

A Child with Blond Hair and Bright Skin in a Family with Brown Colored Skin

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Received: September 23, 2019; **Published:** October 21, 2019

Abstract

Phenylketonuria is a rare genetic disorder due to an inborn error in aromatic amino-acid metabolism leads to a lack of mental abilities and developmental changes. Phenylketonuria is one of an autosomal-recessive inherited metabolic diseases occurs due to excessive accumulation of phenylalanine which can lead to neurological impairment. In this paper we report a case of a 6 month old child Saudi born with the consanguineous parent with distinct amino acid analysis and radiological findings.

Keywords: Phenylketonuria (PKU); Phenylalanine Hydroxylase (PAH); Tetrahydrobiopterin; Large Neutral Amino Acids (LNAA); Neopterin; Biopterin; Saudi; Blond Hair; Brown Skin

Introduction

PKU is an autosomal-recessive inherited metabolic disease in which mutations in Phenylalanine hydroxylase (PAH) gene or the gene encoding its cofactor, tetrahydrobiopterin (BH4) results in decreased catabolic pathway of phenylalanine. The lack of PAH or its cofactor BH4 which results in the accumulation of excess phenylalanine, that impairs intellectual abilities if untreated. The classic PAH deficiency is considered when the serum concentration of unchanged phenylalanine (Phe) crosses the level of 1200- $\mu\text{mol/L}$. The Phe concentration in the range of 600 to 1200- $\mu\text{mol/L}$ is diagnosed as mild PKU, and values < 600- $\mu\text{mol/L}$ are classified as hyperphenylalaninemia (HPA). When the treatment program of a patient with PKU did not start at the early weeks of neo-natal period developmental delay, mental retardation and microcephaly are caused by the accumulation of toxic by products of Phe within its metabolic pathway [1-4].

Case Presentation



Figure 1

A 6 month old female infant was born to consanguineous parent by NVD in our hospital at 7 September 2018. The child cried after birth and weighs 2.2 kgs, HC 32 cm, Length 50 cm. Guthrie test taken but when we are not receiving any results, We ask the parents to come for another sample but they did not come at all (Mother is treated with anti-psychotic drugs and the grandmother is the one taking care of the baby, till this age the father did not add the baby to family card).

There is past history of NICU admission due to LBW and thick meconium stained.

On 29 march 2019, she was admitted in our hospital as the parents complain of diarrhea and vomiting. Our diagnosis was Acute GE with mild dehydration. The grand mother denied any abnormality in the infant or admission to other hospital.

But in our detailed examination, We found

- The baby his head lag and unable to sit even with support
- Microcephaly
- Dysmorphic features
- Fair hair with bright skin in a brown colored family
- Irritability
- Convulsions in this time the grandmother said she has frequent convulsions and they went to private hospital and they said, this is a convulsion and no need treatment
- Hepatomegaly 3 cm below costal margin.

So, from all, we suspect a metabolic problem one of them (PKU). So we did:

- New Guthrie test (Metabolic screen)
- CBG: No acidosis
- Ammonia and Lactate (Not available in our hospital)
- Electrolytes: Normal
- T4 and TSH: Normal
- Abdominal US: Normal
- Brain CT: Mild brain atrophy
- Ophthalmic consultation (No cherry red spots or retinitis pigmentosa).

After 5 days Guthrie test result show, Elevated Phenylalanine 1173.5 $\mu\text{mol/L}$ (Cut off 150) and Elevated Phenylalanine/Tyrosine Ratio at 34.2 (Cut off 0.27 - 2).

In our hospital we give levetiracetam to control the convulsions and urgent referral done to tertiary hospital for advance management.

Discussion

Phenylketonuria

Inheritance is AR.

Incidence from 1 in 14000 to 1 in 20000.

Essential amino acids are not synthesized by the body.

Valine, phenylalanine, threonine, tryptophan, leucine, lysine, Isoleucine, Methionine, Histidine increased due to deficiency of the enzyme phenylalanine hydroxylase (PAH) or of its cofactor tetrahydrobiopterin (BH4) causes accumulation of phenylalanine in body fluids and in the brain. (Hyperphenylalaninemia) and also decrease in tyrosine so it will become an essential amino acid.

