JIMD Reports
DOI: 10.1007/8904_2011_16

Received: 11 September 2009; Revised: 16 December 2010;
Accepted: 14 January 2011; Published online: 22 June 2011
Communicated by: Nenad Blau

Outcomes of Phenylketonuria with Relevance to Follow-Up

F.J. van Spronsen and A. Bélanger-Quintana

Abstract Currently, there is no international consensus on how patients with phenylketonuria (PKU) (or milder forms of hyperphenylalaninaemia) should be followed in clinical practice. Guidelines concerning the frequency and type of assessments that should be made according to age usually focus on blood phenylalanine concentrations. A need exists for improved guidelines on how to do the follow-up of individuals with PKU/milder forms of hyperphenylalaninaemia. An interdisciplinary approach for monitoring patients is required, involving relevant clinical investigations and regular contact with a clinician and dietician/nutritionist as well as contact with social health worker, psychologist and neurologist, at least at request. This chapter presents a scheme for follow-up. However, by no means this scheme aims to present the one for all time follow-up programme. The scheme for follow-up may rather serve as a start for further discussion in larger groups of professionals in collaboration with patients and their parents. A number of questions remain unanswered, and further research is still needed to fine-tune the management of PKU at different ages.

Keywords Follow-up · Guidelines · Neurocognitive outcome · Nutritional deficiencies · Phenylketonuria · Phenylalanine

Abbreviations

IQ	Intelligence quotient
MHP	Mild hyperphenylalaninaemia
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
PAH	Phenylalanine hydroxylase
Phe	Phenylalanine
PKU	Phenylketonuria
QoL	Quality of life

F.J. van Spronsen (✉)
Beatrix Children's Hospital, University Medical Center of Groningen, Groningen, The Netherlands
e-mail: f.j.van.spronsen@bkk.umcg.nl

A. Bélanger-Quintana
Unidad de Enfermedades Metabólicas, Servicio de Pediatría, Hospital Ramón y Caja, Madrid, Spain
e-mail: abelanger.hrc@salud.madrid.org

Introduction

Phenylketonuria (PKU; OMIM 261600) is an inherited autosomal recessive error in amino acid metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase (PAH). Consequently, patients are unable to convert the essential amino acid phenylalanine (Phe) to tyrosine, with the result that plasma and tissue concentrations of Phe are elevated, negatively impacting on cognitive development and function (Scriver and Kaufman 2001). Untreated patients with the most severe form of PAH deficiency, usually termed 'classic' PKU, have Phe concentrations >1,200 μmol/L; less severe forms may be termed as 'mild PKU' (Phe 600–1,200 μmol/L) or 'mild hyperphenylalaninaemia' (MHP; Phe <600 μmol/L) (Blau et al. 2009). However, this classification is not that useful if untreated patients have not reached their maximal Phe concentration at the start of treatment due to early diagnosis with neonatal screening. In this case, the use of other strategies such as genotyping or the determination of dietary Phe tolerance is necessary (Guldberg et al. 1998; van Spronsen et al. 2009a).

Screening for high concentrations of Phe in newborns by heel puncture is crucial for identifying PKU patients, so that treatment can be implemented early to prevent severe mental retardation and allow optimal cognitive development. Prevention of mental retardation has been the primary aim of PKU treatment for a long time (van Spronsen and Burgard 2008), but even among patients with well-controlled Phe concentrations, intellectual outcome is not completely normal (Feillet et al. 2010). Neurocognitive deficits may include

Table 1 Targets of blood phenylalanine concentrations and frequencies for control for different age groups[a]

Issue/age in years	0–1	1–4	4–10	10–12	12–16	>16
Frequency blood phenylalanine/month[b]	4 (1–6)	3 (1–4)	1.5 (1–3)	1 (1–2)	1 (0.5–2)	1 (0.33–2)
Frequency blood amino acid measurements/year[c]	2 (0–4)	1 (0–4)	0 (0–2)	1 (0–1)	1 (0–1)	1 (0–2)
Frequency clinical evaluation/year[c]	9 (2–12)	4 (1–6)	3 (1–4)	2 (1–4)	1 (1–3)	1 (1–2)
Range of target phenylalanine (μmol/L)[d]	120–360 (<400)	120–360 (<400)	120–400 (<480)	120–360 (<900)	120–600 (<900)	120–700 (<900)

