SPECIAL ARTICLE

Development of Guidelines for Treatment of Children With Phenylketonuria: Report of a Meeting at the National Institute of Child Health and Human Development Held August 15, 1995, National Institutes of Health, Bethesda, Maryland

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ABSTRACT. *Objective.* **To convene a small group of experts in diagnosis and management of PKU to discuss the following issues: the Subject Review of PKU management being performed by the American Academy of Pediatrics (AAP) Committee on Genetics (COG), the published British guidelines on PKU management, and the feasibility, suitability, and mechanism of developing PKU management guidelines for the United States.**

Methods. **A 1-day meeting was held at the National Institutes of Health under the auspices of National Institute of Child Health and Human Development, convening experts in PKU diagnosis and management and members of the AAP/COG.**

Results. **The group reviewed the published reports of outcomes of treatment of PKU and the British guidelines that were developed based on those data. It also reviewed the results of surveys of directors of clinics that manage PKU, parents of children with PKU, and young adults with PKU.**

Conclusion. **The group supported the efforts of the AAP/COG to perform this review of PKU management. The group concluded that significant issues need to be resolved to provide sufficient information to establish US guidelines for PKU management. The establishment of such guidelines is an important next step in PKU management in the United States.** *Pediatrics* **1999;104(6). URL: http://www.pediatrics.org/cgi/content/full/104/6/e67; *phenylketonuria, treatment, guidelines, American Academy of Pediatrics.***

ABBREVIATIONS. PKU, phenylketonuria; AAP, American Academy of Pediatrics; COG, Committee on Genetics.

Phenylketonuria (PKU) no longer results in devastating mental retardation. Treatment with a phenylalanine-restricted diet successfully prevents the brain damage that was nearly universal in this condition. Newborn-screening programs in the United States and other parts of the world have been identifying affected children for more than three decades, thus permitting the early diagnosis that makes this successful therapy possible. Nevertheless, the outcome is not always optimal, and PKU treatment programs around the world seek to identify the factors that influence outcomes.[1–9]

Parents of children with PKU have shared this concern. Many parents of children with PKU brought concerns about the stringency and consistency of management of PKU in the United States to a meeting of parents held in 1993 in conjunction with a scientific meeting concerning maternal PKU. Aware of the publication of strict guidelines in the United Kingdom,[10–12] they asked particularly whether current management in the United States will assure an optimal outcome. PKU clinics in the United States have been aware of the publication of the UK guidelines, but there is a lack of unanimity in PKU management in the United States. No US national guidelines exist. Parents perceived a greater stringency in the UK and European management guidelines than the practice in most US programs with which they were familiar. Although individual physicians and clinical centers caring for patients with PKU had begun to compare their practices with the British guidelines, there has been no concerted national examination of PKU management in this light.

The American Academy of Pediatrics (AAP) Committee on Genetics (COG) found this concern consonant with its ongoing considerations and publications concerning issues in newborn screening and maternal PKU. The Committee chose a subject review as the most expedient method of addressing the issues and collected data about PKU treatment practice in the United States. A report of these data will be presented in an accompanying article.

METHODS

During the time that this subject review was being undertaken by the AAP/COG, a meeting of experts in PKU was convened at the National Institute of Child Health and Human Development to discuss the preliminary results of the subject review and to consider the feasibility of developing US guidelines for the management of PKU. This group included the chair of the AAP/COG,

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other members of the committee involved in the project, and selected experts in PKU diagnosis and management.

RESULTS AND DISCUSSION

The group reviewed the published literature on PKU treatment outcome and the published treatment guidelines from the UK. They also heard preliminary data collected in the process of the subject review being performed by the AAP/COG.

The published literature addresses outcome of PKU in the United States and in other countries. The guidelines for PKU management established in the United Kingdom were developed based on outcome studies on patients diagnosed in the United Kingdom.[2] The studies support the position that outcome is related to control of blood phenylalanine concentration, particularly in the early years of life. The British data show that outcome is best when blood phenylalanine concentrations are kept between 120 and 360 μmol/L (2–6 mg/dL); the Irish data suggest that the optimal concentration may be 200 to 400 μmol/L (3.3–6.7 mg/dL).[13] The data also suggest a relationship to parental occupation and other socioeconomic factors.

The surveys performed by the AAP/COG sought information about parental perceptions of clinic management policies, cost of obtaining formula, and factors that influence compliance. The information sought from clinic directors concerned local practice guidelines, opinions about the setting of more universal guidelines, and identification of problems in current treatment protocols. Parents who responded were of high socioeconomic class and educational status. They believed strongly that guidelines should be based on data on outcome studies and not on opinions in ease of compliance. The survey of clinic directors revealed a trend toward lower blood phenylalanine concentrations than had been advised previously. They supported the performance of the subject review by the AAP/COG. They did not all support the development of treatment guidelines.

