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Minireview

Adult phenylketonuria outcome and management

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ABSTRACT

The problem to evaluate treatment outcome in adult PKU (phenylketonuric) patients lies in the heterogeneity of the adult PKU population. This heterogeneity is not only based on the different treatment history of every individual patient but also on the different severity of the underlying defect of the enzyme phenylalanine hydroxylase. Recent, partly double blind studies in adult PKU patients further support recommendation for lifelong treatment. However, it has become evident that dietary treatment is suboptimal and continuation to adulthood often not accepted.

Late detected PKU patients (up to 4–6 years of age) benefit from strict dietary treatment and are able to catch up in intellectual performance. Untreated, severely retarded patients with behavioral changes may benefit from introduction of dietary treatment. However, individual decision is necessary and based on the personal situation of the patient.

In early and well treated patients a number of studies have demonstrated that cognitive and neurosychologic tests are different from controls. In addition there is evidence that patients with higher blood phenylalanine (phe) levels demonstrate more often psychiatric symptoms like depression and anxiety. Medical problems are more often observed: there are certain risks as impaired growth, decreased bone mineral density and nutrional deficits probably caused by dietary treatment with an artificial protein substitute and/or missing compliance with an unpleasant diet. The long term risk of a strict dietary treatment must be balanced with the risk of higher blood phe (mean blood phenylalanine >600–900 μmol/L) on cognitive and neuropsychological functions and psychiatric symptoms. Further studies should consider the role of blood phe exposure for brain development in childhood and for brain function in all ages. Besides mean blood phe, fluctuation of blood phe over time is important. Fluctuation of blood phe is decreased by sapropterin treatment in responsive patients which would on the long term may have positive effects on cognitive outcome. Further studies also should include adult PKU patients.

Contents

Abbbreviations: phe, phenylalanine; PAH, phenylalanine hydroxylase; PKU, phenylketonuria; BH4, tetrahydrobioptern.

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1. Introduction

The problem to evaluate treatment outcome in adult PKU (phenylketonuric) patients lies in the heterogeneity of the adult PKU population. This heterogeneity is not only based on the different treatment history of every individual patient but also on the different severity of the underlying defect of the enzyme phenylalanine hydroxylase (PAH). More than 600 mutations are described so far (http://www.pahdb.mcgill.ca/).

The other problem consists in the fact that there are no prospective studies available and that in later life other modulators as lifestyle and aging become more important when evaluating brain development and brain function. Long term dietary treatment also shows development of other problems like osteopenia or metabolic imbalances.

Having these problems in mind it is clear that up to now there are no evidence based treatment recommendations and only vague recommendations like “lifelong treatment” with very different suggestions for e.g. the blood phe targets as published in a European survey recently [1].

In this review we would like to describe outcome and management of adult PKU patients excluding maternal PKU but describing the different groups of adult PKU patients we see in our metabolic outpatient clinic.

1. PKU patients never treated, 2. PKU patients late treated (start 1–6 years of age) 3. Patients early treated but early or with poor compliance and 4. Patients early treated with good compliance until adulthood.

Data are based on literature review and personal clinical experiences.

2. Untreated adult PKU patients

Patients with untreated PKU are severely retarded in most cases and in addition may show challenging behavioral problems (Table 1). Treatment studies in untreated PKU's are difficult to perform. Besides ethical issues to conduct such studies measurement of improvement is difficult. The results are controversial, the study population always small. In some studies severity of behavioral disturbances may be reduced after introduction of a phe restricted diet [2], Table 1. In a recent placebo controlled study in 17 patients [3] a significant difference between treatment and placebo group using standardized test procedures could not be demonstrated. However, the positive comments of carers in the treatment group were significant in respect to a positive change than in the placebo group. This indicates a positive effect in individual patients and the authors conclude that “this intervention should be offered to these individuals” [3]. According to our personal experiences a close monitoring, not only of the blood phe levels but also of the general health condition of these patients should be performed: excessive weight loss and development of dystrophy might be a severe side effect after introduction of a low phe diet. We also experienced that treatment of patients living still in the family is easier. Experiences of family members with the diet and a better environment may be reasons for this (Trefz, unpublished).

Table 1
Symptoms and change of symptoms in 6 untreated PKU patients under dietary treatment. SIB: self injurious behavior.
Adapted from Baumeister and Baumeister [3].

Patient/symptoms	% change	Treatment (months)
1/SIB	−93%	36
2/Assault/SIB face gouging	−91% −48%	26
3/SIB	−13%	9
4/Tantrums	−69%	9
5/Stereotypes	−54%	3
6/Hyperactivity	No change	3

In summary, a general recommendation for a phe restricted diet in severely retarded PKU patients cannot be given. Individual conditions should be considered and quality of life should not worsen especially in severely retarded patients with behavioral problems. On the other hand in some patients a blood phe level below 900 μmol/L may result in reduction of behavioral problems and increase of attention.

3. Treatment in late diagnosed but treated PKU patients

Introduction of newborn screening and early dietary treatment resulted in the prevention of severe brain damage. However, due to screening failures and immigration of patients from countries where early detection and treatment of PKU is not yet established, there are a number of untreated PKU's in many European centers. In the last 20 years we saw in one center (Reutlingen, Germany) 10 patients missed by newborn screening due to various reasons (Table 2). After introduction of tandem mass spectrometry and a better computerized sample handling in the screening laboratories one can expect that missed cases will be minimized in the future. However, there are still a number of immigrants coming from countries where newborn screening is not yet established.

From early prescreening experiences it is well known that after introduction of dietary treatment in later infancy and childhood partial reversibility of IQ loss may occur. Catch up of development retardation is especially seen in the first 4–6 years of life [4], but there is a large heterogeneity of treatment success as also shown recently in a review by Grosse [5].

As pointed out in this paper and based on personal experiences there is often an impressive improvement of development when introducing a phe restricted diet even in very late detected PKU patients. All of these patients benefit from a dietary treatment with phe levels <600 μmol/L beyond infancy and young adulthood. One may speculate that in these patients elevated blood phe levels cause brain dysfunction more likely than in early treated patients with an unaffected brain.

4. Outcome in early treated but early discontinued patients

For many years dietary treatment of PKU was terminated at 10 years of age, in some countries even at 6 years of age. Investigations in patients with early diet termination revealed that there was a loss of intellectual function [6]. Koch and coworkers [7] could demonstrate that patients continuing the diet until adulthood had a better outcome than those who stopped the diet earlier. In addition in this collaborative study Koch et al. could demonstrate that treatment quality also had an influence on outcome: adults who had continued a dietary control with blood phe levels <15.6 mg/dL had a better IQ

Table 2
Neonatal screening failure in 10 patients with phenylketonuria (Trefz, unpublished); Phe = phenylalanine.

Patient	Age at diagnosis (years)	Phe-level at diagnosis (mg/dL)	Reason for not screening, remarks
1	1.5	28	Born in Brazil
2	9	25	Unclear
3	3.5	32	Mixed blood on screening card
4	1.5	24	Lab mistake
5	7	21	Russian immigrant
6	7	>20	Russian immigrant
7	2.5	27	Turkish guest worker family
8	0.8	>20	Lab mistake
9	1	>20	Lab mistake
10	1.5	>20	Lab mistake, infant with Down Syndome and PKU!