[a]Adapted from van Spronsen et al. (2009b)
[b]Most frequent observed number of blood phenylalanine/amino acid concentration measurement; the complete reported range is given within brackets
[c]Most frequent number of clinical evaluations; the complete reported ranges are given within brackets
[d]Most frequent reported target of phenylalanine concentrations; the complete reported ranges are given within brackets

deficits in executive function tasks such as organization, inhibitory control and planning, which may be responsible for poor levels of academic achievement (Huijbregts et al. 2002; Feldmann et al. 2005; Gassió et al. 2005).

A strong relationship has been established between the control of blood Phe concentrations during infancy and childhood and intelligence quotient (IQ) (Scriver and Kaufman 2001). Therefore, good control of Phe concentrations has been the main objective of treatment, but recommended maximum Phe blood concentrations by age group vary considerably in all age groups in Europe, as do frequencies of monitoring (Table 1).

Only some countries have internationally available reported national guidelines. These guidelines focus on monitoring target Phe concentrations, frequency of blood sampling and clinical evaluations but usually provide inadequate information for the most appropriate follow-up of patients with PKU at different ages (van Spronsen and Burgard 2008). These guidelines, for example, seldom offer advice regarding nutritional issues or type and timing of appropriate neurocognitive tests.

When designing any kind of clinical algorithm for the follow-up of a patient with PKU, it is therefore important to be sure of the objective. Where in the past 'normal cognitive function' was the primary aim, at present 'a life as normal as possible' is the main target for many clinicians (van Spronsen and Burgard 2008), aiming not only at normal neuropsychological test outcomes, but also at normal qualities of life. When aiming at a day-to-day life as normal as possible, target outcomes need to be re-identified. This chapter presents a scheme for follow-up with issues that need attention and consideration for simple or more extensive monitoring (Table 2). This scheme may serve as a start for further discussion to achieve guidelines rather than aiming to present the one for all time follow-up programme. Guidelines need to be developed by larger groups of physicians, psychologists, nutritionists, biochemists and other professionals in cooperation with patients and their parents.

Designing a PKU Follow-Up Programme: Points to Consider

Individually Tailored Treatment

The principal question whether all patients need the same strictness of treatment is unanswered. There is even a clear variation among different countries in the Phe concentrations that determine the beginning of treatment in patients with a positive neonatal screening result (Blau et al. 2010; Feillet et al. 2010). Old reports already claimed that some untreated patients did not develop severe mental retardation (Pitt and Danks 1991). The work of different research groups using magnetic resonance spectroscopy (MRS) have brought this discussion alive again by detecting different brain Phe levels in patients with the same blood Phe concentrations (Weglage et al. 2001; Pietz et al. 2002).

In other diseases such as leukaemia, the type of presentation, biochemical and molecular parameters help to distinguish patients who need a different degree of treatment (Faderl et al. 2010). One would expect that if treatment strategies can be based on molecular data in leukaemia, it should be possible in monogenetic diseases such as PKU with a simple monogenic trait. Studies with DNA have claimed to distinguish patients with more and less severe degrees of PAH deficiency, but at the same time are not always conclusive (Kayaalp et al. 1997). However, it was already in 1999 that Scriver et al. presented ideas why there is not such a simple trait in PKU (Scriver and Waters 1999), elaborating these concepts further in one of his later papers (Scriver 2007). So far, in PKU we have been unable to identify markers that would enable different treatment strategies. Clearly, complex studies in large populations are needed before we can answer to a sufficient degree the question as to which patients need treatment and with which strictness and which do not. Until this question is safely answered, all patients should be offered the same treatment strategy in relation to the therapeutic target Phe concentrations.

