Challenges and Pitfalls in the Management of Phenylketonuria

abstract

Despite recent advances in the management of phenylketonuria and hyperphenylalaninemia, important questions on the management of this disorder remain unanswered. Consensus exists on the need for neonatal screening and early treatment, yet disagreement persists over threshold levels of blood phenylalanine for starting treatment, target blood phenylalanine levels, and the management of older patient groups. The mainstay of treatment is a phenylalanine-restricted diet, but its application varies between and within countries. Beyond diet treatment, there is a lack of consensus on the use of newer treatments such as tetrahydrobiopterin. Although neonatal screening and early treatment has meant that most well-treated children grow up with near-normal IQ scores, the effect of relaxing metabolic control on cognitive and executive function later in life is still not fully understood. Although it is clear from the available literature that the active control of blood phenylalanine levels is of vital importance, there are other treatment-related factors that affect outcome. A uniform and firmly evidence-based approach to the management of phenylketonuria is required. Pediatrics 2010;126:333–341
Phenylketonuria (PKU) is an inborn error of metabolism caused by mutation of the phenylalanine hydroxylase (PAH) gene, which reduces the rate of conversion of phenylalanine to tyrosine. PKU is characterized by elevated blood phenylalanine levels, which are toxic for the brain. The persistently high blood phenylalanine levels characteristic of untreated PKU are associated with mental retardation or delayed cognitive development, growth abnormalities, and behavioral difficulties, among other adverse clinical sequelae. Many advances have been made in PKU management since early attempts to treat patients with a low-phenylalanine diet in the 1950s, not the least of which is the routine detection of hyperphenylalaninemia by neonatal screening in many countries. Although screening has facilitated early intervention to prevent the most serious clinical sequelae of PKU, there remains room for improvement. Indeed, despite decades of experience in the application of phenylalanine-restricted diets, a lack of clear guidance for the management of the condition in patients beyond childhood persists, inconsistent definition of mild hyperphenylalaninemia (implying the possibility of inadequate treatment in some cases), and regional differences in management guidelines (and treatment) may limit the potential for optimized intervention and long-term outcome for patients with PKU. We have a substantial clinical database of treated PKU, and it is time that the management of this disorder become more firmly evidence based. The results of this review highlight the need for a more consistent approach to the management of PKU that focuses more strongly on individual patient outcomes.

**CLINICAL AND MOLECULAR FEATURES OF PKU**

**Current Classification of Hyperphenylalaninemia/PKU**

Hyperphenylalaninemia can be classified into 2 general categories: hyperphenylalaninemia caused by PAH deficiency and hyperphenylalaninemia secondary to tetrahydrobiopterin cofactor deficiency. Classification of the severity of hyperphenylalaninemia/PKU is usually based on blood phenylalanine levels without treatment. Patients with blood phenylalanine levels of 120 to 600 μmol/L (2–10 mg/dL) may be classified as having mild (non-PKU) hyperphenylalaninemia; blood phenylalanine levels of 600 to 1200 μmol/L (10–20 mg/dL) may be classified as mild PKU; and levels of >1200 μmol/L (>20 mg/dL) may be classified as classical PKU. However, cutoffs for blood phenylalanine levels for these classifications vary between countries, and an alternative definition of “mild” or “severe” PKU can be adopted according to whether the patient requires therapeutic intervention or according to actual daily phenylalanine intake tolerance. This uncertainty is compounded by marked differences between countries in the blood phenylalanine level considered to require intervention (Fig 1).

