The Perfect Candidate for BH₄: a PKU Paediatric Case Review

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Background

• Phenylketonuria (PKU) is the most common inherited metabolic disorder due to variants in PAH, encoding phenylalanine hydroxylase.
• The hallmark of untreated PKU is elevated phenylalanine (Phe) level associated with neurocognitive impairment.
• Management includes a very low protein diet supplemented with Phe-free protein substitute formula.
• Sapropterin: the synthetic form of Tetrahydrobiopterin (BH₄), a cofactor for phenylalanine hydroxylase has been shown to improve protein tolerance in patients with residual enzyme activity improving quality of life.
• PKU is autosomal recessive (Ho et al. 2014)

Phenylalanine

\[
\text{Phenylalanine hydroxylase} \rightarrow \text{Tyrosine}
\]

Phenylalanine

\[
\text{BH}_4 \quad \text{qBH}_2
\]

Phenylpyruvate

\[
\text{PLP} \quad \text{Pyruvate} \quad \text{Alanine}
\]

Aminotransferase

Phenylpyruvate

\[
\text{Phenyllactate and phenylacetate}
\]

Tyrosine

\[
\text{DNAJC12 acting as a co-chaperone}
\]

Tyrosinase

Melanin

Spronson et al. 2021
Mutation screening of all coding exons of the PAH (phenylalanine hydroxylase) gene were performed using a combination of DHPLC and sequencing.

In one allele a c.194T>C (p.I65T) missense mutation was identified. This is a previously mutation which according to the Phenylalanine Hydroxylase Locus Knowledgebase (http://www.pahdb.mcgill.ca/) is associated with mild-moderate PKU. According to the BIORP PKU database (http://www.bh4.org/BH4DatabasesBiopku.asp) this mutation is potentially BH4-responsive.

In the other allele a c.818C>T (p.S273F) missense mutation was identified. This mutation has not been previously reported, so its pathogenic significance is unknown at this time.

Conclusions
One disease causing mutation and one possibly disease causing mutation have been identified. These results suggest that this patient would be likely to be responsive to BH4, which is consistent with the results of her previous BH4 load test.
Growth chart
• As an infant, patient was started on XP Analog, then transitioned to XP Maxamaid – both of which are amino acid based Phe-free drink mix containing a balanced mix of the other essential and non-essential amino acids, carbohydrate, vitamins, minerals and trace elements (Nutricia 2016)
• Phenyl-free foods and recipes had to be catered to patient
• After starting BH₄, XP Maxamaid was slowly weaned
• Prior to starting BH₄ at age 3, mother was counting food protein in units at approx. 7.5g/day
• BH₄ dosage was titrated to Phe levels ranging from 10-20mg/kg/day, slowly increasing with growth
• After starting BH₄, food protein was started at 18.3g/day and gradually increased until unrestricted
• This improved quality of life as family were able to eat out at restaurants and cease protein counting
Outcome

- Patient has had normal cardiovascular, respiratory, musculoskeletal examinations throughout
- Patient has now been transitioned to adult services
- She is a dance teacher and is recommencing university studies to become a primary school teacher
- Understands maternal PKU syndrome and need for good Phe control, Sapropterin safe to use in pregnancy
- She is now able to enjoy a fully, varied unrestricted protein diet with heavy protein foods such as prawns, lamb, salmon etc.
- Adult physicians are trialling use of protein shakes (with regular Phe levels) as per patient’s wishes for more extensive exercise

Discussion

- Use of Sapropterin improves metabolic control by upregulation of residual enzyme activity in patients with BH₄ responsiveness.
- A range of dosage and frequency have been suggested in the literature and should be considered based on local policy and patients’ need.
- There is paucity of data on dose adjustment to account for puberty and intercurrent illness.
- A clinically significant response has been defined as a decrease in Phe by more than 30% within 24 hours after a BH₄ challenge (Mitchell et al. 2005), with this patient having a 91% response is clinically optimal
- Correlation between genotype and the responses revealed that although genotype is a major determinant of BH₄ responsiveness, patients with the same genotype may also show disparate responses to this treatment (Ho et al. 2014)

Conclusion

- The use of BH₄ with dietetic supervision in well-selected patients can maintain metabolic control and improve quality of life.
- However elevated Phe levels can still occur.
- Ongoing monitoring, education and support is essential.

References

- Image 1: https://www.sciencedirect.com/topics/medicine-and-dentistry/phenylketonuria