Table 2 Issues of monitoring in standard and expert follow-up in PKU patients

	Standard PKU follow-up	Expert PKU follow-up: differences to standard follow-up
Clinical and nutritional follow-up including visit to paediatrician/physician metabolic disease and dietician metabolic diseases with measures of growth and development	0–12 months: monthly (after parents are accustomed to PKU and its treatment) 1–4 years: every 3 months 4–18 years: every 6 months Adults: every 6–12 months Pregnancy: monthly	
Phenylalanine concentration monitoring	0–12 months: weekly 1–2 years: twice monthly >2 years: monthly Pregnancy: weekly	0–24 months: weekly 2–4 years: twice monthly >4 years: once to twice monthly Pregnancy: twice weekly
Individual adaptation of care		Analysis of DNA and tolerance of phenylalanine with possible consequences for strictness of treatment Investigation of possibility of other treatment strategies for individual including tetrahydrobiopterin
Nutritional investigations	*Yearly*: Haemoglobin, leucocytes, thrombocytes Calcium, phosphate, alkalic phosphatase, ALT	*Yearly:* Blood: holotranscobalamine, methylmalonic acid, homocysteine, total amino acids, pre-albumin, transferrine Urine: calcium, protein, phosphate, creatinine *Every 5 years*: Blood: carnitine, fatty acid profile, zinc, selenium Bone densiometry each 5–10 years starting at 15–20 years of age. Higher frequency when indicated. When abnormal, consider further investigations including markers of bone turnover
Neurological follow-up	Regular clinical evaluations, special attention for tremor, brisk reflexes Specific neurological tests by paediatric/adult neurologist when indicated by the results of paediatrician/physician metabolic disease	MRI with DTI if necessary (MRS is research rather than clinical follow-up)
Neurocognitive function	Regular school reports with special attention for attention, hyperactivity Determination IQ once between 6 and 8 years of age	Response speed test BRIEF if possible
Psychosocial issues and quality of life		Tests need to be developed

BRIEF Behaviour Rating Inventory of Executive Function, *DTI* diffusion tensor imaging

Normal Neurological Outcomes

A strong relationship has been established between the control of blood Phe concentrations during infancy and childhood and IQ. Waisbren et al. (2007) conducted a meta-analysis of 40 studies, which pointed out that in early treated PKU patients, an incremental rise in Phe of 100 μmol/L was predictive of a decline in IQ between 1.3 and 3.1 points at Phe concentrations >423 μmol/L during critical periods from 0 to 12 years of age. However, the relation between IQ and blood Phe concentrations may be more complex. For example, in a study of 46 patients, Anastasoaie et al. (2008) found that IQ tended to relate to the fluctuation of the Phe concentration rather than to the Phe concentrations being above a specific threshold. A recent meta-analysis by Albrecht et al. (2009) demonstrated the negative effects of concurrent Phe concentrations on reaction times among children at levels >250 μmol/L, and >600 μmol/L in adolescents. No clear cut-off value could be estimated for adults, as there is little data relating Phe concentrations and brain function in this age group.

Although well-controlled patients reach a normal IQ, it may be lower than their siblings or classmates. Above this, patients with normal IQ still might have milder neurocognitive deficits such as slow executive function, difficulties in organization and planning, etc. (Huijbregts et al. 2002; Feldmann et al. 2005; Gassió et al. 2005). Most present guidelines do not consider the routine investigation of these functions of which deficits may be minor but at the same

time may be responsible for day-to-day difficulties in the patients and in the end may unnecessarily lead to poor levels of academic achievement in some of the patients.

Notwithstanding the relationship between blood Phe concentrations and outcome, it is to be resolved whether blood Phe concentrations can fully explain the total pathogenesis of brain pathophysiology in PKU (van Spronsen et al. 2009c). Hoeksma et al. (2009) evaluated the cerebral protein synthesis rate in relation to plasma Phe concentration in adult patients with PKU, using positron emission tomography after the administration of intravenous l-[1-^{11}C]-tyrosine. A significant negative relationship ($R^2 = 0.40$, $p < 0.01$) between plasma Phe concentration and cerebral protein synthesis rate was observed in 16 patients with PKU. Individuals with Phe concentrations >600–800 μmol/L experienced a greater decrease in cerebral protein synthesis at these higher plasma Phe concentrations, compared with lower Phe concentrations.