**Influence of Genotypes on Blood Phenylalanine Levels and Correlation With Tetrahydrobiopterin Responsiveness**

Different mutations affect the activity of PAH differently, ranging from little or no effect to effectively complete suppression of the activity of the enzyme. Consequently, genotypes with more severe mutations (eg, p.R408W) result in moderate-to-classical phenotypes with higher untreated blood phenylalanine values, whereas milder mutations (eg, p.E390G) result in mild hyperphenylalaninemia with lesser increases in blood phenylalanine levels. Some mutations of PAH result in a tetrahydrobiopterin-sensitive hyperphenylalaninemia phenotype. For these patients, treatment with exogenous tetrahydrobiopterin results in increased hepatic activity of PAH and reduced hyperphenylalaninemia. Typically, patients with milder severities of PKU respond more strongly to exogenous tetrahydrobiopterin. For example, among a population of 1730 patients with PAH deficiency, marked improvements in phenylalanine hydroxylation rate in response to orally administered 6R-tetrahydrobiopterin occurred in 65% with initial blood phenylalanine levels of 120 to 400 μmol/L, 74% with initial blood phenylalanine levels of 400 to 800 μmol/L, 33% with...
initial blood phenylalanine levels of 800 to 1200 µmol/L, 17% with initial blood phenylalanine levels of 1200 to 1600 µmol/L, and <10% in groups with higher blood phenylalanine levels. These observations open up a new strategy in the management of PKU. It is important to note, however, that although some PAH genotypes can be predicted to be responsive to tetrahydrobiopterin, genotype alone is not a good predictor of the degree of tetrahydrobiopterin responsiveness in the clinical setting, and genotyping should be combined with a tetrahydrobiopterin-loading test or long-term trial of sapropterin dihydrochloride.

**ROLE AND IMPACT OF BLOOD PHENYLALANINE LEVELS IN HYPERPHENYLALANINEMIA/PKU MANAGEMENT**

**Blood Phenylalanine Level and IQ**

Clearly, increased blood phenylalanine levels are associated with neuropsychological impairment, especially in the early years of life. The goal of management of hyperphenylalaninemia in patients with PKU is to prevent the onset or worsening of such complications of the disease. Even early and continuously treated patients with PKU demonstrate lower IQ scores, on average, than matched individuals without PKU. It is important to note that blood phenylalanine control over the first 10 to 12 years of life seems to be a better predictor of cognitive development than point measurements of blood phenylalanine made after this period. Early and maintained control of blood phenylalanine levels, therefore, is crucial for long-term development during adolescence and adulthood.

An increase of 100 µmol/L in blood phenylalanine level was associated in a regression analysis with a 1.3- to 4.1-point reduction in IQ over a phenylalanine range from 394 to 750 µmol/L. Results of another study showed that IQ fell by ~4 points for each 4-week delay in starting treatment in a prospective study of 1031 children with PKU who started treatment within the first 4 months of life. These findings emphasize the importance of establishing adequate control of blood phenylalanine levels soon after birth and at least during the first 10 years of life, when brain development is most rapid, and identified blood phenylalanine level as a suitable surrogate marker for the prevention of cerebral complications of hyperphenylalaninemia in clinical trials. Neuropsychological development is made up of several domains, and the impact of PKU on them is described below.

**Cognitive and Executive Function**

Specific deficits in executive functions, which encompass planning, information-processing, and sustained attention, are common among patients with PKU and are related to increased phenylalanine levels. Among children with PKU, those with the highest persistent blood phenylalanine levels experience greater problems with attention deficit, reduced reaction time, and impaired arithmetic skill, language development, visual perception, visual motor skills, inhibitory control, and cognitive flexibility compared with children with lower blood phenylalanine levels. However, mild deficits in executive function were observed even among some patients with good dietary control (phenylalanine <400 µmol/L) compared with control patients.

**Working Memory**

Deficits in working memory have been observed in early-treated older children and adolescents with PKU but not in younger children, which suggests that a developmental deficit in the function of the prefrontal cortex may occur. In contrast, results of a meta-analysis suggested that there was no significant difference on tests of working memory between continuously treated adults and adolescents with PKU and controls.

**Other Psychological and Neurologic Abnormalities**

A range of psychological disturbances in patients with PKU have been described, including psychiatric illness and symptoms of autism, attention-deficit/hyperactivity disorder, and agoraphobia. Disturbances of emotional well-being in patients with PKU, including feelings of alienation, depression, social isolation, impaired communication, low self-esteem, and poor functioning in social situations, have been described. Untreated PKU has been associated with severe behavioral disorders, including hyperactivity, aggression, and self-harm. Tremors and hyperreflexia have been observed in adult patients with PKU.