The surveys helped to focus areas of concern that might have an impact on the development of guidelines for PKU management in the United States. These concerns were discussed at the meeting and were expanded upon in the group discussion. More information about adults with PKU who have been treated from birth is needed. Extensive follow-up of the patients enrolled in the US PKU Collaborative Study might provide important data on long-term outcome in children diagnosed with PKU by newborn screening. There is considerable interest in trying to clarify the magnetic resonance imaging changes, suggesting demyelination reported in persons with PKU off diet.[14] Although anecdotal reports and personal experience are plentiful, there is a need for a collaborative collection of such cases.

The following issues and questions need to be answered before US guidelines can be developed:

- What is the appropriate phenylalanine concentration at which to initiate and continue treatment? Most people would treat at >10 mg/dL (600 μmol/L). There is not general agreement about 6 mg/dL (360μmol/L) as either a treatment goal or a level at which to begin treatment.[15,16] Additional questions remain about the predictive value of the ratio between tyrosine and phenylalanine and the speed with which the blood phenylalanine is lowered if the concentration exceeds 15 mg/dL (900 μmol/L).
- Should treatment criteria be based on fasting or postprandial blood phenylalanine concentrations?
- What is the consensus on tyrosine supplementation and the role of micronutrients?
- If greater stringency in management before 6 years of age is the consensus, what about stringency after 6 years of age?
- There are major compliance issues with a recommendation for stricter control. What if only 10% of patients can comply? How could more patients be helped to comply? What strategies exist to facilitate compliance with a stricter regimen? Several factors hinder compliance: testing frequency, palatability of the medical foods, restrictiveness of the diet, the limited number of medical and nutritional personnel specialized in this area, psychological factors, and educational and social factors. The cost of the medical foods is a serious factor.
- What about third party payers? How will capitation impact on the ability of PKU families to obtain the critical specialty care in centers with specialized PKU expertise required for optimal PKU management?
- How would US guidelines differ from UK and European guidelines?

Several areas of consensus emerged from this meeting: 1) the AAP/COG should complete its subject review, including careful scientific assessment of the British and European guidelines; 2) the review should address the issues detailed above and recognize that thinking about PKU has changed over the last three decades; and 3) the opinions of parents of children with PKU and young adults with PKU are relevant and need to be considered within the context of scientific review of the data.

Because parental opinions primarily from families of higher educational and socioeconomic status may not be entirely representative, more patient and parent views need to be obtained and critically assessed.

Guidelines will need to take scientific, social, financial, cultural, and personnel concerns into account. A total of ~300 children are born yearly with PKU; these children, along with the children under continuing care, require multifaceted, multidisciplinary care that can be provided only in specialized centers by physicians with special expertise in PKU. Other critical resources include nutritional, neurological, and developmental expertise. Laboratories specializing in clinical biochemical and molecular genetics are crucial adjuncts to the care of these patients as well. Adults with PKU require similar expertise that also can address the special needs of adults with a chronic inborn error of metabolism.

The UK guidelines might form a framework for

the development of US guidelines. These guidelines address most of the issues thoughtfully and scientifically. There is general agreement with many points of these guidelines, particularly regarding the importance of early treatment and the value of close monitoring. Accord is lacking on such details as the phenylalanine level for initiation of dietary treatment, target phenylalanine levels for treatment, and frequency of monitoring.

Areas of general agreement included:

- Concerns about frequency of monitoring might diminish if a practical way to do frequent home monitoring, such as the method for blood glucose, existed.
- The development of more palatable medical foods would revolutionize dietary management, but restrictiveness of dietary management will continue to be a problem.
- One day gene therapy may provide practical help in management, but that day is not imminent.

CONCLUSIONS

The group concluded that an National Institutes of Health Consensus Development Conference would be very valuable in resolving some of these issues. The current development of guidelines for PKU treatment in the United Kingdom, Europe, and other countries in which the health care system differs greatly from that in the United States, is proceeding rapidly. The United States does not have such guidelines. Therefore, expeditious scheduling of a National Institutes of Health Consensus Development Conference would have a real impact on the development of US guidelines.

This working group adjourned its meeting convinced that the discussion had been extremely valuable. It brought together people experienced in PKU diagnosis and management in the context of the development of the AAP/COG subject review. This broad concern about guidelines for the care of children with PKU resulted in the sharing of opinions and concerns, support for the AAP/COG effort, and a commitment to ongoing discussion.

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The following people were workshop participants: Felix de la Cruz, MD, MPH, NICHD; Margretta Reed Seashore, MD, Children's Hospital at Yale-New Haven, Yale University, New Haven, CT, AAP/COG immediate past chair; Sechin Cho, MD, AAP/COG; University of Kansas, Wichita, KS; Rebecca Wappner, MD, AAP/COG; Riley Hospital for Children, Indianapolis, IN; Virginia Schuett, MS, RD, National PKU News, Seattle, WA; Richard Kronmal, PhD, University of Washington, Seattle, WA; Neil Buist, MB, ChB, DCH, Oregon Health Sciences University, Portland, OR; Harvey Levy, MD, Children's Hospital, Boston, MA; Margaret O'Flynn, MD, Children's Hospital, Chicago, IL; and Edward R. B. McCabe, MD, PhD, UCLA, Los Angeles, CA, past chair, AAP/COG.

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