Psychosocial Outcomes

An additional target of significance among patients with PKU includes psychosocial outcome, of which too few studies have been conducted to date. Patients with PKU may suffer severe psychological problems, such as depression, agoraphobia and low self-esteem (Hendrikx et al. 1994; Ris et al. 1994; Sullivan and Chang 1999; Waisbren et al. 1994; Waisbren and Levy 1991; Weglage et al. 1992; Weglage et al. 1994), and improved dietary control may assist with improving these psychological outcomes.

Pietz et al. (1997) assessed psychiatric disorders in patients with PKU and tested whether biochemical control, intellectual functioning, white matter abnormalities visible on magnetic resonance imaging (MRI) and/or style of parenting was related to psychopathology. Findings indicated that a higher percentage of patients with PKU internalize their feelings (25.7% of patients with PKU versus 8.3% of the control group), which are later expressed as psychiatric problems of anxiety, depression and low self-esteem (Pietz et al. 1997). In a retrospective study conducted by Weglage et al. (1992), 34 early treated normally intelligent adolescents with PKU and their parents were tested using several psychometric personality inventories and self-developed questionnaires to assess their psychosocial situation, disease- and diet-specific knowledge. Compared to the control population, patients had a more negative evaluation of their scholastic ability, were less motivated, had a lower tolerance of frustration and gave more negative self-descriptions. They also tended to be less extroverted and had a higher level of dependency on their families.

Nutritional Outcomes

A further main target is to ensure that there are no nutritional deficiencies that may give rise to possible physiological or neurological concerns. These nutritional deficiencies cannot be monitored by simply measuring Phe concentrations. Some guidelines advice concerning a prescriptive total amount of protein, as well as vitamin B_{12} monitoring (Medical Research Council for Phenylketonuria 1993; Abadie et al. 2005). Research papers have studied the possibility and clinical importance of deficiencies of amino acids other than Phe, bone turnover markers (such as deoxypyridinoline, osteocalcin, bone alkaline phosphatase, C-terminal procollagen peptide type I, osteoprotegerin), calcium, carnitine, coenzyme Q_{10}, folates, iron, long-chain polyunsaturated fatty acids, selenium, vitamin A, B_2 and B_{12}, C and E, and zinc (Ambroszkiewicz et al. 2004; Millet et al. 2005; Feillet and Agostini 2010). Effects on bone density, growth and oxidative stress – with possible consequences for intellectual development and neuropsychological function – have been suggested although clear evidence is lacking (Sirtori et al. 2005; Feillet and Agostini 2010).

Until now, there have been no studies that specify in which situations patients are more prone to specific nutritional deficiencies. Is it related to age or growth velocity? Is it related to how strict their diet is, or rather, is it more frequent in patients who relax their diet but still do not have a quantitatively and/or qualitatively normal protein intake? It also remains to be investigated to what degree subclinical nutritional deficits may impair optimal neuropsychological and psychosocial function. It is still unclear, therefore, at what age patients would benefit the most from arranging specific tests to detect nutritional deficits.

It is our opinion that there are probably three moments in life in which nutritional deficiencies of the patient are more prone to appear and therefore patients should be especially monitored: young infants, adolescents and elderly. Young infants have a rapid growth and development. In this age group, nutritional care may focus at deficiencies of essential amino acids and long-chain polyunsaturated fatty acids. Adolescents and adults, on the other hand, may abandon their restrictive diet, think they have normalized their natural protein intake and believe they do not need their amino acid supplements anymore. Such patients tend to be nutritionally deficient, as their intake of natural protein is both of low quantity and quality. In this age, group tests are needed to detect specific nutritional deficits such as vitamin B_{12}, (measuring methylmalonic acid and homocysteine rather than vitamin B_{12} itself) (Vugteveen et al. 2010) which may result in a less optimal physical condition and neurological dysfunction. With regard to elderly, there simply is not enough

experience, but deficiencies may have a remarkable resemblance compared to young infants.

