

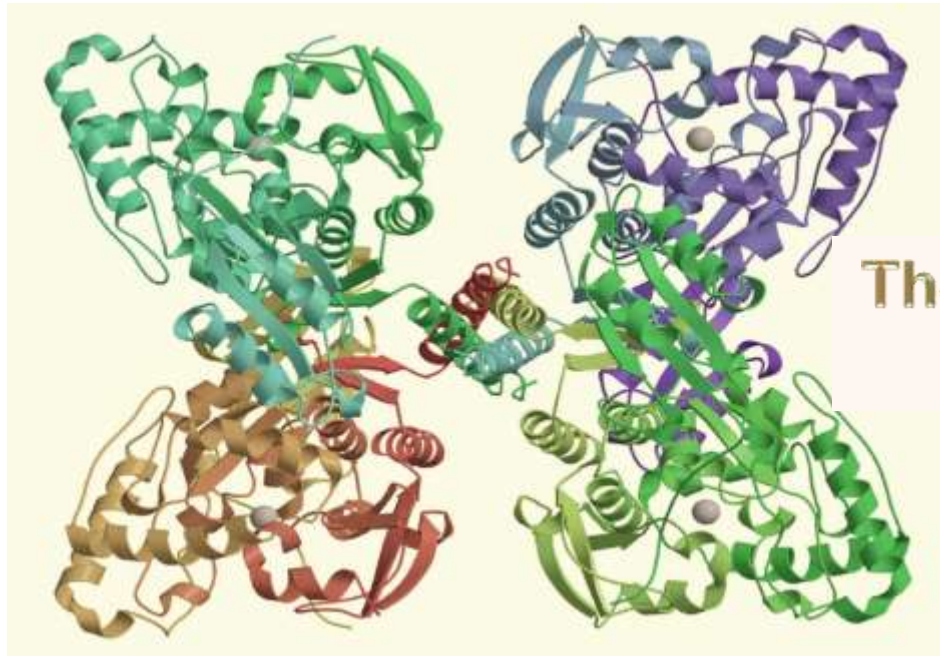


PHENYLKETONURIA

PKU

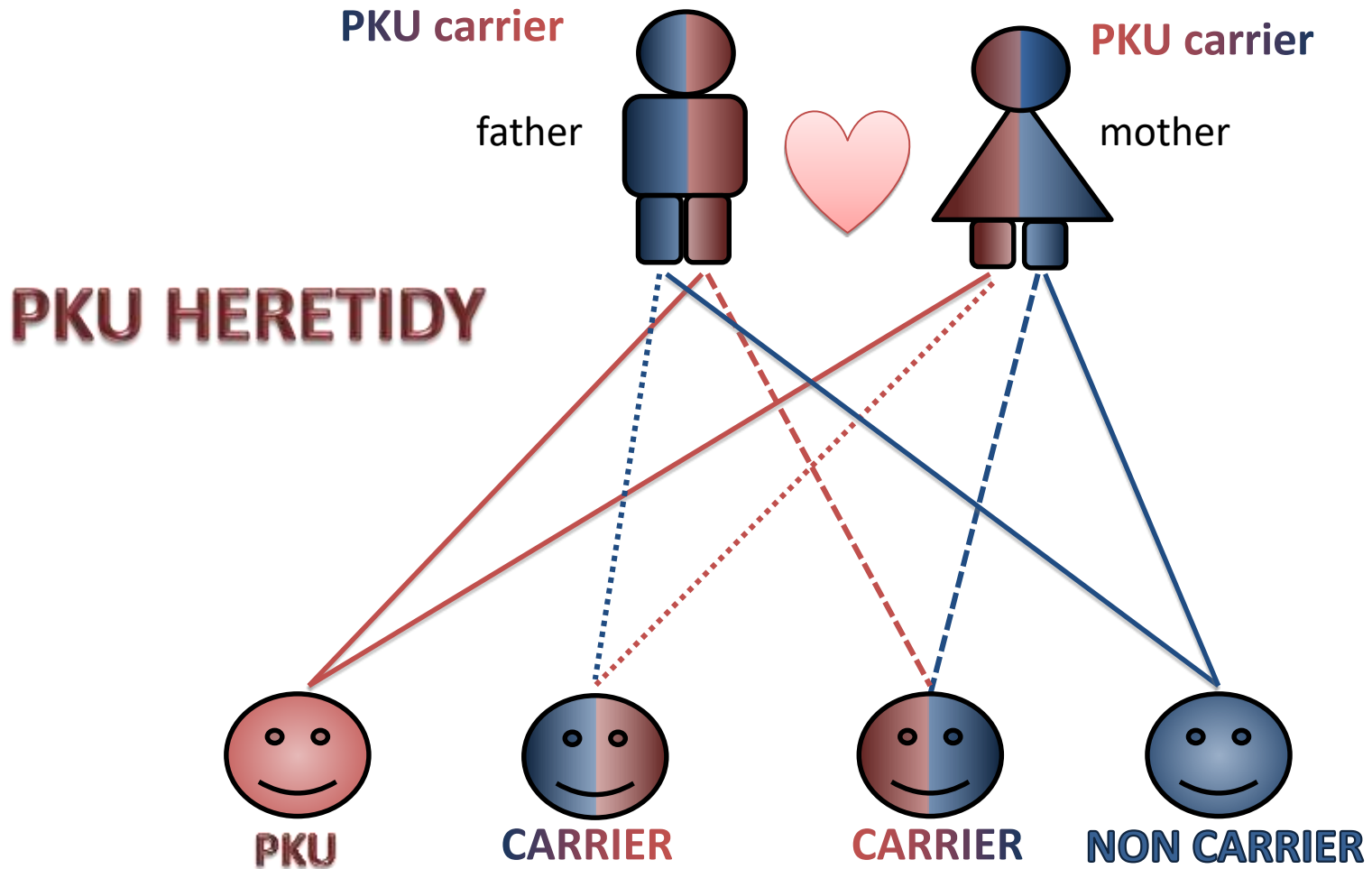
**Astrinia Skapalezou BSc, MSc
Clin. Nutritionist-Metabolic Dietitian
National Neonatal Screening dept.-I.E.M.
Institute of Child Health, Athens, Greece**

Phenylketonuria (PKU OMIM#261600) is an autosomal recessive inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase (PAH), an enzyme that catalyzes the hydroxylation of phenylalanine to tyrosine, the rate-limiting step in phenylalanine catabolism. If undiagnosed and untreated, phenylketonuria can result in impaired postnatal cognitive development resulting from a neurotoxic effect of hyperphenylalaninemia



