detailed fetal ultrasound and a choice of pregnancy termination.

The blood phe levels recommended for control of PKU at all ages in the above guidelines are lower than those previously recommended by this group and are more restrictive than current practice in many clinics in the United States. The working party apparently believed that the data supported the recommendations, and they wished to err on the side of conservatism. To achieve lower blood phe levels will require additional monitoring of blood phe levels, increased compliance and psychosocial support of patients and their families and increased use of special dietary products and medical foods. All these measures will increase the medical cost required to treat PKU. In addition, there is some concern that the optimum blood phe levels recommended by the Working Party may be too restrictive and run the risk for phe malnutrition. Compliance with the recommendations also may not be achievable in some families, or by some patients because of biological, social, and psychological factors. It should be noted that there is not unanimity in the practice of diet adherence in adults. The French, for example, take a more relaxed approach to dietary control in adulthood.35,36

Survey of Parents

Demographics

A total of 1064 parents and young adults with PKU responded to the survey distributed by National PKU News and participating PKU Clinics. The survey covered families in all 50 states. Parents having 1 child with PKU or 2 children with PKU represented 87% and 13%, respectively, of families surveyed. Of the children with PKU, >92% were on diet at the time of survey. The socioeconomic level of survey respondents was moderately high, with 66% completing some college study and 65% of families earning >$30 000 annually.

Most patients established a stable relationship with their clinic; in fact, 68% attended the same clinic for 4 years or longer. PKU was classified as classical in 75% of cases and as hyperphenylalaninemia in 13% of cases. The largest group, 53% of the patients, started the diet between 8 and 14 days after birth, whereas 10% were not started on treatment until after 30 days. At survey time, ~5% of the respondents had stopped the PKU diet.

Current Diet Practice

Most patients answering the questionnaire maintained the PKU diet. However, discontinuing the diet was most likely to occur between 6 and 10 years of age and 11 and 15 years of age. Of the families, >90% understood their clinic to recommend the strict diet be continued for life.

Serum phe Monitoring

Fewer than half of the respondents knew the phe concentration advocated by their clinic. For children <1 year of age, frequently reported ranges were <360 μM (6 mg/dL), whereas for children >1 year of age, a value of <600 μM (10 mg/dL) commonly was recommended. An average blood phe <600 μM (10 mg/dL) was attained for 76% of children monitored in the last year, according to parental or self-reporting. The frequency of monitoring ranged anywhere from every 3 months to weekly. Nevertheless, most patients reported being monitored once a month or on alternate months. Lag time for patients to receive results was usually within 7 days (1–3 days at best, but >14 days at worst).

Costs

Costs associated with PKU treatment are met by medical insurance, self-payment, state health departments, WIC programs (US federally funded financial support for nutrition for financially eligible women, infants, and children), and other means. The low response by families to this question suggests that they are uncertain about the cost of monitoring and how much they pay out-of-pocket for blood tests. Insurance covers the expense of blood tests for 49% of patients. PKU formula usually is paid for by insurance or state programs. However, low protein food is a self-pay expense for 82% of families and creates a financial burden for some families.

Satisfaction

If the American Academy of Pediatrics recommends revision in PKU treatment, the majority of families responding to this survey would be willing to change the practices that they currently follow. A change in diet would be considered by 92% of the families responding and more frequent blood tests would be considered by 87% of families. Reinstitution of diet would be considered by 96% of those...
responding, but that figure represents only ~20% of those off diet who responded.

Survey of PKU Clinic Directors

A total of 87 of 111 clinic directors responded to the survey. They are following 4669 patients, approximately equally divided between patients >12 years of age, and <12 years of age. Of the patients, 93% <12 years of age are still on the phe-restricted diet, whereas only 54% of those >13 years of age remain on dietary restriction.

