

NEWBORN SCREENING & CONGENITAL HYPOTHYROIDISM

VOLUME 1, ISSUE 2

SUMMER 2009

Primary TSH Screen for Congenital Hypothyroidism Mary A. Murray, MD, Pediatric Endocrinologist

Background:

Congenital hypothyroidism (CH) is one of the most common birth defects affecting 1:4000 live births. Early diagnosis and treatment of the newborn results in normal growth and intellectual development. Unfortunately, the rate of false positive newborn screens is high and increased by early hospital discharge after birth and by prematurity. Additional tests added to newborn screening protocols further increase the rate of false positives and the overall number of abnormal screens. Concern has been raised that false positive screens create undue stress on families, excess workload for staff and increased complacency of the newborns' medical providers. Early identification of CH and initiation of treatment remains critical to successful treatment outcomes. Therefore, we have explored how we could decrease the rate of false positives in newborn screening of CH.

Objective:

Our objective was to design a screening protocol utilizing thyroid stimulating hormone (TSH) as the primary measurement (instead of T4) while decreasing the number

of abnormal screens and still identify the true cases of CH.

Design/Methods:

We completed a retrospective review of abnormal results of newborn screening for CH collected by the state newborn screening program using the current primary T4 methodology. We re-analyzed these results using TSH as the primary screen and determined how many of the children would be correctly identified and how many would be incorrectly determined to be normal.

Conclusion:

We concluded that changing to a primary TSH screen for congenital hypothyroidism will decrease the number of false positive results and still correctly identify all children with the disorder. Anxiety for families and medical providers will decrease and staff workload will be reduced.

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Newborn infants with congenital hypothyroidism often appear completely normal up to three months of age. Newborn screening may be the only way of determining if the infant has hypothyroidism and initiating treatment to prevent mental retardation and developmental delays.

Congenital Hypothyroidism Screening: Switch to Primary TSH

Norm Brown, BS MT, Newborn Screening Section Chief, Utah Public Health Laboratories



As part of the Utah Newborn Screening Laboratory quality assurance (QA) program, we continually look for ways to improve the overall quality of our screening results. Because we are a screening laboratory and not a diagnostic one, our testing normally results in a high number of false positive results.

The algorithm used to test for congenital hypothyroidism (CH) is first testing for neonatal

T4 and then for neonatal TSH if the T4 value falls under a cut off value. This algorithm typically produces a high false positive screening rate. In order to lower the false positive rate without sacrificing sensitivity or specificity, we decided to look at other states' algorithms. Several states have changed to a primary TSH and a secondary T4 as their CH screening algorithm.

In order for our newborn screening (NBS) laboratory to make that switch, 140 patients with abnormal thyroid tests were evaluated. Results showed that by switching to a primary TSH with cut off values of $< 1 \mu\text{U}/\text{mL}$ and $> 40 \mu\text{U}/\text{mL}$ followed by a secondary T4,

we would decrease the number of false positive specimens, increase overall sensitivity and maintain specificity.

A TSH value of $> 230 \mu\text{U}/\text{mL}$ exceeds the highest standard screening curve and the computer automatically triggers a secondary T4 in duplicate. The reagent for screening blood spot specimens for CH is manufactured by PerkinElmer Life and Analytical Sciences. Information may be accessed from their website at: www.perkinelmergenetics.com



Pediatric Endocrinologists Available for Consultation

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UTAH'S HISTORY: NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

Jan M. Kilpack, RN BSN, Nurse Consultant, Utah Department of Health - Newborn Screening Program

Congenital hypothyroidism (CH) screening has been part of the Utah Department of Health (UDOH) Newborn Screening Program since 1979. It was included in the original battery of screening tests along with those for phenylketonuria (PKU) and galactosemia. Indicators for congenital hypothyroidism are a low thyroxine (T4) level and/or an elevated thyroid stimulating hormone (TSH) level.

On December 1, 1994, CH was added to the test battery for screening second specimens along with PKU. This decision was based on Utah data showing approximately 30% of newborns with CH were missed on the first screen. These newborns were missed because the hormone that controls thyroxine (T4) level, thyroid

stimulating hormone (TSH), has a physiological surge at birth. Also, when the TSH level is high, the T4 level in a newborn with CH may initially appear normal due to maternal hormone coverage prior to birth.

From 1979 until now, criteria used to determine a positive or abnormal newborn screening result for congenital hypothyroidism was T4 (Primary T4). When a screening specimen has a T4 value less than or equal to 4.0 µg/dL (<= 4.0 µg/dL) or the T4 value is in the lowest tenth percentile (10%) of values for the day, the same specimen is retested in duplicate for the TSH level. The specimen was reported out by the lab as a positive or abnormal result suggestive of CH when the T4 value was less than or equal to

4.0 µg/dL (<= 4.0 µg/dL) and/or the TSH value greater than or equal to 25.0 µU/mL (>= 25.0 µU/mL).