The protein structure of PAH enzyme

PKU IS AN INBORN ERROR OF HUMAN METABOLISM



**PKU IS INHERITED TO THE CHILD BY BOTH PARENTS
EQUALLY**

**The PKU baby is protected
during pregnancy...**



...thanks to his/her mother's metabolism

PKU starts to appear after the 1st meal

PKU



PKU



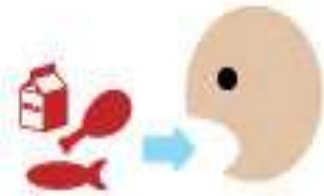
PEOPLE with classical **PKU** CAN NOT

- . use **PHE** into their body
- . convert **PHE** to tyrosine



LATE DIAGNOSED – OF DIET PKU PERSON





Foods with Phe are eaten



A defective enzyme (PAH) in the body fails to break down the Phe



This leads to high Phe levels in the blood

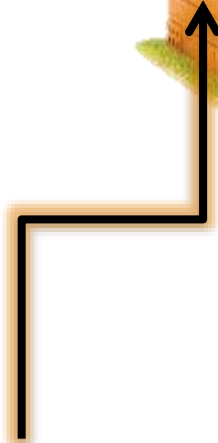


This leads to problems in thinking and behavior



What is PHENYLALANINE?