Treatment Practice

The phe level at which treatment is begun was ≤10 mg/dL for 82% of the clinics. Most clinics recommend diet for life: 79% for males and 85% for females. This practice has been in place for >7 years for 54 of the 87 clinics. The most commonly advocated phe concentration was 2 to 6 mg/dL for patients ≤12 years of age, and 2 to 10 mg/dL for patients >12 years of age. Serum phe concentrations are monitored more frequently at the younger age groups. The mean frequency for monitoring those patients <1 year of age was 3.6 times per month, with a range of 1 to 8 times. By 18 years of age, the mean was 1.02 times per month, with a range of 0 to 4. Nearly half of the laboratories (41/87) continue to use the McCaman-Robins fluorometric method for measuring blood phe concentrations. The Guthrie method and quantitative column chromatography were each used by 19 of 87 clinics. Lag time to receive results ranged from 1 to 10 days, with most clinics obtaining results within 1 to 3 days from being obtained. Most clinics do not use a phe challenge. A total of 60 clinics (69%) never use the challenge test; 21 clinics (24%) use a challenge if there is a question of the differentiation of variant from classical PKU; and only 6 clinics (7%) used a phe challenge to diagnose all children (Table 1).

Cost

Costs were borne by a variety of mechanisms, including medical insurance, self-payment, State Health Departments, Federal women’s and children’s services, and other undefined means. Trouble obtaining formula began in adulthood, with most programs reporting little trouble obtaining formula for infants. Cost per blood test ranged from $10 to $20 to >$80. In half of the centers, the cost was between $10 and $50; for 22 centers the testing was free.

Guidelines

No clinic thought that the British guidelines were too lenient; 21 clinics believed that the British guidelines were too strict; and 46 responded that the British guidelines were as strict as needed (Table 2). Most clinics (76/87) supported the AAP/COG effort to review the subject, and most were willing to make changes based on AAP/COG recommendations.

Concerns

Several major concerns were identified by the clinic directors. These include compliance, cost, issues related to adolescents and young adults, reinstitution of diet, and developmental monitoring.

Compliance

Problems surrounding compliance were a major area of concern to many clinic directors. The issues mentioned included: cost, palatability of formulas, availability and cost of low protein foods, family skills and dynamics, family beliefs that diet can be discontinued, teenagers not coming to clinic and not complying with diet, isolation in rural communities, reinstitution of diet, need for additional personnel, especially nutrition personnel, lack of cooperation from schools, need for support personnel, getting patients to keep diet records, care of illegal aliens, problems treating patients who transfer from a less strict program, and geographical distance.

Cost

Current funding and reimbursement for PKU clinics are threatened, and stricter guidelines will increase cost. The high cost of low protein foods and lack of insurance programs paying for low protein foods or for formula in some states were all issues. The cost of testing is a problem for some, and stricter guidelines will require rapid, high quality quantitative measurement of phe and tyrosine. Not all states receive revenue from screening programs for use in treatment, many managed care organizations do not accept the need for specialist management of PKU, and funding for staff, especially nutritionists, is in jeopardy.

Adolescents and Young Adults

Compliance, reimbursement, issues of independence, and prepregnancy management were the major issues identified.

TABLE 1. Treatment Practices Reported by Clinic Directors

<table>
<thead>
<tr>
<th>Treatment Practice</th>
<th>Number of Clinics (n = 87)</th>
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<tbody>
<tr>
<td>Blood phenylalanine threshold for treatment</td>
<td></td>
</tr>
<tr>
<td>≤5 mg/dL</td>
<td>15</td>
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<tr>
<td>&gt;10 mg/dL</td>
<td>50</td>
</tr>
<tr>
<td>&gt;20 mg/dL</td>
<td>5</td>
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<tr>
<td>Diet for life</td>
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<tr>
<td>Males</td>
<td>69</td>
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<tr>
<td>Females</td>
<td>74</td>
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<tr>
<td>Phenylalanine challenge</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>60</td>
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<tr>
<td>If question of diagnosis</td>
<td>21</td>
</tr>
<tr>
<td>Always</td>
<td>6</td>
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</table>

TABLE 2. Opinion of British Guidelines

<table>
<thead>
<tr>
<th>Clinic Directors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Clinics (n = 87)</td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Opinion</td>
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<tr>
<td>Too strict</td>
</tr>
<tr>
<td>As strict as needed</td>
</tr>
<tr>
<td>Not strict enough</td>
</tr>
<tr>
<td>Not familiar with guidelines</td>
</tr>
<tr>
<td>No answer</td>
</tr>
</tbody>
</table>
Reinstitution of Diet

Reinstitution of diet was believed to be very difficult or nearly impossible in many clinics. It requires funding, staff, support, and improved understanding of the psychology of compliance.