Pregnancy is another delicate situation in which dietary restrictions might need to be intensified for the sake of the foetus. Notwithstanding the fact that outcome is very good when Phe restriction is started clearly before conception and continued throughout pregnancy, there are nutritional issues. First of all, it sometimes proves difficult to prevent Phe concentrations from being too low in the second half of pregnancy when there is a high need of Phe due to growth velocity of both child and placenta. Tyrosine is an ongoing subject for debate. Should tyrosine be supplemented during pregnancy and how should the amount of supplementation be determined? There is a need of long-chain polyunsaturated fatty acids. Carnitine concentrations can be very low, but whether supplementation is needed is unclear. With regard to vitamins, there is the risk of vitamin A toxicity rather than deficiency.

Quality of Life Outcomes

As with the lack of PKU studies assessing psychosocial outcomes, there is also a dearth in the number of studies that assess quality of life (QoL) in patients with PKU. Two of the ones that have done so, however, display conflicting outcomes. Bosch et al. (2007) conducted a study to assess the course of life, socio-demographic outcomes and health-related QoL in 32 young adult patients (aged 18–30 years) with PKU who remained on treatment. Findings from the completed Course of Life questionnaire (Grootenhuis et al. 2003), the RAND-36 Health Survey and the cognitive scale of the TNO-AZL Adult Quality of Life questionnaire (Fekkes et al. 2000) were comparable to controls except for the higher percentage of patients requiring special education in primary school; this was, however, comparable with that of the patients' peers. The precise meaning of this finding for treatment strategies remains unanswered. In conclusion, Bosch et al. (2007) surmised that while PKU is a chronic disease with the burden of strict dietary control, early and continuously treated patients with PKU can enjoy a normal health-related QoL.

By contrast, Simon et al. (2008) showed that 47% of 67 young adult patients with PKU in Germany lived with their parents (compared with 25% in the general population), and more than 75% of male patients were not involved in a steady relationship. In addition, 9% of female and 18% of male patients had children, compared with approximately 50% of subjects in the general population in the same age group. Therefore, the data of Simon et al. (2008) substantiate the findings of another German study of Weglage et al. (1992) concerning decreased autonomy, and by that show that in PKU psychosocial issues still need to be addressed to achieve normal QoL outcome.

New studies will have to reveal whether the differences in data of Bosch et al. (2007) compared to Simon et al. (2008) and Weglage et al. (1992) are due to differences in study design and/or study groups.

To date, there is no study correlating psychosocial and QoL issues with levels of blood Phe, and the stringency of Phe dietary restriction to achieve these Phe concentrations. Furthermore, little data on the influence of family issues and style of parenting on QoL are available. We also have no data about the relation between neuropsychological and psychosocial outcomes at low(er) and high(er) Phe concentrations (during various periods of life), and the effort it takes for patients to achieve these concentrations. Therefore, we cannot be sure of the relationship of cause and effect. It might very well be that, on the one hand, stringent dietary restrictions resulting in well-controlled Phe concentrations allow the best possible neurocognitive outcomes in the tests applied, but that, on the other hand, such a stringent dietary restriction may imply a restriction of social life and psychosocial well-being that results in the incapability of patients to completely use their biological potentials of neurocognitive skills in day-to-day life. At this moment, it is unclear whether a lower than optimal control of Phe concentrations, the stringent dietary restrictions or a combination of both negatively influence self-esteem in PKU patients (Hendrikx et al. 1994; Weglage et al. 1992), and consequently result in less autonomy (Weglage et al. 1992; Simon et al. 2008).

Crone et al. (2005) reported that too a strict handling of the dietary limitations is not necessarily associated with lower Phe concentrations. Therefore, teaching coping strategies to our patients and their families may be of more importance than considered previously, not only at the moment of diagnosis but also at all other age groups, such as adolescence and adulthood.

Designing a PKU Follow-Up Programme: What Elements Should It Contain?

Table 2 contains the elements that we believe need attention in the follow-up of PKU patients. A PKU centre is the likely venue for this follow-up. These centres should always have a metabolic paediatrician/adult physician, a dietician or nutritionist, and a clinical biochemist. Other staff who ideally should be included in this interdisciplinary team is a social health worker, a psychologist, a neurologist and a specialized nurse. One study showed that centralized expert teams provide better care than smaller centres (Camfield et al. 2004). However, the question remains as to what specifications distinguish PKU expert centres from teams

who provide more standard care to their patients, who should decide on this issue and on what basis. At present, the suggested 'expert' follow-up does not include specific neuropsychological test batteries, MRS, positron emission tomography and extensive questionnaires on the QoL, as these are considered to be research rather than expert care.

