

Amino Acid Metabolism Disorders

Phenylketonuria (PKU)

Hyperphenylalanemia is an amino acid disorder caused by decreased activity, impaired synthesis or recycling of phenylalanine hydroxylase or its cofactor, tetrahydrobiopterin (BH₄). Classical phenylketonuria (PKU) is caused by deficiency of phenylalanine hydroxylase. Without this enzyme, the body is unable to convert phenylalanine (PHE) into tyrosine (TYR). Phenylalanine accumulates in the blood, urine, and central nervous system. If left untreated, the infant will experience profound mental retardation. She or he could also have decreased pigmentation of the skin and hair, a musty odor, unusual behavior, and/or seizures. Screening for PKU can also identify infants with benign hyperphenylalaninemia, defects of biopterin cofactor biosynthesis and defects of biopterin cofactor regeneration.

Inheritance:	Autosomal recessive
Estimated Incidence:	PKU—1:16,000 Benign hyperphenylalaninemia—unknown Defects of biopterin cofactors biosynthesis or regeneration—unknown, thought to be very rare
Abnormal Screen Result:	Elevated PHE Elevated PHE/TYR
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	Repeat PHE as soon as possible on filter paper. No formula/feeding change until results of repeat known. If PHE is still elevated in the repeat specimen, refer to pediatric metabolic specialist. Further diagnostic evaluation may be necessary to rule out BH ₄ defects. Initiate PHE restricted diet in coordination with metabolic dietitian.
Neonatal Presentation:	None.
Treatment:	PKU/defects of biopterin cofactor biosynthesis or regeneration—PHE restricted diet for life. BH ₄ defects require additional diagnostic evaluation and treatment. Benign hyperphenylalaninemia—usually none

Special Considerations

Maternal PKU and Hyperphenylalaninemia--Women with poorly controlled classical PKU have an increased risk of pregnancy loss. In studies of women with classical PKU,

when PHE levels were not strictly controlled, the following outcomes were found in 90% of such pregnancies: intrauterine growth retardation, microcephaly, mental retardation and/or birth defects, particularly congenital heart defects. Therefore, it is vital that women with PKU maintain phenylalanine levels between 120 and 360 $\mu\text{M/L}$. Excellent control prior to conception and during pregnancy can prevent damage to the developing fetus.

Maple Syrup Urine Disease (MSUD)

Maple syrup urine disease (MSUD) is caused by deficiencies in the branched chain keto-acid dehydrogenase complex leading to the accumulation of leucine (LEU), isoleucine (ILE), valine (VAL) and alloisoleucine. Cerumen, urine or sweat may smell faintly of maple syrup. Untreated infants with classic MSUD who survive infancy have retarded physical and mental development. Milder variants have been reported and may not be picked up by newborn screening.

Inheritance: Autosomal recessive

Estimated Incidence: 1:185,000

Abnormal Screen Result: Elevated VAL
Elevated LEU + ILE

Method of Notification: All abnormal results called to physician of record

Next Steps if Abnormal: **Potential medical emergency.** See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions.

Repeat VAL and LEU + ILE as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.

Neonatal Presentation: May show neurological impairment in first week of life. Lethargy and poor suck are often the first signs followed by abnormal muscle tone, involuntary movements, seizures and coma.

Treatment: LEU restricted/ILE, VAL controlled diet for life. Some affected persons with a less severe form of MSUD are thiamine responsive.

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

Homocystinuria

Homocystinuria is caused primarily by a deficiency in the enzyme cystothionine synthetase leading to the accumulation of methionine (MET) in the blood. Untreated infants are at risk for mental retardation, dislocated lens, marfanoid body type, developmental delay and thromboembolism. Screening for homocystinuria may also identify infants with hypermethioninemia. Primary hypermethioninemia that is not caused by other disorders, liver disease or excess methionine intake appears to be extremely rare.