depicting the human body as... a house



the **WALLS** play the role of the body **PROTEIN**

NON PKU wall



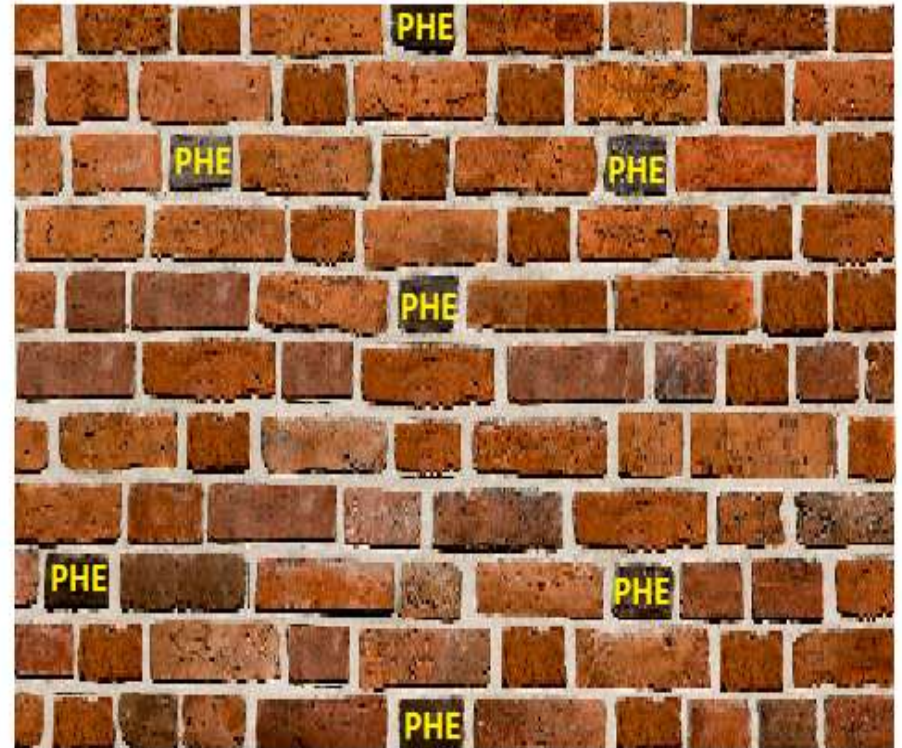
needs MORE PHE

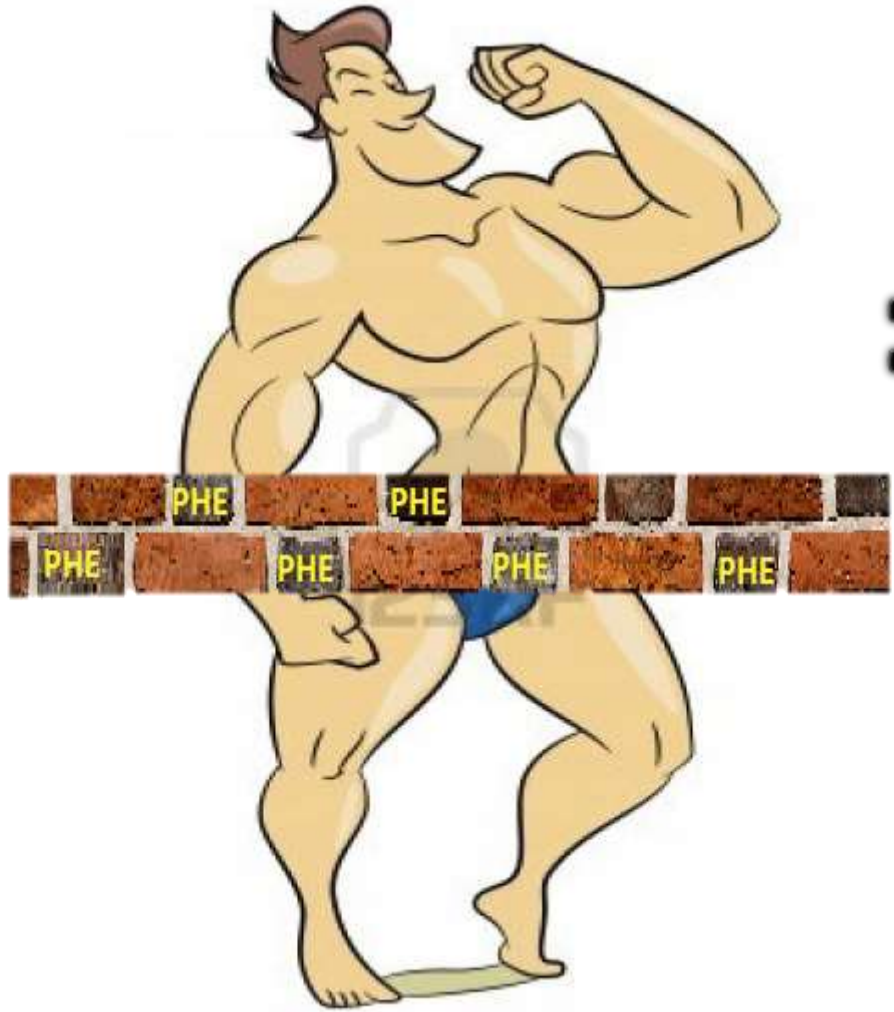


PKU wall



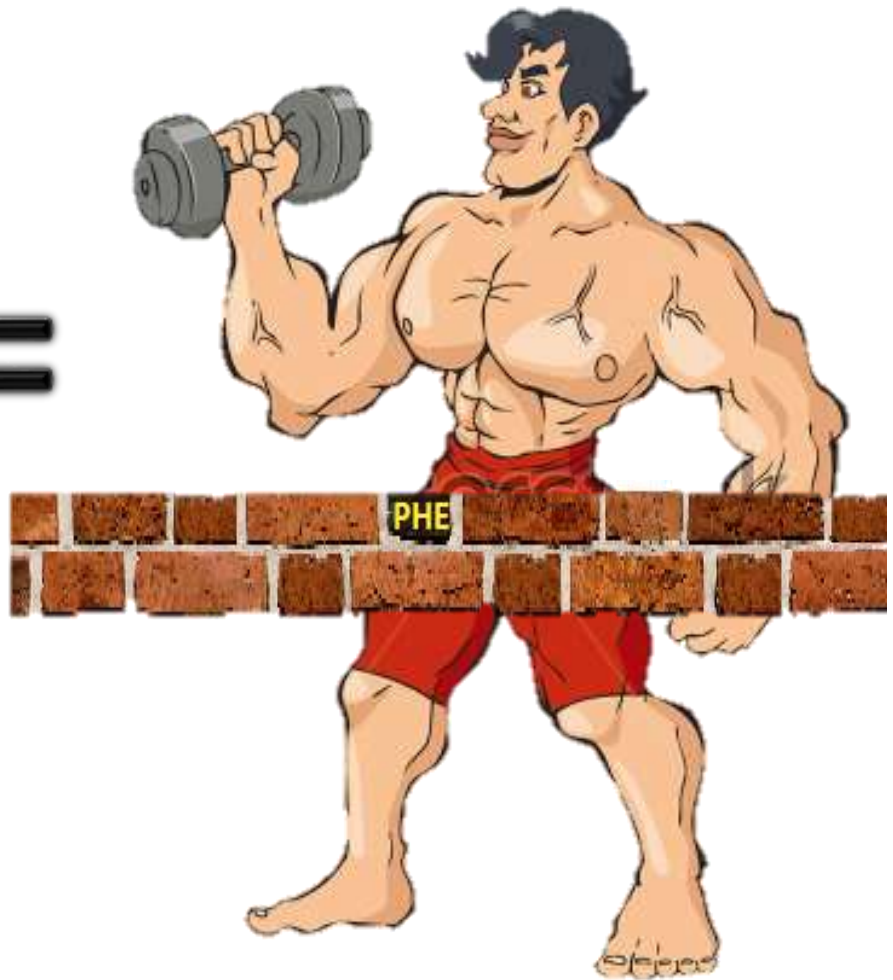
needs LESS PHE





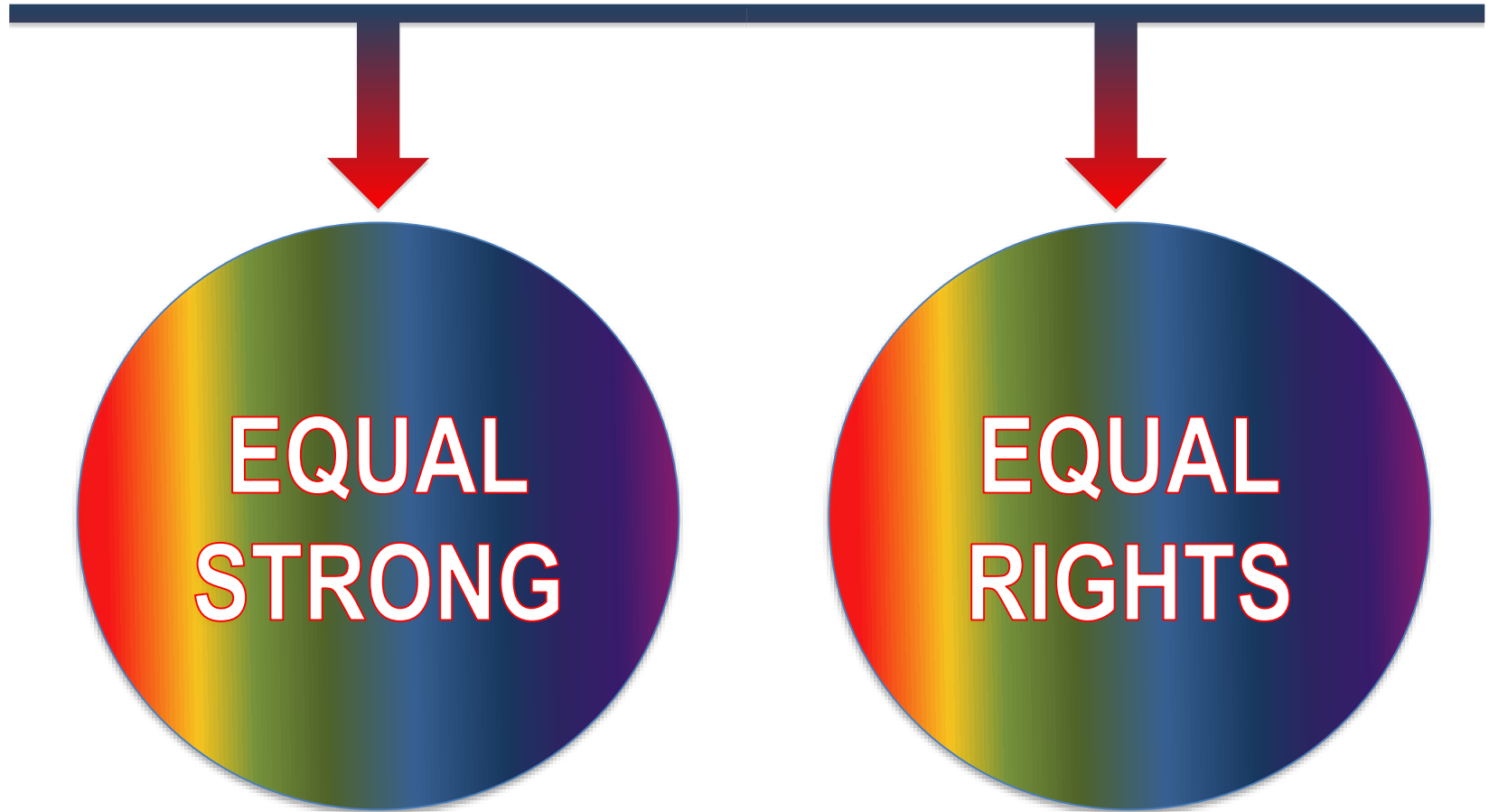
NON PKU

=



PKU

PKU DIET



**EQUAL
STRONG**

**EQUAL
RIGHTS**



High Phenylalanine Foods:

Low Phenylalanine Foods:

Fish
 A whole fish, likely salmon or trout.