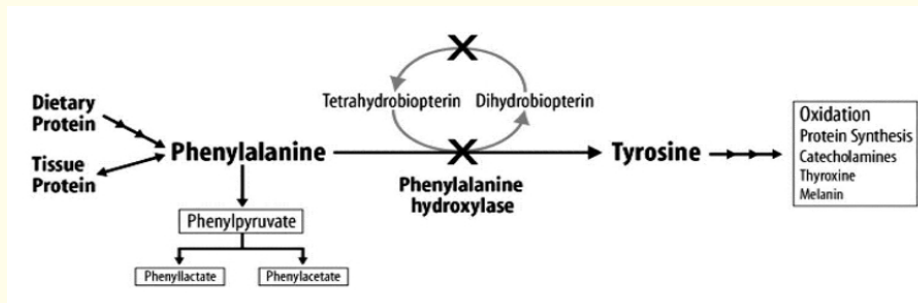
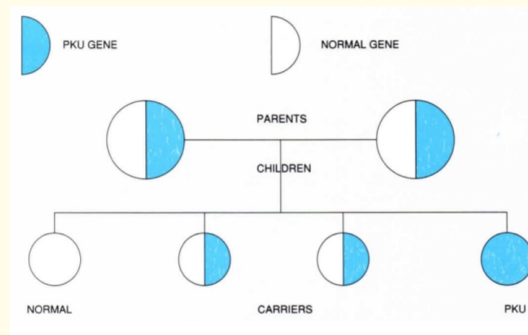
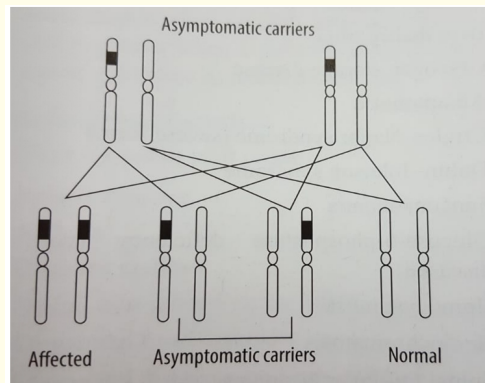
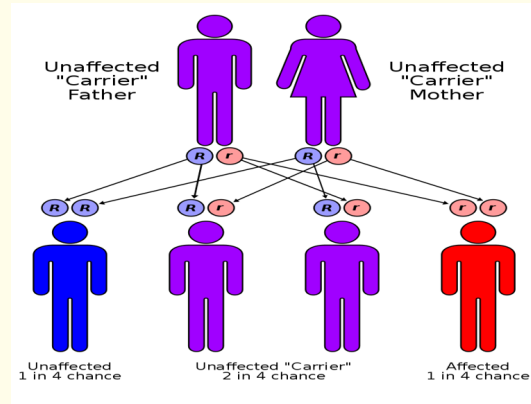


Figure 2

Hyperphenylalaninemia and according to the degree of PAH deficiency: Either very high plasma concentration > 20 mg/dL (> 1,200 μmol/L). (Classic phenylketonuria). Or mildly elevated levels 2 - < 20 mg/dl or 120 - < 1200 μmol/L

↑↑ phenylalanine	
CNS toxicity and damage	Metabolized by alternate pathway which leads to produce aphenylketones
Mental retardation	Phenyl lacatate
Hyperactivity	Acetate
Seizures	Pyruvate
Studied by MRS	Which have no role in CNS injury and causes unpleasant mousy odor

Table 1

↓↓Tyrosine		
↓Melanin	↓ Dopa	↓Tryptophan
Fair skin	↓ plasma level of catecholamines	↓ serotonin
Blue eye		
Blond hair		