**Mechanisms of Cognitive Deficits Induced by Hyperphenylalaninemia**

**Effects of Hyperphenylalaninemia on Brain Function**

Hyperphenylalaninemia may damage the brain through several mechanisms (Fig 2). Hyperphenylalaninemia has been shown to disrupt myelination of nerve fibers, with delayed or reduced myelination in children and loss of myelin in adults, although no causal link between dysmyelination and cognitive deficit has been demonstrated conclusively. In addition, altered neurotransmitter function may play a part. The reduced supply of tyrosine that results from low or absent rates of phenylalanine hydroxylation may, in turn, reduce the synthesis of dopamine (and subsequently norepinephrine), with a consequent impairment of neurotransmission.
nergic systems are believed to underlie important neurocognitive functions within the prefrontal cortex, although again, a definitive etiologic link with PKU-associated cognitive dysfunction has yet to be proven. Pre-frontal cortex dysfunction is known to impair executive functions (including cognitive functions) in older patients. Phenylalanine competes for transport into the brain with other large, neutral amino acids (LNAAs), which may reduce further the availability of tyrosine for conversion to dopamine and of tryptophan for conversion to serotonin. Experimental evidence indicates that hyperphenylalaninemia may interfere with glutamatergic systems, which are essential for normal brain development, the cholesterol biosynthetic pathway (via the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A), or glycolysis (possibly via inhibition of pyruvate kinase). Altered protein synthesis may also contribute to the etiology of cerebral dysfunction in PKU. Elevated phenylalanine levels may reduce the availability of these amino acids for incorporation into protein.

Importance of Variability of Lifetime Blood and Brain Phenylalanine Concentrations

High variability of blood, in addition to absolute, phenylalanine levels may impair cognitive function. Findings from a retrospective analysis of data from 46 early-treated children with PKU used the SD of blood phenylalanine levels over time as a measure of variability of this parameter. Correlations between blood phenylalanine-level variability and IQ tended to be stronger than correlations between lifetime blood phenylalanine levels and IQ, although correlations did not achieve statistical significance. Another study of 64 patients did reveal a significant correlation between IQ and an index of variability of blood phenylalanine levels during long-term dietary management. Thus, controlling the variability of blood phenylalanine levels might represent an important goal of therapy in addition to maintaining average phenylalanine levels within the recommended range. Additional analyses of this type are required in children and older individuals to establish whether increased variability of phenylalanine exacerbates the adverse effects of hyperphenylalaninemia itself.

AGE AS A FACTOR IN HYPERPHENYLALANINEMIA/PKU MANAGEMENT

Adequate blood phenylalanine-level control early in life protects the patient from neurologic damage, at least to some extent, as described above. Accordingly, intervention to control blood phenylalanine levels when hyperphenylalaninemia is discovered by neonatal screening is standard procedure. However, reviews since the 1980s have highlighted a continued risk of neuropsychological dysfunction during adolescence and adulthood, and most experts in the field recommend lifelong treatment. In particular, although guidelines tend to provide clear management recommendations for younger patients (e.g., up to 12 years in US guidelines), specific recommendations for older patients are often lacking, as evidenced by wide variations in blood phenylalanine-level targets. Some dietary relaxation may be possible in some cases as the patient grows older, and there is a relative consensus for relaxing the restrictiveness of the diet from adolescence onward but little consensus on by how much. Adult patients often require an individualized management approach, because it is well known that different adult patients will develop different clinical consequences for the same

FIGURE 2
Summary of potential mechanisms of neurocognitive impairment by hyperphenylalaninemia (see text for references). Phe indicates phenylalanine; BBB, blood-brain barrier; LAT1, L-type amino acid carrier; BH4, tetrahydrobiopterin; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; Tyr, tyrosine; Trp, tryptophan.
level of phenylalanine. These patient-to-patient differences are probably related to interactions of multiple genes. Accordingly, experts in the field have recently called for a unified guideline that includes guidance on the individualized management of adult patients with PKU. However, although the management of children is strongly evidence based, the development of a clear guideline for adults would only be possible when more data are available on various treatments received by this group. Research that focuses on adolescents and adults is required and should address not only IQ and prefrontal executive functions but also the psychosocial burden of treatment.