Meat
 Slices of raw meat, possibly chicken or beef.

Beans
 A green bean.

Dairy
 A carton of milk and a wedge of cheese.

Wheat
 Slices of white bread.

Eggs
 A cracked egg on a plate.

Nuts & Legumes
 A few nuts, possibly almonds.

Diet Soda
 A can of diet soda with a red and yellow label.

ASPARTAME
 A logo for aspartame, consisting of the word "ASPARTAME" in a red oval with a diagonal slash through it.

High-Protein Foods

Most Vegetables
 Corn, broccoli, green bell pepper, tomato, and cucumber.

Most Fruit
 Pineapple and purple grapes.

Sugars
 A can of sugar.

Special Formula
 A can of special formula.

Special Breads, Cookies, Crackers
 A slice of white bread, a cookie, and a cracker.

Low-Protein Foods



COMMON FOOD GROUPS

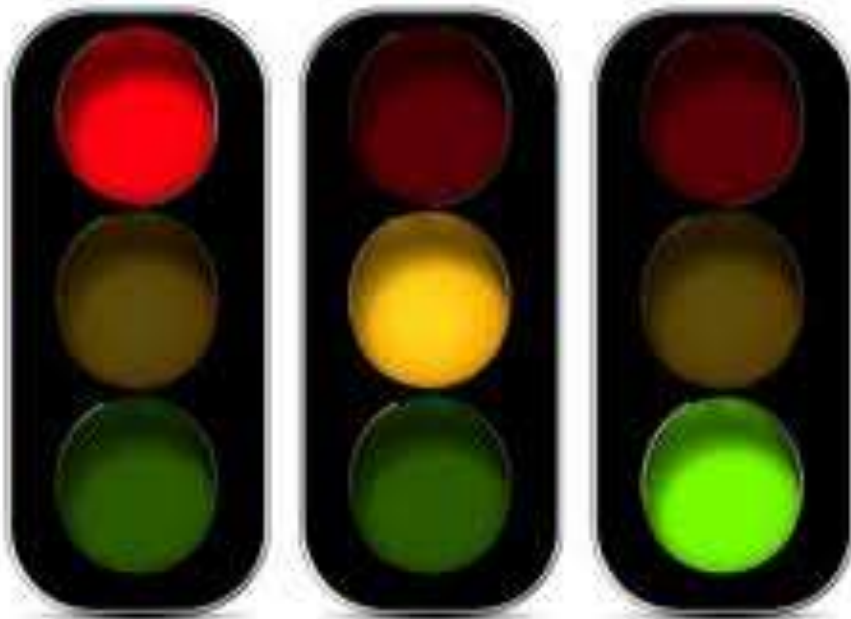


PKU FOOD GROUPS

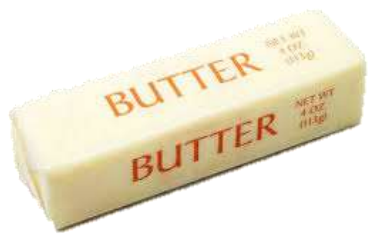
PKU FOOD PYRAMID



TRAFFIC LIGHT SYSTEM



**USE TRAFFIC
LIGHT SYSTEM
TO CHOOSE
THE RIGHT
FOODS FOR
PKU DIET**



+ special food







ALL FAMILY MEMBERS MUST HAVE THEIR MEALS TOGETHER





INTERNET



LOW PROTEIN FOOD

FOOD FOR ALLERGY

DIABETIC FOOD



Gluten Free



Lactose free



Egg free

Food Icons

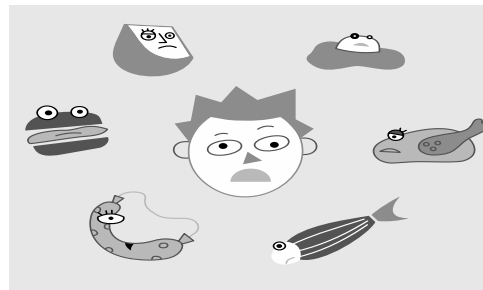
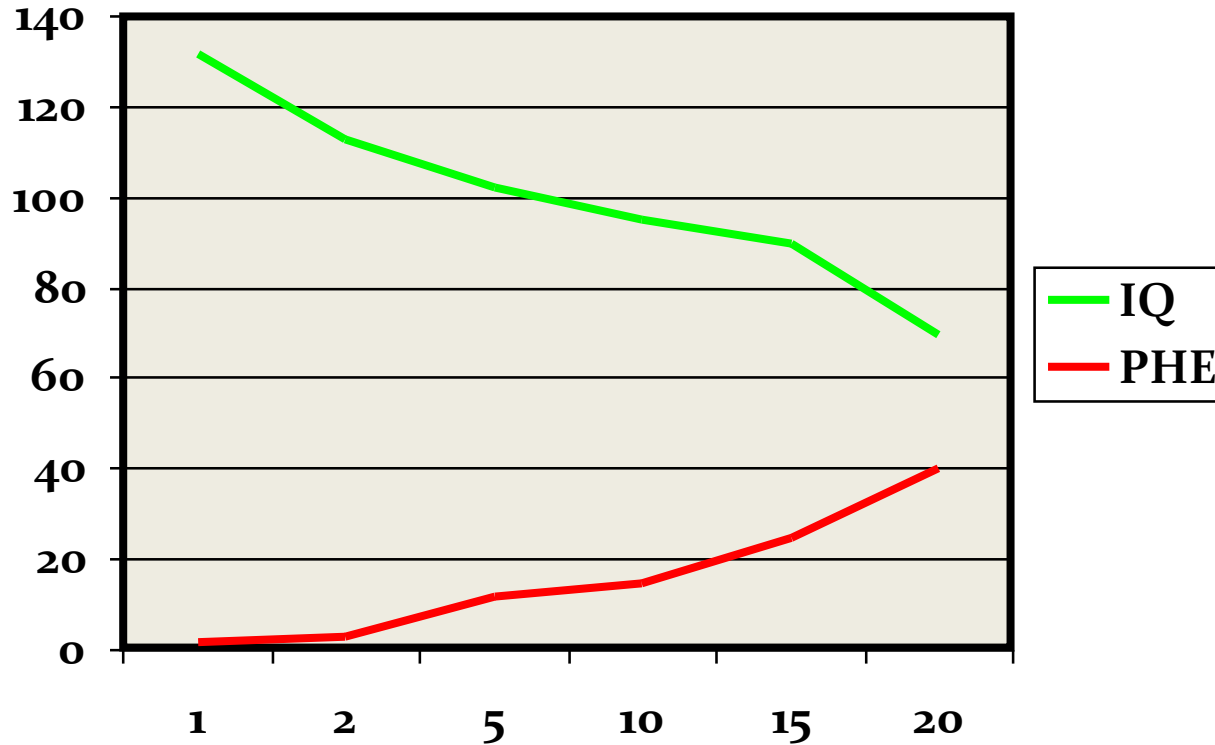