Using the same criteria, if the first specimen results are a critical value with a TSH of > 230 µU/mL or the first and second specimens are abnormal (but noncritical) or the second specimen alone is abnormal, confirmatory laboratory testing (serum free T4 and serum TSH) is completed. Review of Utah's screening results in correlation with follow-up confirmatory testing results, has revealed a large number of false positive results on the second screen. As a result, a change in screening criteria has been implemented.

Please refer to table below for CH outcome findings for years 2005 through 2008.

CONGENITAL HYPOTHYROIDISM (CH) Newborn Screening Disorder Outcome for CH Abnormal Screens	2005		2006		2007		2008		4 Year Totals & Averages	
	Outcome	% of CH Category	4 Year Total Outcome	4 Year % of CH Category						
Primary congenital hypothyroidism	23	7.44%	16	5.82%	19	5.07%	17	4.40%	75	5.58%
Secondary congenital hypothyroidism	0	0.00%	1	0.36%	0	0.00%	2	0.52%	3	0.22%
TBG deficiency	8	2.59%	8	2.91%	10	2.67%	2	0.52%	28	2.08%
Other diagnosis	0	0.00%	3	1.09%	1	0.27%	0	0.00%	4	0.30%
Normal Confirmatory testing	34	11.00%	51	18.55%	53	14.13%	65	16.84%	203	15.09%
Abnormal screening/normal recall specimen	244	78.96%	196	71.27%	292	77.87%	300	77.72%	1032	76.73%
CH Yearly Totals and Averages	309		275		375		386		1345	

New Screening Criteria:

As of July 1, 2009, initial screening is a Primary TSH. If the TSH level is greater than 40.0 µU/mL (> 40.0 µU/mL), using the same specimen, the T4 level is tested in duplicate (second T4 confirms the first T4). The specimen is now reported out by the lab as a positive or abnormal result suggestive of congenital hypothyroidism when the TSH value is greater than 40.0 µU/mL (> 40.0 µU/mL) or when the TSH is less than 1 (<1 µU/mL) and the T4 value is less than or equal to 4.0 µg/dL (<= 4.0 µg/dL).

When the first specimen results are a critical value (TSH > 230 µU/mL) or the first and second specimens are abnormal or the second specimen alone is abnormal, the infant is referred back to the medical home for confirmatory testing (serum free T4 and serum TSH) and possible endocrinology consultation. Using a Primary TSH is expected to decrease the number of false positive screens and promote early detection of congenital hypothyroidism followed with immediate treatment. The desired outcome is prevention of neurological delays and mental retardation from an undiagnosed, untreated disorder.

CONGENITAL HYPOTHYROIDISM OVERVIEW

Mary A. Murray, MD, Pediatric Endocrinologist

Introduction

Congenital hypothyroidism (CH) is a deficiency of thyroid hormone (thyroxine) in newborn infants, occurring in 1:3,000 to 1:4,000 live births. Thyroid hormone (thyroxine or T4) is absolutely essential for normal growth and neurological development in infants. Untreated, a deficiency of thyroid hormone in early life results in severe neurological impairment, permanent mental retardation, and growth failure. When CH is detected early and treatment initiated, developmental delays and mental retardation are prevented. Early identification and treatment results in normal growth and normal mental development.

Etiology

The most common cause of CH is thyroid dysgenesis accounting for 75% of cases and resulting from thyroid gland aplasia, hypoplasia and ectopy. Thyroid dysmorphogenesis accounts for 10% of cases and results from abnormal iodine trapping, organification, abnormal thyroglobulin synthesis, or other enzyme deficiencies. Thyrotropin or thyroid stimulating hormone (TSH) deficiency causes 5% of cases and is usually associated with hypothalamic or pituitary hormone deficiencies. These infants may have an apparently normal first newborn screen. Transient causes account for the remaining 10% of cases and could result from maternal iodine deficiency, drugs, or maternal antibodies.

Clinical Signs and Symptoms

Most infants with CH appear normal at birth. Clinical signs and symptoms may be nonspecific or very subtle. Less than 5% of infants with CH are detected at birth by physical examination.

The most common presentations of CH include: prolonged gestation, enlarged anterior and/or posterior fontanelles, large protruding tongue, umbilical hernia, facial myxedema, and hypotonia. Over the first few weeks of life, additional signs and symptoms may include hyperbilirubinemia, apnea and bradycardia, hypothermia, hoarse cry, lethargy, hearing loss, constipation, poor feeding, abdominal distention and vomiting.

Intervention and Treatment

Upon notification of an abnormal newborn screen, the result should be verified by checking serum free T4 and serum TSH in the local laboratory. It is not necessary to do imaging studies to localize the thyroid tissue; this may result in delay of treatment.

Once confirmed, treatment is begun by administration of synthetic levothyroxine; synthroid, levoxyl and levothroid are examples of preparations available. Newborns usually require 10-15 $\mu\text{g}/\text{kg}/\text{day}$; the goal is to normalize the TSH as rapidly as possible. It is not necessary to do imaging studies to localize the thyroid tissue; this may result in delay of treatment. Treatment for a term newborn should be begun with 50 mcg daily for 1-2 weeks

and then the dose may be reduced to 37.5 mcg by mouth daily. There is no stable liquid preparation of levothyroxine. While there are recipes available for compounding a liquid preparation, they are not stable and should not be used. The tablet should be dissolved in 5-10 ml of water and given to the baby with an oral syringe at the beginning of a feeding to ensure it is all consumed (of the current formulations, levoxyl is the most easily dissolved tablet).