Phe concentrations are still a key element in the monitoring of PKU patients, but other biochemical parameters should be considered to be able to assess their importance in the future, such as the fluctuation of these concentrations and the ratio of Phe to tyrosine and the other amino acids. Patients of all ages and phenotypes (on strict diet or not) deserve nutritional monitoring to avoid nutritional deficiencies. The strictness of their diet, age and personal situation should be taken into account to determine specific parameters.

Patients should be routinely followed to assess neurological outcome. A clinical neurological examination can be done by any experienced paediatrician/adult physician. Referral to a neurologist is advised in cases in which abnormalities are found. Additional neurological imaging (e.g. cerebral MRI) is encouraged in such cases. It should be remembered, however, that the relation between an abnormal MRI and clinical outcome is not that strong. Although a better control should try to be obtained, abnormalities on a MRI should not be used to impress the patient and by this means try to improve the adherence to treatment. When using MRI, the use of more advanced techniques such as diffusion tensor imaging is advocated. At this moment, the use of MRS and positron emission tomography studies is for research rather than day-to-day follow-up.

IQ testing is considered appropriate for research and routine purposes at least until the age of 7. We encourage the use of neuropsychological tests (especially in patients over 7 years of age) to assess neuropsychological deficits such as executive function deficits. It is preferable to use standardized batteries of tests to achieve a greater degree of certainty. In this light, it is of importance to note that simple speed tests may be of practical value (Albrecht et al. 2009), whereas rather more complex neuropsychological batteries are needed for research. The Behaviour Rating Inventory of Executive Function (BRIEF) for paediatric ages and BRIEF-A for adults, a questionnaire, can be used but availability is especially in English and Spanish language (Waisbren and White 2010).

Measuring psychosocial outcome has become of more importance. A simple standardized questionnaire that could be used in a clinical setting would be of great help to understand the needs of the patients in different moments of their lives. It would be of added value when the QoL of patients and their families could be assessed with a simple standardized questionnaire as well. The report of Waisbren and White (2010) is the first one to present some ideas about such tests including the Behaviour Assessment System for Children (BASC-II), the Beck Anxiety Inventory 2nd edition for adults (BAI-II) and the Beck Depression Inventory 2nd edition (BDI-II) for adults. However, the usefulness of the BASC-II, the BAI-II and the BDI-II has to be proven in PKU patients, and therefore, research is necessary before these tests can be considered daily clinical practice for either standard or specialized care.

Conclusion

Notwithstanding the large library of knowledge in PKU, there is still no clear picture of how a follow-up programme can be successfully delivered. Once an individual has been diagnosed with PKU and is undergoing treatment, he or she deserves adequate follow-up during his or her entire lifespan, with differences as personal circumstances change at different ages. Each follow-up programme should be in the best interest of the patients with regards to their disease severity, age and other relevant factors, such as the desire to become pregnant.

This chapter tries to present a start for a follow-up programme. By no means, however, this chapter is aimed to present the one for all time follow-up programme. By giving some specific ideas on the programme, it may serve as a start for further discussion. Metabolic physicians, nutritionists, psychologists, biochemists, social health workers and specialized nurses are needed to achieve guidelines, in collaboration with parents and patients.

Competing Interests

Francjan van Spronsen and Amaya Bélanger-Quintana are both members of the scientific advisory board of Merck Serono S.A. – Geneva, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany) regarding treatment for phenylketonuria. Francjan J van Spronsen received grants and honoraria from Milupa, Scientific Hospital Supplies, Nutricia, and Merck Serono S.A. Amaya Bélanger-Quintana received grants from Mead-Johnson and Merck Serono S.A.