GLUTEN FREE FOOD



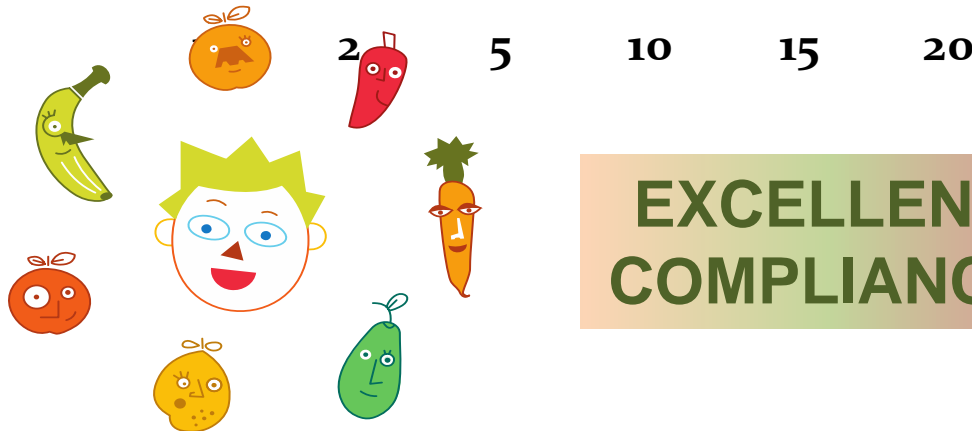
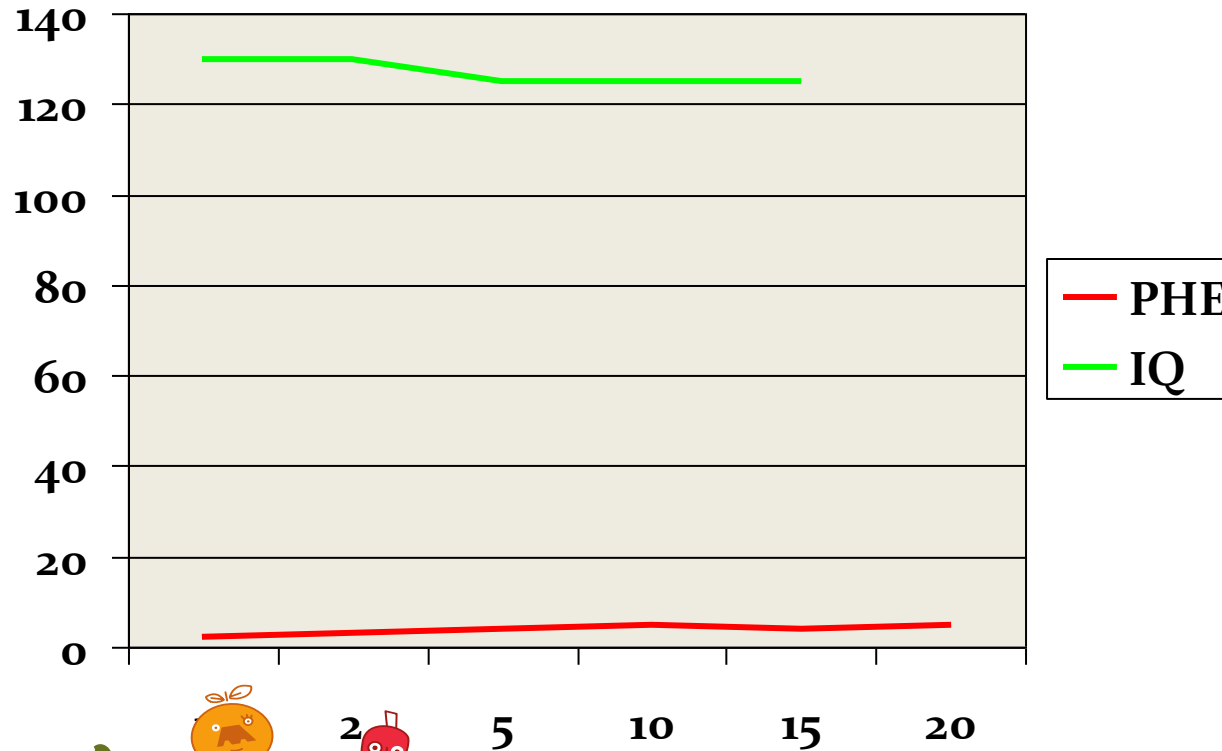
Gluten free