MATERNAL PKU
PKU during pregnancy exposes the developing fetus to elevated blood phenylalanine concentrations, which leads to low birth weight, microcephaly, facial dysmorphism, developmental retardation, and congenital heart disease. One clinical trial has identified a blood phenylalanine level of 350 μmol/L as the critical threshold beyond which the risk of fetal damage increases markedly. Results of another study showed that development at the age of 1 year and IQ at 8 years was higher for offspring of mothers who started their phenylalanine-restricted diet before pregnancy compared with those who started the diet within their first trimester. These observations are important clinically, because pregnancies are often unplanned, and conception, therefore, frequently occurs in women who are not following a phenylalanine-restricted diet.

The continuation of sustained metabolic control with adequate control of maternal blood phenylalanine levels is difficult to achieve throughout the pregnancy. It is important to monitor nutritional follow-up in the later gestational stages. The use of maternal tyrosine supplementation in addition to amino acid supplements has been studied, particularly in cases of tyrosine deficiency; however, so far, no clear relationship between tyrosine concentrations, intake, and outcome in maternal PKU has been demonstrated.

ADVANCES IN HYPERPHENYLALANINEMIA/PKU MANAGEMENT

Dietary Supplements
Phenylalanine-Free Protein Formulas
By definition, the phenylalanine-restricted diet is low in natural high-protein foods. Remaining nutritional requirements are obtained from phenylalanine-free protein substitutes that contain amino acids, with the content of carbohydrate, lipids, trace elements, vitamins, and essential fatty acids varying between preparations. As with any chronic disease, variations in the support provided by health care systems to patients in helping to manage their diet, both among countries and between individual treatment centers, remain a key concern within the management of PKU. The problem is particularly acute for patients with PKU in many areas, however. Turkey, for example, has a high prevalence of PKU compared with other countries but has a relatively low ratio of specialist dieticians to patients. Also, an increased cost burden is often important, given the absolute dependence on special foods for avoiding neurologic impairment (discussed separately below). Improvements in the palatability, presentation, convenience, and nutritional composition of supplements have helped improve long-term compliance with phenylalanine-restricted diets, although there remains room for further improvement in this area.

Glycomacropeptide
Glycomacropeptide is a protein derived from cheese whey that is the only known dietary protein that is naturally free of phenylalanine in its purified form (it is free of all aromatic amino acids). It does, however, provide amino acids that are necessary for health (branched-chain and other essential amino acids) and has been shown to reduce blood and brain phenylalanine levels in a murine model of PKU. Glycomacropeptide is acceptable to patients and may help to support dietary compliance by and nutritional management of patients with PKU by supplementing missing amino acids other than phenylalanine.

LNAA Supplementation
LNAs may also have a role in PKU therapy, particularly for patients who are off-diet or who do not adhere to the proper diet. LNAs have been shown to decrease blood or brain phenylalanine levels and to increase blood tyrosine levels. Further evaluations of this therapy to clarify its role in the routine management of PKU are now required.

Sapropterin Dihydrochloride (Tetrahydrobiopterin)
A soluble tablet formulation of tetrahydrobiopterin (sapropterin dihydrochloride) is now available in the United States and Europe. Reductions (≥30%) in mean plasma phenylalanine level have been demonstrated in controlled clinical trials in 20% to 56% of patients with PKU in response to a tetrahydrobiopterin-loading test. As with previous studies of the effects of exogenous tetrahydrobiopterin on blood phenylalanine levels, patients with relatively mild hyperphenylalaninemia phenotypes are more likely to respond to this treatment than patients with more severe forms of...
PKU.\textsuperscript{73} Results of a study of neonates indicated that conducting a tetrahydrobiopterin-loading test in this population was clinically worthwhile, because it facilitated the rapid achievement of metabolic control in subjects with tetrahydrobiopterin-responsive PKU.\textsuperscript{76} However, care should be taken not to postpone adequate treatment in nonresponsive patients with PKU who are especially prone to harm from high phenylalanine concentrations, especially within populations with a low expected number of patients with tetrahydrobiopterin responsiveness.