Table 2

Classic Phenylketonuria

- Normal at birth.
- Then gradual Profound intellectual disability:
 - 50 - 70% IQ < 35
 - 88 - 90% IQ < 65.
 - 2 - 5% IQ = normal
- Severe vomiting.
- Hyperactivity.
- Autistic behaviors (purposeless hand movements, rhythmic rocking, and athetosis) lighter than unaffected siblings.
- Some may have a seborrheic or eczematoid rash, usually mild.
- Neurologic signs: Seizures (25%) with 50% abnormal EEG, Spasticity, Hyperreflexia, Tremors.
- Microcephaly, prominent maxillae.
- Widely spaced teeth, enamel hypoplasia.
- Growth retardation.
- Osteopenia, Osteoporosis

Milder form of Hyperphenylalaninemia

Non-PKU Hyperphenylalaninemia

- Does not excrete phenyl ketones in urine
- May require dietary therapy
- possibility of deficiency of BH4

Diagnosis

- Neonatal Screening TMS = Guthrie test done after 24 - 48 of delivery and protein intake.
- Plasma phenylalanine concentration.
- Phenyl ketones in urine (Ferric chloride) If no screening program.

Treatment

- Low-phenylalanine diet to prevent phenylalanine deficiency (lethargy, FTT, anorexia, anemia, rashes, diarrhea, up to death).
- Adequate intake of tyrosine which become an essential amino acids.
- Optimal phenylalanine levels
 - 2 - 6 mg/dL in neonate up to 12 years
 - 2 - 15 mg/dl in older individuals for life long
- Other treatment modalities
 - A: LNAAs large neutral amino acids which compete with phenylalanine for transport from GI to blood and from blood through BBB to brain.
 - B: Oral administration of BH₄, Sapropterin dihydrochloride KUVAN but here we need some PAH activity the dose is 10 mg/kg/day and this is benefits in up to 40% of patients.
 - C: Phenylalanine ammonia lyase.

Pregnancy in PKU Women

1. If without treatment
 - ↑ phenylalanine in her blood
 - Offspring with high risk to..... ↓ IQ level
 - Microcephaly
 - FTT
 - Congenital malformations, like CHD
2. If with treatment (most important before pregnancy and/or by 8 WK gestation at the last)
 - Level between 2 - 6 mg/dL or 120 - 360 μmol/l throughout pregnancy.

Tetrahydrobiopterin BH₄

Incidence of BH₄ deficiency is 1/50000.

BH₄ also cofactor for

1. Tyrosine hydroxylase.....↓ Dopamine neurotransmitter
2. Tryptophan Hydroxylase.....↓ Serotonin neurotransmitter

The degradation of BH₄ leads to urine secretion of Neopterin and Biopterin.

Prenatal diagnosis is possible using biopsy from chorionic villi.

Plasma phenylalanine may be high as Classic PKU or in the range of milder form.

Neurologic Symptoms due to neurotransmitters disorders

- Extrapyramidal signs (choreoathetotic or dystonic limb movements, axial and truncal hypotonia, hypokinesia),
- Autonomic abnormalities, Intellectual disability, Seizures, Hypersalivation,
- Hyperprolactinemia due to hypothalamic dopamine deficiency.

Symptoms usually progressive with marked diurnal fluctuation.