BLOOD PHE and IQ



Non compliance

BLOOD PHE and IQ

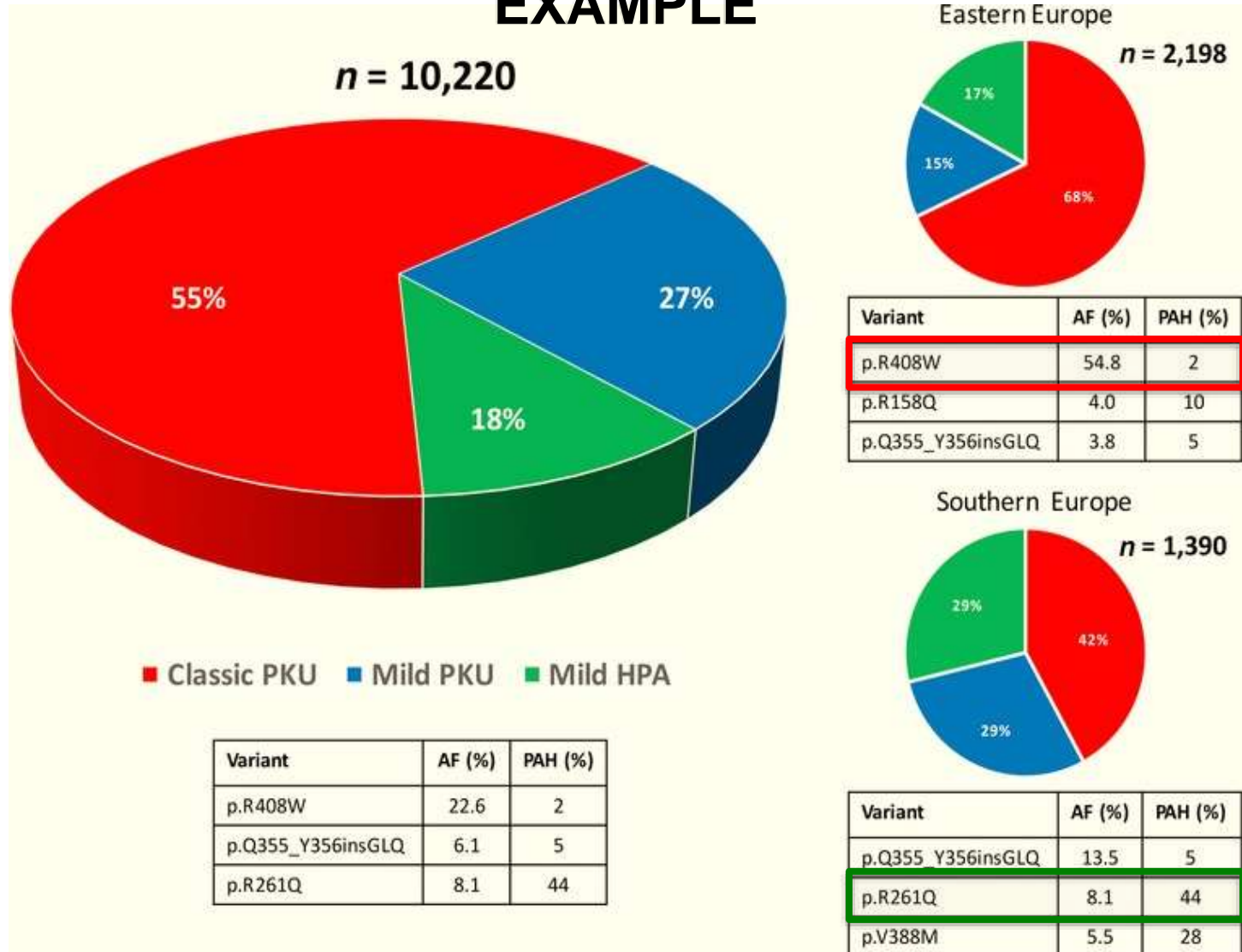


**EXCELLENT
COMPLIANCE**

PKU CLINICAL PHENOTYPES

<u>CLINICAL PHENOTYPE</u>	<u>OF DIET BLOOD PHE LEVELS</u>	<u>DIETETIC PHE TOLERANCE</u>
Non PKU hyperphenylalaninemia (MHP)	<600 $\mu\text{mol/L}$ < 10 mg/dl	>1000 mg /day
Mild or atypical phenylketonuria (mPKU)	600-1200 $\mu\text{mol/L}$ 10-20 mg/dl	450 - 1000 mg/day
<u>Classical or severe phenylketonuria (sPKU)</u>	>1200 $\mu\text{mol/L}$ >20 mg/dl	250 - 450 mg/ημέρα

GLOBAL DISTRIBUTION OF PKU PHENOTYPES + TWO EUROPEAN DISTRICT EXAMPLE



(Blau N. Human Mutation, 2016)

2014

REVIEW

Open Access

Requirements for a minimum standard of care for phenylketonuria: the patients' perspective

Tobias S Hegdalen^{1,2*}, Paul van Berckel³, Godefridus Hammeerschroek⁴, Marinka Chruskowi⁵ and Rosalia Perceval Salvador⁶

Abstract

Phenylketonuria (PKU, OMIM#261600) is an inherited disorder that affects about one in every 10,000 children born in Europe. Early and continuous application of a modified diet is regarded as a largely successful in preventing the devastating brain damage associated with untreated PKU. The management of PKU is demanding; there are few national guidelines, and those tend to be incomplete and implemented sporadically. In this article, the first ever pan-European patients' and carers' perspective on optimal PKU care, the European Society for Phenylketonuria and Allied Disorders (E.S.PKU) proposes recommendations for a minimum standard of care for PKU to underpin the development of new pan-European guidelines for the management of PKU. New standards of best practice should guarantee equal access to screening, treatment and monitoring throughout Europe. Screening protocols and interpretation of screening results should be harmonized. Improved Care of Europe are required in line with current European standards to guarantee a defined standard of multidisciplinary treatment and care for all levels of and social aspects of PKU. Women of childbearing age require especially intensive management, due to the risk of severe fetal or foetal demise confirmed by uncontrolled PKU. All aspects of treatment should be reimbursed to ensure uniform access across Europe to guidelines-driven, evidence-based care. The E.S.PKU urges PKU healthcare professionals caring for people with PKU to take the lead in developing evidence based guidelines on PKU, while continuing to play an active role in working in the voice of patients and their families, whose lives are affected by the condition.

Keywords: Phenylketonuria, Standards of care, Screening, Guidelines, Europe, Care of Europe, Healthcare equity, Patient advocacy, Patient group, Patient voice

Introduction

Phenylketonuria (PKU, OMIM#261600) is a rare inherited disorder that affects around one in every 10,000 children born in Europe [1]. The metabolic defect underlying PKU is a mutation in the gene coding for the enzyme, phenylalanine hydroxylase (PAH), which is responsible for the transformation of phenylalanine into tyrosine [2-4]. Impairment of PAH activity in PKU causes increased levels of phenylalanine that if untreated cause devastating damage to the brain, with severe mental disability, reduced IQ, seizures and tics, impaired executive function, psychological and behavioural issues and

More patients with PKU are identified during neonatal screening [5] and all patients then require lifelong treatment [5]. The mainstay of the therapeutic management of PKU is a modified diet that includes specially processed low leucine protein, and phenylalanine-free amino acid supplements [6]. Maximising adequate adherence to this diet is challenging, but essential in preventing the severe brain damage associated with uncontrolled blood phenylalanine, and allowing individuals with PKU to lead full and successful lives [5,7-9]. A pharmacologic treatment option, sapropterin, is available for prescriptions in a growing number of countries [10,11]. A number of other pharm-



ALTER, Belgium – 20 January 2014 – the first ever pan-European patient/carers perspective on optimal care of the rare genetic disorder phenylketonuria (PKU) has been published in the Orphanet Journal of Rare Diseases

REVIEW

Open Access

The complete European guidelines on phenylketonuria: diagnosis and treatment



A. M. J. van Wageningen¹, A. MacDonald², K. Allery³, A. Blango-Gonzalez⁴, H. Blau^{5,6}, A. W. Bosch⁷, A. Buñuel⁸, J. Campese⁹, F. Colla¹⁰, M. Gnanoli¹¹, S. C. Hudrych¹², S. Kearney¹³, V. Jozwiłł¹⁴, J. Maller¹⁵, A. C. Munari¹⁶, M. van Rijn¹⁷, J. Tefti¹⁸, J. H. Wake¹⁹ and T. J. van Gennip^{20*}