**Pegylated Recombinant Phenylalanine Ammonia Lyase**

PAH itself is not suitable for injection into patients with PKU because of poor stability and the requirement for its tetrahydrobiopterin cofactor. Phenylalanine ammonia lyase (PAL) is a plant-derived enzyme that also degrades phenylalanine (without synthesizing tyrosine), but it is more stable than PAH and does not require a cofactor. Pegylated PAL (PEG-PAL) is a novel formulation of PAL that is currently undergoing clinical trials. This new treatment modality has shown promising results in a phase I study, with a mean blood phenylalanine level reduction of 62% and no study, with a mean blood phenylalanine level reduction of 62% and no serious adverse reactions.\textsuperscript{77} The efficacy and tolerability phase II trial data will be available by the end of 2010.

**Gene Therapy**

PKU is also a potential candidate for gene therapy, possibly via transplantation of cells engineered to express a phenylalanine-metabolizing system or via targeted insertion of the necessary genes into a suitable organ (eg, skeletal muscle) in patients.\textsuperscript{78} The latter approach has been demonstrated in an animal model of PKU, with promising results,\textsuperscript{79} but such treatments are some way from routine clinical use.

**UNANSWERED QUESTIONS AND KEY ISSUES IN PKU MANAGEMENT**

**Cost of Therapy**

The cost of PKU treatment is fully reimbursed in many developed countries. Nevertheless, meeting the cost of the special diet remains an obstacle to the management of patients with PKU in many countries. In the United States, especially, this cost remains a major concern, because many adults with PKU, including some with health insurance, cannot obtain financial assistance for special foods.\textsuperscript{80,81} It has been estimated that ~4 patients in every 5 self-pays for special foods in the United States.\textsuperscript{92} Reimbursement practices in other countries vary. Even in the United Kingdom, where special foods are available via prescription from the National Health Service, each individual item is subject to a prescription fee for patients older than 16 years.

Maternal PKU presents a particular problem. Ideally, control of blood phenylalanine levels should be achieved before conception to protect the fetus from any period of hyperphenylalaninemia. However, proof of an already established pregnancy is often required in the United States before reimbursement of medical foods is possible.\textsuperscript{80}

**Threshold for Starting Treatment**

There is general agreement regarding the need to control blood levels of phenylalanine. However, there is no consensus regarding the threshold for starting treatment, the ideal target ranges of phenylalanine concentration at different ages to support the maintenance of optimal cognitive function (see Fig 1), and whether (and how) treatment should be continued into adulthood.\textsuperscript{10,30,60} Achieving such a consensus is not straightforward. For example, although clear increases in blood phenylalanine levels have been shown to increase the risk of cognitive impairment in meta-analyses (see above), similar blood phenylalanine levels may promote very different outcomes in individual patients with PKU.\textsuperscript{85}

**Hyperphenylalaninemia and Outcome**

In addition, data on the clinical outcomes of patients with phenylalanine levels of 360 to 600 \(\mu\)mol/L are scarce, although results of 1 study of untreated patients with this severity of hyperphenylalaninemia showed no evidence of cognitive impairment.\textsuperscript{84} Variations between centers in dietary treatment and support systems exacerbate the situation further. In practice, the patient’s background, age, and life stage need to be carefully considered, in addition to the blood phenylalanine levels. For older patients and those at the milder end of the hyperphenylalaninemia spectrum, it is unclear whether the advantages of treatment would outweigh the considerable burden imposed on patients’ lives by dietary phenylalanine restriction.