References

Abadie V, Berthelot J, Feillet F et al (2005) Association française pour le dépistage et la prevention des handicaps de l'enfant (AFDPHE). Arch Pediatr 12:594–601

Albrecht J, Garbade SF, Burgard P (2009) Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: a meta-analysis. Neurosci Biobehav Rev 33:414–421

Ambroszkiewicz J, Gajewska J, Laskowska-Klita T (2004) A study of bone turnover markers in prepubertal children with phenylketonuria. Eur J Pediatr 163:177–178

Anastasoaie V, Kurzius L, Forbes P, Waisbren S (2008) Stability of blood phenylalanine levels and IQ in children with phenylketonuria. Mol Genet Metab 95:17–20

Blau N, Bélanger-Quintana A, Demirkol M et al (2009) Optimizing the use of sapropterin (BH4) in the management of phenylketonuria. Mol Genet Metab 96:158–163

Blau N, van Spronsen FJ, Levy HL (2010) Phenylketonuria. Lancet 376:1417–1427

Bosch AM, Tybout W, van Spronsen FJ, de Valk HW, Wijburg FA, Grootenhuis MA (2007) The course of life and quality of life of early and continuously treated Dutch patients with phenylketonuria. J Inherit Metab Dis 30:29–34

Camfield CS, Joseph M, Hurley T, Campbell K, Sanderson S, Camfield PR (2004) Optimal management of phenylketonuria: a centralized expert team is more successful than a decentralized model of care. J Pediatr 145:53–57

Crone MR, van Spronsen FJ, Oudshoorn K, Bekhof J, van Rijn G, Verkerk PH (2005) Behavioural factors related to metabolic control in patients with phenylketonuria. J Inherit Metab Dis 28:627–637

Faderl S, O'Brien S, Pui CH et al (2010) Adult acute lymphoblastic leukemia: concepts and strategies. Cancer 116:1165–1176

Feillet F, Agostini C (2010) Nutritional issues in treating phenylketonuria. J Inherit Metab Dis 33:659–664, Epub Feb 2010

Feillet F, van Spronsen FJ, Macdonald A et al (2010) Challenges and pitfalls in the management of phenylketonuria. Pediatrics 126:233–241

Fekkes M, Theunissen NC, Brugman E et al (2000) Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1-5-year-old children. Qual Life Res 9:961–972

Feldmann R, Denecke J, Grenzebach M, Weglage J (2005) Frontal lobe-dependent functions in treated phenylketonuria: blood phenylalanine concentrations and long-term deficits in adolescents and young adults. J Inherit Metab Dis 28:445–455

Gassió R, Artuch R, Vilaseca MA et al (2005) Cognitive functions in classic phenylketonuria and mild hyperphenylalaninaemia: experience in a paediatric population. Dev Med Child Neurol 47: 443–448

Grootenhuis MA, Stam H, Destree-Vonk A, Heijmans HSA, Last BF (2003) Levensloop vragenlijst voor jong-volwassenen (Course of life questionnaire for Young adults). Gedrag en Gezondheid 31:336–350

Guldberg P, Rey F, Zschocke J, Romano V, François B, Michiels L et al (1998) A European multicenter study of phenylalanine hydroxylase deficiency: classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype. Am J Hum Genet 63:71–79

Hendrikx MM, van der Schot LW, Slijper FM, Huisman J, Kalverboer AF (1994) Phenylketonuria and some aspects of emotional development. Eur J Pediatr 153:832–835

Hoeksma M, Reijngoud DJ, Pruim J, de Valk HW, Paans AM, van Spronsen FJ (2009) Phenylketonuria: high plasma phenylalanine decreases cerebral protein synthesis. Mol Genet Metab 96:177–182

Huijbregts SC, de Sonneville LM, Licht R, van Spronsen FJ, Verkerk PH, Sergeant JA (2002) Sustained attention and inhibition of cognitive interference in treated phenylketonuria: associations with concurrent and lifetime phenylalanine concentrations. Neuropsychologia 40:7–15

Kayaalp E, Treacy E, Waters PJ, Byck S, Nowacki P, Scriver CR (1997) Human phenylalanine hydroxylase mutations and hyperphenylalaninemia phenotypes: a metanalysis of genotype-phenotype correlations. Am J Hum Genet 61:1309–1317