Abstract: Phenylketonuria (PKU) is an autosomal recessive clinical form of phenylalanine metabolism caused by deficiency in the enzyme phenylalanine hydroxylase. This converts phenylalanine into tyrosine. If left untreated, PKU results in increased phenylalanine concentrations in blood and brain, which cause severe intellectual disability, epilepsy and behavioural problems. PKU management differs widely across Europe and therefore these guidelines have been developed aiming to optimize and standardize PKU care. Professionals from 12 different European countries developed the guidelines according to the AGREE (Appraisal of Guidelines for Research and Evaluation) method. Literature search, critical appraisal and evidence grading were conducted according to the SIGN (Scottish Intercollegiate Guidelines Network) method. The Delphi method was used when there was no or little evidence available. General conclusions included the guidelines using these methods. 39 statements were formulated based on the highest quality evidence available. The level of evidence of most recommendations is C to D. Although study designs and patient numbers are not optimal, many statements are convincing, important and relevant. In addition, knowledge gaps are identified which require further research in order to deliver better care for the future.

Keywords: Consensus, Guidelines, Phenylalanine hydroxylase deficiency, PAH deficiency, Phenylketonuria, PKU, Hypophenylalaninemia, Phenylalanine, Treatment, Management, Recommendations, Tyrosylhydroxylase, Substrate

Background

Phenylketonuria (PKU; MeSHcode #204000) is a very rare autosomal recessive clinical form of phenylalanine (Phe) metabolism caused by variants in the gene encoding phenylalanine hydroxylase (PAH). PAH normally converts the toxic toxicant (Tyr) requiring the cofactor tetrahydrobiopterin (BH4), into tyrosine (Tyr) and iron (Fig. 1) [1]. PAH deficiency leads to accumulation of Phe in the blood and brain. Untreated, PKU is characterized by irreversible intellectual disability, microcephaly, motor deficits, scoliosis, tooth, autism, seizures, developmental problems, abnormal behaviour and psychiatric symptoms. The precise pathogenesis

of these symptoms is still unclear (Fig. 2) [2]. As high blood Phe concentrations are strongly related to neurocognitive outcome, existing treatments aim at decreasing blood Phe concentrations. PKU was identified in 1934 by Guthrie when he detected glyoxylic acid in the urine of affected individuals and in 1953, Bickel has reported the effectiveness of a low-Phe diet in a child with PKU. In the 1960s, Guthrie developed a simple test to detect hypophenylalaninemia (HPA) in large populations. This led to PKU becoming the first disorder to benefit from newborn screening. In such detection and treatment prevented mental retardation. However, the NBS screen is for HPA and this is defined as any blood Phe >120 µmol/L. Therefore, in most positive NBS for Phe, primary phenylalanine hydroxylase deficiency should be

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2017



Panel 3: Key recommendations for patients with phenylketonuria (PKU)

The grades range from ✓ (no possibility to assess the level of evidence because of a lack of any published work on this issue) to as high as B. The key recommendations were either based on evidence (if level of evidence was A or B using the SIGN method) or by consensus (using the Delphi method) if the level of evidence was C or D, or the so-called good practice points that are not based on any evidence if the level was ✓.

Statement 1

Grade of recommendation: ✓

To maintain blood phenylalanine concentrations in the recommended range, patients with phenylalanine hydroxylase (PAH) deficiency can be classified as either not requiring treatment, or requiring diet or tetrahydrobiopterin (BH4), or both.

Statement 2

Grade of recommendation:* C

In the differential diagnosis of hyperphenylalaninaemia, of any degree, BH4 deficiencies should be excluded by measurement of pterins in blood or urine and dihydropteridine reductase activity in dried blood spot.

Statement 3

Grade of recommendation: D/C

Patients with untreated blood phenylalanine concentrations less than 360 µmol/L do not require treatment. Patients with untreated blood phenylalanine levels more than 360 µmol/L should be treated. Patients with untreated phenylalanine levels between 360 µmol/L and 600 µmol/L should be treated until the age of 12 years. Patients with untreated phenylalanine levels more than 600 µmol/L should be treated for life.

Statement 4

Grade of recommendation: C

All adults with PKU should have life-long, systematic follow-up in specialised metabolic centres, because of specific risks that might occur during adulthood.

Statement 5

Grade of recommendation: B

In treated patients with PKU up to the age of 12 years, target

Statement 7

Grade of recommendation: B

In pregnant patients treated for PKU the target phenylalanine concentrations should be 120–360 µmol/L.

Statement 8

Grade of recommendation: B

Women with untreated blood phenylalanine concentrations less than 360 µmol/L do not require treatment to lower blood phenylalanine before or during pregnancy.

Statement 9

Grade of recommendation: C

An annual nutritional review is required for any patient who is on a prescribed low phenylalanine diet or is self-restricting high protein foods. Such review must include a clinical examination including the anthropometric parameters (weight, height, BMI). We also recommended that plasma aminoacids, plasma homocysteine or methylmalonic acid, haemoglobin, mean corpuscular volume, and ferritin are measured. All other micronutrients (vitamins and minerals including calcium, zinc, selenium) or hormones (parathyroid hormone) can be considered if clinically indicated.

Statement 10

Grade of recommendation: ✓


In patients younger than 12 years, when more than 50% of the phenylalanine concentrations are out of target range over a period of 6 months, consider: (1) increased frequency of blood phenylalanine monitoring and outpatient visits and re-education, (2) psychology consultation or social worker intervention, and (3) hospital admission. When around 100% of blood phenylalanine concentrations are out of target range over a period of 6 months and there are other signs of failure of adherence, such as lack of cooperation, clinic non-attendance, or unresolved issues outside PKU consider consultation with social services and child safeguarding measures.

*Level of evidence is chosen as C because of the high number of data notwithstanding that most included papers are of descriptive nature.

KEY RECOMMENDATIONS

Statement 3 Grade of recommendation: D/C Patients with untreated blood phenylalanine concentrations less than 360 $\mu\text{mol/L}$ do not require treatment. Patients with untreated blood phenylalanine levels more than 360 $\mu\text{mol/L}$ should be treated. Patients with untreated phenylalanine levels between 360 $\mu\text{mol/L}$ and 600 $\mu\text{mol/L}$ should be treated until the age of 12 years. Patients with untreated phenylalanine levels more than 600 $\mu\text{mol/L}$ should be treated for life.

Statement 5 Grade of recommendation: B In treated patients with PKU up to the age of 12 years, target phenylalanine concentrations should be 120–360 $\mu\text{mol/L}$. **Statement 6 Grade of recommendation: D** In treated patients with PKU aged 12 years or older, the target phenylalanine concentrations should be 120–600 $\mu\text{mol/L}$.



