

## **Endocrine and Enzyme Disorders**

## Congenital Hypothyroidism (CH)

Congenital hypothyroidism (CH) is inadequate thyroid hormone (T3 and/or T4) production in newborn infants. When the T3 and/or T4 levels drop too low, the pituitary gland produces excess Thyroid Stimulating Hormone (TSH) to stimulate the thyroid gland to produce more thyroid hormones.

The finding of an **elevated TSH and low Free T4** indicates primary hypothyroidism due to disease in the thyroid gland.

Thyroid hormones are necessary for proper central nervous system (CNS) development. Deficiency of thyroid hormones in an infant usually results in intellectual disability (ID) and poor growth. The most common causes are total or partial failure of the gland to develop (aplasia or hypoplasia) or development of the gland in an abnormal place (ectopic gland).

Disease can occur due to an anatomic defect in the gland, an inborn error of thyroid metabolism, or iodine deficiency. **CH is the most common neonatal endocrine disorder.** Historically, thyroid dysgenesis was thought to account for approximately 80% of cases.

However, studies have reported a change in epidemiology, with a doubling in incidence to around 1 in 1,500 live newborns. This is thought to be due in part to an increase in congenital hypothyroidism with thyroid gland-in-situ (GIS).

Lower TSH screening cutoffs may also be driving this increase in diagnosis. Although diverse ethnicities of the screened population, increased multiple and premature births, and iodine status are contributing factors. Some infants identified as having primary congenital hypothyroidism may have transient disease and not permanent congenital hypothyroidism.

Inheritance: Most cases of CH are not genetic

Estimated Incidence: 1:1,500

**Abnormal Screen Result: Elevated TSH**

Method of Notification: All results where the TSH is  $\geq 40$   $\mu\text{IU/mL}$  are called and faxed to the provider of record. All other abnormal TSH results are mailed to the provider of record.

**Next Steps if Abnormal:** **Repeat TSH as soon as possible** on filter paper or obtain serum TSH and free T4 collection at any nearby lab. In addition, perform serum thyroid function tests **and** consider referral to a pediatric endocrinologist if TSH is  $\geq 100$   $\mu\text{IU}$  in the first specimen.

If TSH is still abnormal on repeat testing, refer to a pediatric endocrinologist for further evaluation. **Report all findings to the SC Newborn Screening Program.**

Neonatal Presentation: None

Treatment: Thyroxine replacement medication.

### **Special Considerations**

***Specimen Collection in the First 24 Hours of Life*** - Interpretation of TSH results is more difficult if the specimen is collected within the first 24 hours of life. This is due in part to the physiologic surge in TSH shortly after birth.

***Premature Infants*** - In some premature infants there is an occasional physiologic elevated TSH level at birth. These effects are usually transient, but these infants need to be closely monitored to ensure that T4 and TSH levels achieve normal range as the infants mature.

***Formula type*** - Infants diagnosed with congenital hypothyroidism should not be routinely fed soy based infant formula. It is thought that soy binds with thyroxine replacement medication and slows its absorption.

***Later Developing Hypothyroidism*** - Many infants with hypothyroidism are detected on the first specimen even when it is collected within the first 24 hours of life. However, in a few cases hypothyroidism develops in the weeks after the initial screening test would have been collected.

**Physicians must remain alert to clinical signs of hypothyroidism in older infants despite normal initial screening results.**

## **Congenital Adrenal Hyperplasia (CAH)**

Congenital adrenal hyperplasia (CAH) is an enzyme defect which affects the functioning of the adrenal cortex. A metabolic block produces varying degrees of insufficiency of corticosteroids (cortisone and aldosterone) and an excess of male sex hormones.

Females may have ambiguous or male-like genitalia and will undergo increasing masculinization if untreated. Infants with the salt-losing form of the disorder can develop an acute crisis with failure to thrive, dehydration, and shock in the first month of life.

Untreated males may present with precocious puberty at 3 to 5 years of age, and untreated females may be virilized. Androgenic compounds also cause accelerated early growth with premature fusion of the epiphyses and ultimate short stature.

Inheritance: Autosomal recessive

Estimated Incidence: 1:16,000

**Abnormal Screen Result: Elevated 17-OH Progesterone (17-OHP)**

Method of Notification: All results where the 17-OHP is  $\geq 48$  ng/mL in infants with birth weights  $\geq 2500$  g are called and faxed to provider of record. All results where the 17-OHP is  $\geq 130$  ng/mL in infants with birth weights  $< 2500$  g are called and faxed to the provider of record.

Any other abnormal 17-OHP results are mailed to the provider of record.

**Next Steps if Abnormal: Potential medical emergency! See the infant as soon as possible to ascertain health status.** Repeat 17-OHP as soon as possible on filter paper or obtain serum 17-OHP collection at any nearby lab. Contact a pediatric endocrinologist for further instructions if indicated.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to the SC Newborn Screening Program.**

Neonatal Presentation: Females may have ambiguous genitalia.

Treatment: Replacement of deficient hormones. If the infant does not have the salt-losing form of CAH, only glucocorticoid (cortisone) is required. For infants with the salt-losing form of CAH, mineralocorticoid (aldosterone) is required in addition to cortisone. Increased dosages of medications are usually required in times of stress, trauma, illness, or surgery.

### **Special Considerations**

***Specimen Collection in the First 24 Hours of Life*** - Interpretation of 17-OHP results are more difficult if the specimen is collected within the first 24 hours of life. This is due in part to the physiologic surge in 17-OHP shortly after birth.

***Premature/Sick Infants*** - A large percentage (relative to the overall birth population) of infants with abnormal 17-OHP results are premature and/or sick infants. This is a physiologic response to the stress of prematurity and/or illness.

## **Biotinidase Deficiency (BIO)**

Biotinidase (BIOT) is a key enzyme in the biotin cycle. Biotinidase releases biotin from dietary proteins and recycles biotin. Free biotin is necessary for activation of four carboxylase enzymes. Carboxylases are important enzymes in the metabolism of amino acids, gluconeogenesis, and in the synthesis of fatty acids.

Infants who have untreated biotinidase deficiency may develop hypotonia, seizures, ataxia, developmental delays, breathing problems, hair loss, and hearing loss. Screening may also identify infants with partial biotinidase deficiency or carrier status.

Inheritance: Autosomal recessive

Estimated Inheritance: 1:60,000

### **Abnormal 1<sup>st</sup> tier Screen: Deficient Biotinidase (BIO)**

Method of Notification: All abnormal 1<sup>st</sup> and 2<sup>nd</sup> tier screening results are called, faxed, and/or sent to the provider of record.

**Next Steps if Abnormal:** When quantity allows, a portion of the initial sample will be reflexed to 2nd tier testing. If initial BIO is decreased and no mutations are found on 2nd tier test, see infant to ascertain health status. If 2nd tier test results are within normal limits, no further bloodspots are needed.

If 2<sup>nd</sup> tier results are abnormal, contact a pediatric metabolic specialist for further instructions. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to the SC Newborn Screening Program.**

Neonatal Presentation: Usually none. However, some affected infants have symptoms as early as one week of age.

Treatment: Daily biotin supplements for life.

### **Special Considerations**

**Transfusion** - Transfusion of red blood cells prior to drawing the newborn screening specimen may affect the biotinidase result. Repeat screening for biotinidase should be done 120 days after the last transfusion. If the date of the last transfusion is unknown, put the date of hospital discharge on the collection form next to “**Transfused**”.