Re-evaluation of the infant and repeat laboratory evaluation should take place within 2 to 4 weeks after the initiation of treatment and a minimum of every 3 months during the first 3 years of life. Laboratory evaluation to assess treatment includes a serum free T4 and serum TSH.

After the age of three years, the child should be re-evaluated as to whether continuing therapy is needed. Children with moderate elevations of TSH, e.g.; 40-100, may be false positives or they may be real. Thyroid supplementation is stopped, and a TSH checked about 1-2 weeks later. If normal, then it was a false positive. If high, then it was real and supplementation starts again.

Soy formula and iron preparations may interfere with levothyroxine absorption. Therefore, levothyroxine administration should be separated from iron supplements by at least one hour. If a child is converted to a soy based formula, blood levels should be checked and the dose adjusted as indicated by those levels.

GENETICS AND CONGENITAL HYPOTHYROIDISM

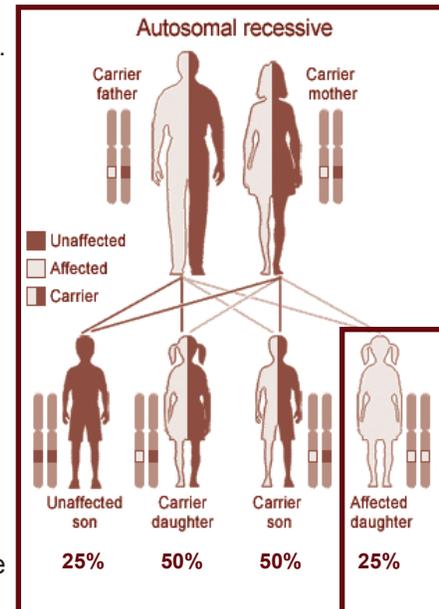
Rena J. Vanzo, MS, Licensed Genetic Counselor, University of Utah Department of Medical Genetics

Congenital hypothyroidism (CH) is one of many medical conditions screened for in the newborn period. If an infant's newborn screen is suggestive of CH, follow-up or confirmatory studies are recommended. After a definitive diagnosis has been made, the parents of an infant with CH will have many questions, including how CH is treated and what impact the diagnosis may have on other family members. The treatment is well-defined, an endocrinologist is usually involved to monitor thyroid hormone replacement therapy, which is generally very successful for infants and older individuals with CH. Alternatively, the impact of the diagnosis on other family members may be more complicated.

For most cases of CH, it is difficult to identify a specific cause. A majority of the time, the likelihood for an additional family member to be diagnosed with CH is probably less than 1%. However, some infants diagnosed with CH may have the condition as a result of a single family trait. Family traits are passed from one generation to the next in structures called chromosomes, which contain genes. Genes come in pairs, as we get one of each pair from each parent. A gene codes for a specific protein or segment of protein that leads to a particular characteristic or function. With regard to CH, the product of a single gene may be so crucial for thyroid structure and function that an error

(also called a mutation) within that gene disrupts normal development. Unfortunately, many different genes play a vital role in normal thyroid structure and function and gene testing for CH is usually not feasible.

Certainly, the presence of more than one family member with CH would be just cause for additional review. In some cases, both parents will "carry" one copy of a single gene mutation, but will not have any related signs or symptoms because they also have one copy of an unchanged gene that functions well enough. However, their child may inherit the gene mutation from each parent, and will have CH because he or she does not possess any copies of the unchanged gene. This would be considered a "recessive" trait by genetic standards. In other cases, a single gene mutation (in only one gene copy) causes CH, and the gene mutation is said to be a "dominant" trait. It is important to realize that the expression of some dominant traits can be modified or masked by other heritable traits or environmental influences. Additionally, and in rare cases, it is possible for an infant diagnosed with CH to have an underlying chromosome alteration. Because thousands of genes are distributed across all 46 chromosomes, a deletion, duplication, or other alteration could affect multiple developmental processes. Primary



care providers should consider this possibility if the infant has co-occurring growth failure, birth defects, developmental delay, or a collection of mild, atypical physical features. In these situations, a formal genetic evaluation may be needed in order to determine what other medical complications the child could be at risk of experiencing.

Remember that every infant, regardless of family medical history, is screened for the presence of CH at birth. In the overwhelming majority of cases, the infant does not have additional medical problems and, with appropriate treatment, grows to lead a very healthy life.

KEEP IN MIND
PREMATURE INFANTS HAVE THE SAME
INCIDENCE OF CONGENITAL HYPOTHYROIDISM
AS FULL TERM INFANTS!





Newborn
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Results showed that by switching to a primary TSH with cut off values of $< 1 \mu\text{U/mL}$ and $> 40 \mu\text{U/mL}$ followed by a secondary T4, we would decrease the number of false positive specimens, increase overall sensitivity and maintain specificity.