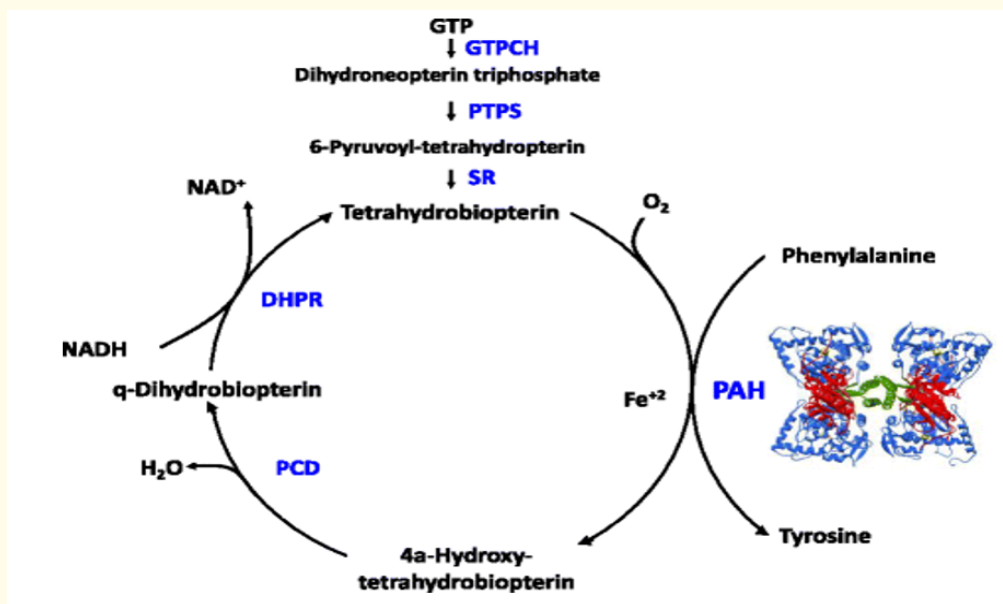


Figure 3

6-pyruvayl Tetrahydropterin synthase 6-PTS	Guanosine Triphosphate Cyclohydrolase GTPCH	Dihydropteridine Reductase DHPR	Pterincarbinolamine Dehydratase deficiency PCD
50 % of cases	25 % of cases	12.5 % of cases	12.5 % of cases
Enzyme assay in liver, Kidney and RBCS	Enzyme assay in liver, Mononuclear and Fibroblasts	Enzyme assay in liver, and WBCS	Enzyme assay in liver, and Kidney
In urine ↑ Neopterin ↓ Biopterin	In urine ↓ Neopterin ↓ Biopterin	In urine ↓ Neopterin ↓ Biopterin	In urine ↑ 7- Biopterin
On chromosome 11q23.1	On chromosome 14q22.1	On chromosome 14q22.1	On chromosome 10q22.1

Table 3

Diagnosis

- 1- Measuring Neopterin and Biopterin in body fluid ex. Urine.
- 2- In CSF decreased levels dopamine and serotonin and their metabolites in all patients.
- 3- BH4 Loading Test

We give 20 mg/kg of BH4: Which will normalize plasma phenylalanine in all patients with BH4 deficiency within 4-8 hrs, but to do this test the plasma phenylalanine should be >400 μmol/L for the accuracy of the test, so in case of BH4 deficiency the serum phenylalanine remain normal for at least one week without a phenylalanine restricted diet.

- 4- Enzyme Assay
- 5- Genetic Testing

Treatment

- Oral supplementation of BH4 (5 - 20 mg/kg/day) (Kuvan).
- Lifelong supplement with neurotransmitter precursors such as L -dopa (+ carbidopa).
- to inhibit degradation of L -dopa before it enters the CNS and 5-hydroxytryptophan but the response is not optimal.
- Avoid drugs like TMP/SMX, methotrexate, and other antileukemic agents due to inhibition of dihydropteridine reductase enzyme DHR activity.

Conclusion

- PKU is an autosomal recessive inborn error. Due to which an impaired ability to metabolize the essential amino acid phenylalanine occurs that may cause the disease.
- Neonatal Screening and early treatment leads to positive clinical outcomes.
- PKU can be discovered late so we should consider IEM disorder in unexplained neurological findings, FTT and delayed milestone.
- PKU should follow-up at a specialist metabolic clinic.

Bibliography

1. Pervez Akbar Khan. "Metabolic Diseases". Basis of Pediatrics, 9th Edition (2019): 493-502.
2. Robert M Kliegman., *et al.* "Defects in Metabolism of Amino Acids". (Ole g A Shchelochkov and Charles P Venditti). Nelson Textbook of Pediatrics, 21st International Edition, Volume 1 (2020): Ch103.
3. van Wegberg AMJ., *et al.* "The complete European guidelines on phenylketonuria: diagnosis and treatment". *Orphanet Journal of Rare Diseases* 12.1 (2017): 162.
4. Ziba Soltani., *et al.* "First Case Report of EX3del4765 Mutation in PAH Gene in Asian Population". *Iranian Red Crescent Medical Journal* 18.2 (2016): e21633.

Volume 8 Issue 11 November 2019

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