Medical Research Council for Phenylketonuria (1993) Recommendations on the dietary management of phenylketonuria. Report of Medical Research Council Working Party on phenylketonuria. Arch Dis Child 68:426–427

Millet P, Vilaseca MA, Valls C et al (2005) Is deoxypyridinoline a good resorption markerto detect osteopenia in phenylketonuria? Clin Biochem 38:1127–1132

Pietz J, Fätkenheuer B, Burgard P, Armbruster M, Esser G, Schmidt H (1997) Psychiatric disorders in adult patients with early-treated phenylketonuria. Pediatrics 99:345–350

Pietz J, Rupp A, Burgard P, Boesch C, Kreis R (2002) No evidence for individual blood-brain barrier phenylalanine transport to influence clinical outcome in typical phenylketonuria patients. Ann Neurol 52:382–383

Pitt DB, Danks DM (1991) The natural history of untreated phenylketonuria over 20 years. J Paediatr Child Health 27:189–190

Ris MD, Williams SE, Hunt MM, Berry HK, Leslie N (1994) Early-treated phenylketonuria:adult neuropsychologic outcome. J Pediatr 124:388–392

Scriver CR (2007) The PAH gene, phenylketonuria, and a paradigm shift. Hum Mutat 28:831–845

Scriver CR, Kaufman S (2001) Hyperphenylalaninemia: phenylalanine hydroxylase deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Vogelstein B (eds) The metabolic and molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, pp 1667–1724

Scriver CR, Waters PJ (1999) Monogenic traits are not simple: lessons from phenylketonuria. Trends Genet 15:267–272

Simon E, Schwarz M, Roos J et al (2008) Evaluation of quality of life and description of the sociodemographic state in adolescent and young adult patients with phenylketonuria (PKU). Health Qual Life Outcomes 26:25

Sirtori LR, Dutra-Filho CS et al (2005) Oxidative stress in patients with phenylketonuria. Biochim Biophys Acta 1740:68–73

Sullivan JE, Chang P (1999) Review: emotional and behavioural functioning in phenylketonuria. J Pediatr Psychol 24:281–299

van Spronsen FJ, Burgard P (2008) The truth of treating patients with phenylketonuria after childhood: the need for a new guideline. J Inherit Metab Dis 31:673–679

van Spronsen FJ, van Rijn M, Dorgelo B et al (2009a) Phenylalanine tolerance can already reliably be assessed at the age of 2 years in patients with PKU. J Inherit Metab Dis 32:27–31

van Spronsen FJ, Ahring KK, Gizewska M (2009b) PKU – What is daily practice in various centres in Europe? J Inherit Metab Dis 32:58–64

van Spronsen FJ, Hoeksma M, Reijngoud DJ (2009c) Brain dysfunction in phenylketonuria: is phenylalanine toxicity the only possible cause? J Inherit Metab Dis 32:46–51

Vugteveen I, Hoeksma M, Bjorke Monsem AL et al (2010) Serum vitamin B_{12} concentrations within reference values do not exclude functional vitamin B_{12} deficiency in PKU patients of various ages. Mol Genet Metab 102:13–17, Epub October 2010

Waisbren SE, Levy HL (1991) Agoraphobia in phenylketonuria. J Inherit Metab Dis 14:755–764

Waisbren S, White DA (2010) Screening for cognitive and social-emotional problems in individuals with PKU: tools for use in the metabolic clinic. Mol Genet Metab 99(Suppl 1):S96–S99

Waisbren SE, Brown MJ, de Sonneville LM, Levy HL (1994) Review of neuropsychological functioning in treated phenylketonuria: an information processing approach. Acta Paediatr 407:98–103

Waisbren SE, Noel K, Fahrbach K et al (2007) Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab 92:63–70

Weglage J, Fünders B, Wilken B et al (1992) Psychological and social findings in adolescents with phenylketonuria. Eur J Pediatr 151:522–525

Weglage J, Rupp A, Schmidt E (1994) Personality characteristics in patients with phenylketonuria treated early. Pediatr Res 35:611–613

Weglage J, Wiedermann D, Denecke J et al (2001) Individual blood-brain barrier phenylalanine transport determines clinical outcome in phenylketonuria. Ann Neurol 50(463):467