Serum phe Monitoring

Many issues relate to serum phe monitoring. Cost is important, especially if more frequent testing is required. However, quality cannot be sacrificed. Low cost accurate quantitative determinations of phe and tyrosine with rapid turn around time need to be performed by laboratories selected by the clinical directors. Improved methods, which might include methods for quantitative tests on blood spots and methodology analogous to diabetes monitoring, are needed.

Developmental Monitoring

This kind of monitoring is needed but not well funded.

Guidelines

The answers from clinic directors surveyed suggested that some clinics have already revised their management and adhere to stricter guidelines. They believe that the data support the recommendations that such guidelines would make. Some question the reality of ever achieving compliance in adults and older teens. Some would like guidelines not to be as strict as the British guidelines and want to keep guidelines realistic and treatment tailored to the individual. They recognize the need for support groups. Some clinic directors questioned the need for stricter guidelines, because they do not see serious pathology in patients on less restrictive dietary management. They await additional data supporting the use of more restrictive management.

DISCUSSION

The literature on the outcome of PKU treatment supports the conclusion that outcome in PKU is related to the concentration of phe in the blood of affected individuals, especially in the first 6 years of life. Although there is not a consensus in the literature, the trend is toward supporting a concentration of phe in the blood that is not below the bottom of the normal range and does not exceed 6 mg/dL (360 μM). The published British guidelines recommend stricter compliance to the phe-restricted diet than many United States clinics have used.

The following issues have been identified by the parents of children with PKU and directors of PKU clinics in the United States.

- Compliance
- Cost
- Needs of teenagers and young adults
- Reinstitution of diet after discontinuation
- Serum phe monitoring
- Developmental monitoring
- Personnel

New recommendations should:

- Recognize the need for the data to support the recommendations
- Recognize the need to treat each patient as an individual
- Be realistic and achievable
- Address the requirements for implementation
- Acknowledge the need for support groups

Some US clinics are already following stricter guidelines. Compliance with stricter guidelines raises many serious issues. The views of PKU clinic directors, parents, and patients with PKU must play an important role in the development of guidelines for PKU management. Parents, young adults with PKU, and clinic directors were primarily in agreement with potential AAP recommendations for stricter dietary control and acceptance of a requirement for additional blood tests. Clinic directors were less in favor of possible reinstitution of diet for those no longer being restricted (Table 3). An National Institutes of Health Consensus Development Conference might provide the mechanism for broad discussion among experts in PKU management and others concerned with guideline development.

ACKNOWLEDGMENTS

We are grateful for the help and participation from the American Academy of Pediatrics, Committee on Genetics, the parents and young adults with PKU, PKU clinic directors who responded to the surveys, and National PKU News, a nonprofit organization designed to serve parents, professionals, and others involved in treating PKU, for assistance in developing and mailing the survey and data collection, and Merle Conway of Seattle, WA, and Sean and Dorothy Corry of Mill Creek, WA for data entry. We appreciate the encouragement from Dr Felix de la Cruz, NICHD.

REFERENCES

5. Guthrie R, Susi A. A simple phenylalanine method for detecting phe

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TABLE 3. Response to Possible AAP Recommendations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parents or Young Adults (Percentage of Those Responding)</th>
<th>Clinic Directors (Percentage of Responses) (n = 87)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes No Maybe Responses</td>
<td>Yes No Maybe No Response</td>
</tr>
<tr>
<td>Stricter control</td>
<td>64.6 7.9 27.5 983</td>
<td>64.4 9.2 26.4 0.0</td>
</tr>
<tr>
<td>More blood tests</td>
<td>61.2 12.3 25.5 984</td>
<td>52.9 8.0 37.9 1.1</td>
</tr>
<tr>
<td>Reinstitute diet</td>
<td>71.3 3.2 25.5 282</td>
<td>47.1 8.0 43.7 1.1</td>
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Margretta Reed Seashore, Rebecca Wappner, Sechin Cho, Felix de la Cruz, Rebecca Wappner, Sechin Cho, Richard A. Kronmal, Virginia Schuett and Margretta Reed Seashore

_Pediatrics_ 1999;104;e68
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