Inheritance:	Autosomal recessive
Estimated Incidence:	Homocystinuria—1:200,000 Primary hypermethioninemia—unknown, thought to be very rare
Abnormal Screen Result:	Elevated MET
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat MET as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	None
Treatment:	Some affected persons respond to Vitamin B 6, the cofactor of cystothionine synthetase, with biochemical correction or improvement. If affected persons show only partial response or are nonresponsive to Vitamin B 6, then a MET restricted diet for life is necessary. Betaine, a medication that lowers homocysteine, is often used.

Citrullinemia

Citrullinemia I is a urea cycle disorder caused primarily by a deficiency of the enzyme argininosuccinic acid synthetase. Citrulline (CIT) and ammonia build up in the blood which can lead to lethargy, seizures, coma and death. Citrullinemia II is also a urea cycle disorder. It is caused by a deficiency of the protein citrin which is necessary for many metabolic processes. In the neonatal onset type of CIT II, bile flow is blocked.

Inheritance:	Autosomal recessive
Estimated Incidence:	CIT I—1:57,000 CIT II—1:100,000 primarily in persons of Japanese, East Asian or Middle Eastern ancestry
Abnormal Screen Result:	Elevated CIT
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	Potential medical emergency. See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Emergency treatment may include provision of sufficient nonprotein calories to prevent catabolism, sodium benzoate or sodium phenylacetate, IV arginine (ARG). Dialysis may be necessary to lower ammonia level. Repeat CIT as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	May show neurological deterioration in first week of life. Lethargy, poor feeding, vomiting, grunting respirations, tachypnea, and hypothermia progress to seizures, encephalopathy and death unless quickly treated.
Treatment:	High calorie, protein restricted, ARG supplemented diet. Sodium benzoate, sodium phenylacetate, sodium phenylbutyrate may be used to help decrease accumulated toxic precursors

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illness can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern.

Argininosuccinic Aciduria

Argininosuccinic aciduria is a urea cycle disorder caused primarily by a deficiency of the enzyme argininosuccinic acid lyase. Argininosuccinic acid, citrulline (CIT) and ammonia build up in the blood which can lead to lethargy, seizures, coma and death.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:70,000
Abnormal Screen Result:	Elevated CIT
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	Potential medical emergency. See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Emergency treatment may include provision of sufficient nonprotein calories to prevent catabolism, sodium benzoate or sodium phenylacetate, IV arginine (ARG). Dialysis may be necessary to lower ammonia level. Repeat CIT as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	May show neurological deterioration in first week of life. Lethargy, poor feeding, vomiting, respiratory alkalosis, and hypothermia progress to seizures, encephalopathy and death unless quickly treated.
Treatment:	High calorie, protein restricted, ARG supplemented diet. Na benzoate, Na phenylacetate, Na phenylbutyrate may be used to help decrease accumulated toxic precursors

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illness can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern.

Tyrosinemia

Tyrosinemia I (TYR I) is caused by a deficiency in the enzyme fumarylacetoacetase. Untreated infants are at risk for liver failure, jaundice, growth retardation and eventual hepatocellular carcinoma. Tyrosinemia Type II or III (TYR II or III) can also be identified by screening. TYR II is caused by a deficiency in the enzyme tyrosine aminotransferase. TYR III is caused by a deficiency in the enzyme 4-OH phenylpyruvate dioxygenase. Untreated infants with TYR II are at risk for eye and skin lesions with neurological problems including developmental delay. The clinical features of TYR III are not well described; however, mental retardation and behavioral problems have been found in affected persons.

Inheritance:	Autosomal recessive
Estimated Incidence:	TYR I—1:100,000 TYR II—1:250,000 TYR III—unknown, thought to be very rare
Abnormal Screen Result:	TYR I—Elevated succinylacetone (SUAC) TYR II or III—Elevated TYR with normal SUAC
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat SUAC and TYR as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	All forms—usually none.
Treatment:	TYR I—TYR and PHE restricted diet for life. NTBC (Nitisinone) also used to inhibit the degradation of tyrosine and the formation of toxic metabolites. Liver transplantation if indicated. TYR II or III—TYR and PHE restricted diet for life.

Special Considerations

Premature/sick infants—Transient Tyrosinemia of the Newborn is the most common amino acid disorder found in infants, especially those who are premature and/or sick. However, prompt repeat screening is needed as a precaution.