American College of Medical Genetics and Genomics (ACMG) PKU Diagnosis and Management Guidelines Summary[1]

PAH Deficiency *(pg 2)*

- This guideline recommends a unifying nomenclature and therefore refers to the spectrum of PAH deficiency, not specifically relying on the blood Phe level, although we recognize that the most severe form is still likely to be referred to as "classical PKU" in many settings

Newborn Screening (NBS) and Diagnostic Testing *(pg 3)*

Key Takeaways

- NBS for phenylalanine hydroxylase (PAH) deficiency in the United States is now primarily performed by tandem mass spectrometry

Conclusions

- Quantitative blood amino acids should be performed as part of the diagnostic testing for follow-up of a positive NBS
- Additional testing is needed to define the cause of elevated blood phenylalanine (PHE) and should include analysis of the pterin metabolism
- PAH genotyping is indicated for improving therapy planning

Pharmacotherapy *(pgs 5-6)*

Key Takeaways

- Sapropterin is currently the only Food and Drug Administration (FDA)-approved medication for the treatment of PAH deficiency and may be useful in reducing PHE levels in responsive patients
- Experience with sapropterin under the age of 4 years is limited*
- Response to sapropterin is not accurately predicted by genotype and thus should be documented by formal testing

Conclusions

- Any combination of therapies that facilitate improvement in blood PHE levels for a given individual is appropriate; therapies may be combined and should be individualized
- Every PAH-deficient patient should be offered a trial of sapropterin therapy to assess responsiveness except for those with two null mutations in *trans*

Treatment for Life *(pg 7)*

Key Takeaways

- Patients who have discontinued therapy will likely experience neuropsychological improvements with reinstitution of therapy
- Patients with late or untreated PAH deficiency may benefit from institution of therapy

Conclusions

- Treatment for PAH deficiency should be lifelong for patients with untreated PHE levels >360 µmol/l
- Maintaining a treated PHE level of 120–360 µmol/l is recommended for all patients of all ages

Maternal PAH Deficiency *(pg 7)*

Key Takeaways

- Fetal development is optimal when maternal PHE levels are <360 µmol/l prior to conception
- There is a linear relationship between maternal PHE levels >360 µmol/l throughout gestation and lower IQ of the developing fetus
- Elevated blood PHE levels in the first 8–10 weeks of gestation are associated with an increased risk of congenital heart defects (CHD) and poor fetal growth

*After the ACMG Guidelines were published, data from PKU-015 study, which included 93 pediatric patients aged 1 month to 6 years, was added to the prescribing information for sapropterin.

Maternal PAH Deficiency *(pg 8)*

Conclusions

- Achievement of maternal PHE levels <360 µmol/l prior to conception is recommended
- Large neutral amino acids (LNAAs) are not recommended for use during pregnancy
- Sapropterin is a class C medication and may be used during pregnancy following discussion of the benefit and risks to mother and fetus
- Routine prenatal care and monitoring should be supplemented by close monitoring of fetal growth and assessment for fetal CHD by a high-risk obstetrics group
- Mothers with PAH deficiency may safely breastfeed
- Mothers with PAH deficiency should maintain a PHE-restricted diet, including use of medical foods, postpartum for optimal maternal/infant outcomes

Genetic Counseling *(pg 9)*

Key Takeaways

- PAH deficiency is inherited in an autosomal recessive manner
- DNA-based carrier testing of at-risk family members is available
- There are ethnic differences in the population incidence and carrier frequency of PAH deficiency
- Prenatal diagnosis for PAH deficiency is only available using DNA-based methodologies

Conclusions

- Genetic counseling should be provided as an ongoing process for individuals with PAH deficiency and their families

Neurocognitive and Psychological Outcomes *(pg 9)*

Key Takeaways

- Intelligence in patients with optimally treated PAH deficiency is in the normal range but lower than that in sib controls
- The incidence of nonintellectual psychological symptoms, especially impairment in executive function, is increased in PAH deficiency

Conclusions

- The risk for neurocognitive or psychological symptoms in PAH deficiency is related to age of onset of therapy, lifelong PHE levels, and adherence to treatment. Age-specific neuropsychiatric and cognitive testing is necessary to adequately assess clinical needs
- Appropriate intellectual and mental health assessments are an important component of care for individuals affected with PKU

Transition to Adulthood *(pg 10)*

Key Takeaways

- Adult-focused treatment centers are optimal for older patients but are unavailable in many areas
- Transition programs for adolescents with PAH deficiency should foster independence

Conclusions

- Treatment for life mandates the need for medical insurance to provide coverage for medications and medical foods regardless of age

Reference: 1. Vockley J, Andersson HC, Antshel KM, et al; for the American College of Medical Genetics and Genomics Therapeutic Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014;16(2):188-200.

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