**Managing Elderly Patients**

Patients diagnosed with PKU by neonatal screening in the 1960s are now in middle age, and the next 2 decades will provide the first clinical experience of managing early-treated elderly patients. The effects of long-term dietary restriction in old age are difficult to predict. Restricted diets in patients with PKU may alter antioxidant status as a result of deficiency of selenium\textsuperscript{85} or coenzyme Q10 deficiency.\textsuperscript{86} Some data indicate that lipid peroxidation or DNA damage are increased in patients with PKU, even when phenylalanine concentrations are high.

**ISSUES IN PKU MANAGEMENT**

UNANSWERED QUESTIONS AND KEY ISSUES IN PKU MANAGEMENT

Cost of Therapy

The cost of PKU treatment is fully reimbursed in many developed countries. Nevertheless, meeting the cost of the special diet remains an obstacle to the management of patients with PKU in many countries. In the United States, especially, this cost remains a major concern, because many adults with PKU, including some with health insurance, cannot obtain financial assistance for special foods.\textsuperscript{80,81} It has been estimated that ~4 patients in every 5 self-pays for special foods in the United States.\textsuperscript{92} Reimbursement practices in other countries vary. Even in the United Kingdom, where special foods are available via prescription from the National Health Service, each individual item is subject to a prescription fee for patients older than 16 years.

Maternal PKU presents a particular problem. Ideally, control of blood phenylalanine levels should be achieved before conception to protect the fetus from any period of hyperphenylalaninemia. However, proof of an already established pregnancy is often required in the United States before reimbursement of medical foods is possible.\textsuperscript{80}

**Threshold for Starting Treatment**

There is general agreement regarding the need to control blood levels of phenylalanine. However, there is no consensus regarding the threshold for starting treatment, the ideal target ranges of phenylalanine concentration at different ages to support the maintenance of optimal cognitive function (see Fig 1), and whether (and how) treatment should be continued into adulthood.\textsuperscript{10,30,60} Achieving such a consensus is not straightforward. For example, although clear increases in blood phenylalanine levels have been shown to increase the risk of cognitive impairment in meta-analyses (see above), similar blood phenylalanine levels may promote very different outcomes in individual patients with PKU.\textsuperscript{85}

**Hyperphenylalaninemia and Outcome**

In addition, data on the clinical outcomes of patients with phenylalanine levels of 360 to 600 \(\mu\)mol/L are scarce, although results of 1 study of untreated patients with this severity of hyperphenylalaninemia showed no evidence of cognitive impairment.\textsuperscript{84} Variations between centers in dietary treatment and support systems exacerbate the situation further. In practice, the patient’s background, age, and life stage need to be carefully considered, in addition to the blood phenylalanine levels. For older patients and those at the milder end of the hyperphenylalaninemia spectrum, it is unclear whether the advantages of treatment would outweigh the considerable burden imposed on patients’ lives by dietary phenylalanine restriction.

**Managing Elderly Patients**

Patients diagnosed with PKU by neonatal screening in the 1960s are now in middle age, and the next 2 decades will provide the first clinical experience of managing early-treated elderly patients. The effects of long-term dietary restriction in old age are difficult to predict. Restricted diets in patients with PKU may alter antioxidant status as a result of deficiency of selenium\textsuperscript{85} or coenzyme Q10 deficiency.\textsuperscript{86} Some data indicate that lipid peroxidation or DNA damage are increased in patients with PKU, even when phenylalanine concentrations are high.
anine levels are under control.87,88 We do not know today if our patients will be at risk for earlier-onset dementia or other forms of neurologic decline; follow-up of all adult patients is of a great importance, and the appearance of such neurologic disorders would be the strongest evidence to date that patients should continue with the diet (or other treatment) for life.

REFERENCES


Place of New Therapies

The availability of new treatment strategies may address some of these challenges, such as continuing improvements in phenylalanine-free protein formulas and the recent introduction of sapropterin dihydrochloride into the management of the subset of patients with tetrahydrobiopterin-responsive PKU.17 There remains a clear need for a global consensus on the aims of treatment for PKU and the optimum strategies for achieving them.