STATEMENT #34. Grade of recommendation:  **C**

In infants with PKU, breast-feeding in combination with a Phe-free infant L-amino acid formula should be encouraged. It is associated with long-term satisfactory blood Phe control and growth.

Statement 4 Grade of recommendation: C All adults with PKU should have life-long, systematic follow-up in specialised metabolic centres, because of specific risks that might occur during adulthood

Statement 7 Grade of recommendation: B In pregnant patients treated for PKU the target phenylalanine concentrations should be 120–360 $\mu\text{mol/L}$

TARGET BLOOD PHE LEVELS

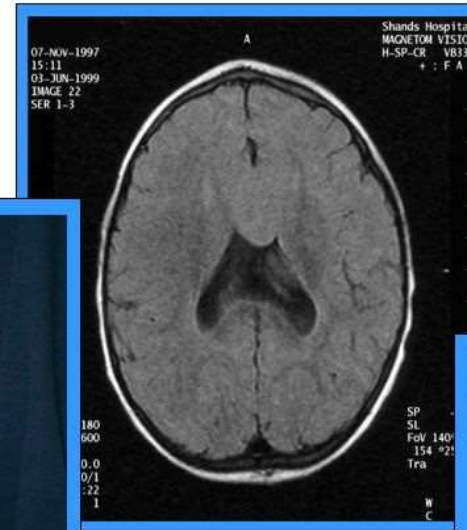
- 0-12 YEARS  2 – 6 mg/dl (120-360 μ mol/L)
2 – 4 mg/dl = perfect levels
- > 12 YEARS  6-10 mg/dl (360-600 μ mol/L)

GIRLS: IDEALLY < 6 mg/dl at all ages (MATERNAL PKU)

MATERNAL PKU SYNDROME

- Mental retardation
- Microcephaly
- Congenital Heart Disease
- Small for date

Maternal PKU – Severe mental retardation, microcephaly, cardiac abnormalities

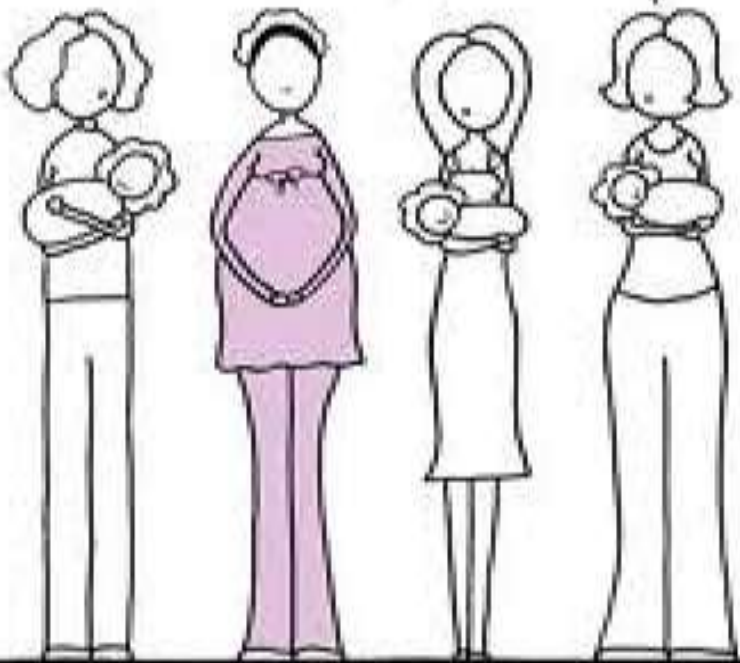


mother : fetus phe → 1:1,5 (1,1-2,9)

The fetus

- **is exposed to higher phe concentration than the mother**
- **is at risk to be affected even by small blood phe fluctuations**
- **is at the highest risk of developing damages during the 1st trimester of pregnancy**

YOU SHOULD NOT FORGET



**EVERY PKU WOMAN
CAN DELIVER
A HEALTHY BABY.**

JUST STAY ON DIET

**Target blood phe : 2-6 mg/dl
(120 – 360 μ mol/L)**

**2,5 – 4 mg/dl = perfect balance
(150 – 240 μ mol/L)**

KUVAN

- **Synthetic form of BH4**
- **BH4 is natural compound of PAH**
- **First non dietetic successful therapeutic approach of PKU.**



KUVAN

- Responsiveness depends mostly on genotype
- Some mutations respond better than others
- Null mutations do not respond

BUT

- **Genotype – phenotype correlations sometimes show surprising or unexpected results.**
- **No genotype needed for PKU patients of diet for many years.**

BH4 responsiveness In this Review we defined BH4 responsiveness as an increase of 100% or more in natural protein or improved biochemical control (>75% of phenylalanine levels in target range), or both, on a dose of BH4 that ranges between 10–20 mg/kg bodyweight (with a maximum dose of 1000 or 1400 mg per day in some countries).

- **Age > 4 yrs**
- **Responsiveness test starting dose: 10 mg/Kg BW**
- **20 mg/Kg BW is maximum dose**
- **Very strict dietetic control during the responsiveness test**
- **Target: $\geq 30\%$ μείωση των επιπέδων phe αίματος και $\geq 50\%$ dietetic phe tolerance**

Statement 1

Grade of recommendation: ✓

To maintain blood phenylalanine concentrations in the recommended range, patients with phenylalanine hydroxylase (PAH) deficiency can be classified as either not requiring treatment, or requiring diet or tetrahydrobiopterin (BH4), or both.

New PKU patients' classification

- **No treatment**
- **Low phe diet**
- **BH4 supplementantation**
- **Low phe diet + BH4**





Support PKU Awareness

supportourribbons.com

What all countries need to do ???



Newborn screening!!!

INSTITUTE OF CHILD HEALTH



Ινστιτούτο Υγείας του Παιδιού



www.ich.gr



1969
Screening pilot phase

1972
Start of the Greek National
Neonatal Screening Program



Births: $\sim 100.000/\text{year}$

PKU - HyperPHE: $\sim 8-10$ neonates/year

Diagnosis age: $\sim 10-15$ days



Ινστιτούτο Υγείας του Παιδιού

Routine Procedure after abnormal findings in PKU Guthrie Test

- Urgent invitation to the clinic (phone call)
- Confirmation of diagnosis → Guthrie - Total blood amino acid profile – Phe:Tyr ratio
- Differential diagnosis → Biopterines - DHPR activity in blood spots - 24h loading test with BH4
- Onset of treatment
- Genotyping



~~PKU~~

PKU



~~PKU~~

PKU



DIET

Thank you



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