

Current Recommendations and Guidelines for Diet for Life

Jerry Feldman, MD, PhD
Program Director, Newborn Screening Management Program
Children's Hospital of Michigan
Wayne State University School of Medicine
jfeldman@chcm.gvsu.edu

History of Phenylketonuria

- First inborn error of metabolism identified through population-based screening
 - First described in 1934
 - First treated patient in the 1950s
- Underlying biochemical diagnosis identified as deficiency of phenylalanine hydroxylase (PAH)

History of PAH Deficiency

- PAH deficiency accurately describes spectrum of clinical phenotypes
- Many different terms used over the years which relied on blood phenylalanine level if untreated
 - “hyperphenylalaninemia” →→→“classic”
- PAH deficiency now preferred as unifying diagnosis

History of PAH Deficiency Treatment

- Initiation of diet therapy recommended for all infants identified, primarily through NBS
- Dietary reference intakes dependent on many factors, including amount of PAH activity, patient age, growth rate, concurrent illnesses, etc
 - Blood phe level final determinant of dietary phe intake
- Low protein foods and phe-free medical formulas medically necessary – should be regarded as medications!

History of PAH Deficiency Treatment

- Until recently, diet was the only treatment option
- Synthetic form (Saproterin) of PAH cofactor, tetrahydrobiopterin (BH4), approved in 2007
 - Helps increase metabolism of phe in patients with some remaining PAH activity
- Polyethyleneglycol conjugated phenylalanine ammonium lyase (PEG-PAL)
 - Breaks down blood phe by a different mechanism
 - Requires daily subcutaneous injection

History of PAH Deficiency Treatment

- Difficult to find information about history of treatment, but best I can figure, treatment was initially maintained through early childhood, then age 18, and now Diet for Life
 - 1972, diet discontinuation in early school age was the most common practice
 - From a personal note from a dietitian in Wisconsin
 - »“By around 1978, a number of children in our clinic who stopped the diet had already developed problems...We finally adopted a policy of continuing the diet indefinitely in 1978 or 1979. At that time, there was also increasing evidence in the scientific literature suggesting it was unsafe to stop the diet at a young age”.

NIH Consensus Statement - 1993

- 1993 National PKU Treatment Guidelines and Standards are developed at a National Institutes of Health Consensus Conference to make PKU treatment more uniform in the US. "Treatment for Life" is emphasized though not universally prescribed

Diet for Life – NIH Consensus Statement 2000

- To achieve optimal metabolic control and outcome, a restricted-Phe diet ...most likely will be medically required for virtually all individuals with classical PKU for their entire lifetimes
- ...data suggest that elevated Phe levels in adolescents and adults adversely affect aspects of cognitive function, ...deterioration of adult PKU patients after diet discontinuation
- Persons who have discontinued diet should contact their clinic advisability of resuming treatment

NIH Consensus 2000

- A programmatic, multidisciplinary approach to lifelong care is required for the treatment of PKU with sensitivity to the transition from screening to treatment. Continuity of care from infancy through adulthood is considered medically necessary for optimal outcomes for individuals with PKU.

NIH Consensus Statement 2000

- Conclusion...
Metabolic control is necessary across the lifespan of individuals with PKU

Current Recommendations – Why Treatment for Life?

- Essential to optimal functioning of individuals with PAH deficiency
- Adverse neurocognitive and psychiatric symptoms if relaxation of diet later in life
 - Deficits in executive functioning
 - Anxiety, depression, phobias
- Can be disabling resulting in lower level of educational attainment and socioeconomic status

Maternal Phenylketonuria

- Success of newborn screening programs over last 40 years → women with PKU having children
- Past treatment: stopping diet during adolescence
 - Treatment now: lifelong dietary restriction
- Elevated maternal phe levels cause birth defects (teratogenic effect)
 - Infants are unaffected with PKU but....
 - Cognitive impairment, small head size, heart defects, growth deficiency
- Why is maternal management difficult?

Current Recommendations – Why Treatment for Life?

- Difficult to return to metabolic control once off diet
- Adherence requires tasks such as planning and organization.....that rely on executive functioning abilities.....that are impacted by high phe levels



Current Recommendations

- Treatment for PAH deficiency should be lifelong for patients with “classic PKU”
- Treatment for maternal PKU must be instituted prior to conception and continue post-partum for optimal maternal/infant outcomes
- Treatment for life mandates the need for medical insurance to provide coverage for medications and medical foods regardless of age

History of PAH Deficiency Treatment

- Any combination of therapies that facilitate improvement in blood phe levels is appropriate
- Therapies may be combined and should be individualized

Other Treatments for Inborn Errors of Metabolism

- Organ Transplantation (liver)
- Bone Marrow Transplantation
- Enzyme Replacement Therapy: currently 6 Lysosomal Storage Disorders
 - Approved for Gaucher disease, Fabry disease, Pompe disease, Hurler, Hunter and MPS-VI
- Gene Therapy – research only

Next Generation Newborn Screening

- Whole Exome or Whole Genome Sequencing–screen for any disorder for which the mutations are known
 - Genetic metabolic disorders
 - Immunodeficiency disorders
 - Muscular dystrophies
 - Cystic fibrosis
 - Hemoglobinopathies
 - Chromosome abnormalities
- Proteomics



Questions are guaranteed in life; Answers aren't.