ACKNOWLEDGMENTS

This work was supported by an educational grant from Merck Serono SA (Geneva, Switzerland) and in part by Swiss National Science Foundation grant 3100A4-119982/1 (to Dr Blau). Dr Mike Gwilt assisted with development of the manuscript.
29. VanZutphen KH, Packman W, Sporri L, et al. Executive functioning in children and ado-
30. Albrecht J, Garbade SF, Burgard P. Neuropsychological speed tests and blood phenyla-
31. Huijbregts SC, de Sonneville LM, Licht R, van Spronsen FJ, Verkerk PH, Sergeant JA. Sustained attention and inhibition of cognitive interference in treated phenylketonuria: associ-
32. White DA, Nortz MJ, Mandernach T, Hunting-
35. Möller HE, Weglage J, Wiedermann D, Ullrich K. Blood-brain barrier phenylalanine trans-
port and individual vulnerability in phenylket-
39. Antshel KM, Waisbren SE. Developmental timing of exposure to elevated levels of phen-
43. Waisbren SE, Zaff J. Personality disorder in young women with treated phenylketonu-
44. Weglage J, Fünders B, Wilken B, et al. Psychological and social findings in adoles-
48. Shefer S, Tint GS, Jean-Guillaume D, et al. Is there a relationship between 3-hydroxy-3-
52. Dyer CA. Pathophysiology of phenylketonu-
55. Hoeksma M, Reijngoud DJ, Pruim J, de Valk HW, Paans AM, van Spronser FJ. Phenylketonuria: high plasma phenylala-
56. Kalsner LR, Rohr FJ, Strauss KA, Korsos MS, Levy HL. Tyrosine supplementation in phenylketonuria: diurnal blood tyrosine lev-
57. Anastasoaei V, Kurzius L, Forbes P, Waisbren S. Stability of blood phenylalanine lev-
58. Kalsner LR, Rohr FJ, Strauss KA, Corson MS, Levy HL. Tyrosine supplementation in phenylketonuria: diurnal blood tyrosine lev-
60. Möller HE, Weglage J, Wiedermann D, Ullrich K. Blood-brain barrier phenylalanine trans-
port and individual vulnerability in phenylket-
61. van Spronsen FJ, Burgard P. The truth of patients with phenylketonuria after-
62. Levy HL, Waisbren SE. Effects of untreated maternal phenylketonuria and hyperphenyl-
63. Widaman KF, Azen C. Relation of prenatal phenylalanine exposure to infant and child-
hood cognitive outcomes: results from the International Maternal PKU Collaborative Study. Pedi-
atrics. 2005;112(6 Pt 2):1537–1543
64. Maillof F, Libburn M, Baudin J, Morley DW, Lee PJ. Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of varia-
65. Rohr FJ, Lobbregt D, Levy HL. Tyrosine sup-
plementation in the treatment of maternal

---

The text appears to be a collection of references, likely from a scientific or medical journal, discussing various aspects of phenylketonuria. The references span a range of topics from neuropsychological testing and behavioral outcomes to the impact of phenylalanine on cortical and brain function. The text includes studies on the cognitive and neurological effects of phenylketonuria, the assessment of attention and inhibition, and the role of specific neurotransmitters in affected individuals. The references also touch upon the clinical management and treatment aspects, including the impact of early intervention and the effects of phenylalanine on brain structure and function.
(Continued from first page)

for contributions to the Scientific Advisory Board on PKU and has received honoraria for consulting or lecturing from Merck Serono SA, Dr Blau has received grants for educational and scientific work from BioMarin Pharmaceuticals (United States) and Merck Serono SA; Dr Demirkol’s contributions to the Scientific Advisory Board on PKU were supported by Merck Serono SA; Dr Giovannini is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU from Merck Serono SA, and Dr van Spronsen is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU and has received honoraria for consulting or lecturing from ShS International and Merck Serono SA.