



**NEWBORN SCREENING
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5-Oxoprolinuria (Glutathione synthetase deficiency) Information for Physicians and Other Health Care Professionals

Definition 5-oxoprolinuria, or pyroglutamic aciduria, is an inherited disorder of amino acid metabolism, caused by an enzymatic defect in glutathione co-enzyme production. 5-oxoproline, a by-product of glutathione deficiency, accumulates in blood and cerebrospinal fluid, is excreted in urine and is the compound detected by newborn screening.

Newborn screening in Illinois includes testing for the following type of 5-oxoprolinuria:

Glutathione synthetase deficiency (GSD)

Clinical Symptoms Clinically, there are two forms of glutathione synthetase deficiency. The most severe form, generalized GSD, is expressed in multiple tissues, while the second, usually milder form, erythrocyte GSD, is expressed only in erythrocytes.

Generalized GSD results in reduced glutathione levels in erythrocytes, leukocytes, fibroblasts and other tissues. Symptoms, including metabolic acidosis, hemolytic anemia, jaundice and urinary excretion of large amounts of 5-oxoproline, may be present within the first few days of life. Diagnosis is possible during the neonatal period. Infants with GSD are susceptible to severe metabolic decompensation shortly after birth and later in life during intercurrent illnesses. Without treatment, progressive neurological symptoms such as ataxia, spasticity and/or seizures may result from chronic metabolic acidosis.

Erythrocyte GSD results in reduced glutathione levels in erythrocytes, but not in other tissues. This reduction of glutathione levels may cause a mild form of hemolytic anemia and, occasionally, splenomegaly. Erythrocyte GSD does not usually result in urinary excretion of 5-oxoproline or metabolic and neurological complications.

Newborn Screening and Definitive Diagnosis In Illinois, newborn screening for glutathione synthetase deficiency is performed using tandem mass spectrometry. False positive and false negative results may be possible with this screening; not all cases of GSD will be detected by newborn screening. Infants with a presumptive positive screening test require prompt follow-up. **When receiving a presumptive positive result, the clinician should immediately check on the clinical status of the baby and refer the infant to a metabolic disease specialist.**

Treatment Early diagnosis and prompt treatment is essential for an improved prognosis. Individuals with GSD require prompt correction of any metabolic acidosis and/or hyperbilirubinemia to help prevent brain damage. Oral maintenance doses of sodium bicarbonate or citrate may help to correct chronic acidosis. Anemia may require transfusions and any electrolyte imbalances should be corrected. Patients with generalized GSD may have heightened sensitivity to oxidative stress, and large doses of vitamin E and vitamin C may be indicated. Aggressive medical management is necessary during any intercurrent illness. The infant/child should be admitted for medical care, including administration of intravenous therapies to prevent/treat metabolic acidosis and/or electrolyte imbalances. Caution in the administration of drug therapies that are known to precipitate hemolytic crises also may be indicated.

Incidence Glutathione synthetase deficiency is an extremely rare condition and the actual incidence is unknown.

Inheritance Pattern Glutathione synthetase deficiency is inherited in an autosomal recessive pattern. As an autosomal recessive disorder, the parents of a child with this condition are unaffected healthy carriers of the condition, and have one normal gene and one abnormal gene. With each pregnancy, carrier parents have a 25 percent chance of having a child with

two copies of the abnormal gene, resulting in glutathione synthetase deficiency. Carrier parents have a 50 percent chance of having a child who is an unaffected carrier and a 25 percent chance of having an unaffected, non-carrier child. These risks would hold true for each pregnancy. All siblings of infants diagnosed with GSD should be tested. Genetic counseling services should be offered to the family.

Physiology Glutathione synthetase is a necessary enzyme for bio-synthesis of glutathione, a co-enzyme essential to many cellular functions including serving a key role in cellular protection from toxic substances. GSD is an inherited enzyme defect that results in massive urinary excretion of 5-oxoproline, a by-product of reduced glutathione production. Reduced cellular glutathione levels result in the disease manifestations.

Key Points for Parents Avoid overly alarming the child's parents if the diagnosis has not yet been confirmed. If the child needs additional testing or diagnostic evaluation, make certain that the parents understand the importance of following the pediatrician's and/or specialist's recommendations for additional testing and referrals.

Follow-up After Confirmation of Diagnosis These guidelines should be followed after a diagnosis of glutathione synthetase deficiency has been confirmed:

1. **Parents should understand treatment is lifelong and compliance with medical management and awareness of and prompt attention to episode triggers, including any illness, are imperative to the child's health, growth and development.**
2. Infants and children with glutathione synthetase deficiency should have regular follow-up appointments with a metabolic disease specialist.
3. **Parents should be advised that if a child shows warning signs of the disorder, such as lethargy or vomiting, they should immediately seek medical attention.** A medical plan created by the metabolic specialist and the primary care provider should be developed for these acute episodes.
4. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being. A multi-disciplinary approach including the following specialties is recommended: pediatrics, genetics and nutrition. Parents should understand treatment is not curative and all morbidity cannot be prevented.
5. Genetic counseling services are recommended. A list of genetic counselors and geneticists whose services are available through the Illinois Department of Public Health should be given to the parents if they have not already seen a geneticist.
6. Provide a list of available support services in the community, such as the local health department, Early Intervention service providers and the University of Illinois at Chicago Division of Specialized Care for Children.
7. Additional information about newborn screening can be found at:
 - Baby's First Test: <http://www.babysfirsttest.org/>
Health Resource and Service Administration (HRSA), Grant no. U36MC16509, Quality Assessment of the Newborn Screening System.
 - National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/gtr/>
National Center for Biotechnology Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda MD, 20894 USA.

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