Abnormal Newborn Endocrine Screens
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Endocrinology/Studios

NYS Newborn Screen
• Newborn Screening Program, under the direction of the Wadsworth Center’s Division of Genetics, performs more than 11 million screens annually
• Tests are conducted on the quarter of a million babies born each year in New York State

Goal of Newborn Screening
• early identification of children at increased risk for selected metabolic or genetic diseases
  – avoid metabolic crises
  – prevent irreversible neurological and developmental sequelae
• every state in the nation provides newborn screening for phenylketonuria (PKU) and congenital hypothyroidism
  – early identification and treatment change the potential course of the infant’s life

Robert Guthrie, MD, PhD
• Microbiologist and pediatrician at State University of New York, Buffalo
  – devised a simple, inexpensive test which allowed screening for PKU to be done shortly after birth
• Early 1960s he coordinated a twenty-nine state pilot study of 400,000 newborns
  – Successfully identified infants affected with PKU
  – Other states instituted screening programs immediately
• In 1965, NYS law mandated PKU screening for all newborns
NYS Newborn Screening Program Summary 1965-2002

<table>
<thead>
<tr>
<th>Condition</th>
<th>Year Testing Initiated</th>
<th>Live Births</th>
<th>Confirmed Cases</th>
<th>Disease Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>1965</td>
<td>10.23 million</td>
<td>542</td>
<td>1:18,872</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1968</td>
<td>8.16 million</td>
<td>150</td>
<td>1:54,391</td>
</tr>
<tr>
<td>MSUD</td>
<td>1968</td>
<td>8.16 million</td>
<td>34</td>
<td>1:239,062</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>1975</td>
<td>7.30 million</td>
<td>19</td>
<td>1:384,142</td>
</tr>
<tr>
<td>Hemizygous Sickle Cell</td>
<td>1975</td>
<td>7.30 million</td>
<td>3,932</td>
<td>1:1,856</td>
</tr>
<tr>
<td>SC/CC/Other</td>
<td>1975</td>
<td>7.30 million</td>
<td>3,002</td>
<td>1:2,431</td>
</tr>
<tr>
<td>Primary Hypothyroidism</td>
<td>1978</td>
<td>6.35 million</td>
<td>3,086</td>
<td>1:2,057</td>
</tr>
<tr>
<td>Biotinidase Def</td>
<td>1987</td>
<td>4.36 million</td>
<td>56</td>
<td>1:17,834</td>
</tr>
<tr>
<td>HIV-1</td>
<td>1997</td>
<td>1.54 million</td>
<td>AIDS institute</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>2002</td>
<td>58,913</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>MEADD</td>
<td>2002</td>
<td>60,479</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>CAH</td>
<td>2003</td>
<td>15,441</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

NYS Newborn Screen Collection

- Saturate marked areas of a filter paper card with blood obtained by skin puncture of the heel
- Called the Guthrie spot
- Required from every baby born in NYS
- AAP recommends that the specimen not be collected until the newborn is at least 24 hours old

Timeline for Specimen Collection

<table>
<thead>
<tr>
<th>Days of Life</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Hours)</td>
<td>Birth</td>
<td>24</td>
<td>48</td>
<td>72</td>
<td>96</td>
</tr>
</tbody>
</table>

Specimen Quality
- Limited
- Satisfactory
- Optimal

Handling of Specimens

- Warm heel
- Clean with alcohol, wipe dry with gauze
- With lancet, puncture at a slight angle
- Wipe away the first drop of blood with a dry sterile gauze pad, as it is likely to contain tissue fluids that contaminate the specimen
- Allow a second, large drop of blood to form
- Lightly touch filter paper to this large drop of blood. Allow blood to soak through completely into preprinted circle, repeat
- Allow blood spots to air-dry for at least four hours in a horizontal position (flat, no direct heat and sunlight, no refrigeration)
- Mail dried blood collection forms to Wadsworth Center within 24 hours of collection.

Sources of Error

- Residual alcohol may cause hemolysis of the blood specimen resulting in an invalid specimen
- Failure to wipe away first drop may contain tissue fluids that contaminate specimen
- Milking may cause an admixture of tissue fluids with blood specimen, resulting in an invalid specimen
- Holding specimens for >24 hours may result in specimens too old to test
**Results**

- Preliminary screening results for all tests are generally available the day after the samples have been accessioned.
- Confirmation of results depends on the specific verification test, with the longest procedures taking seven days.

**Thyroid Hormone**

- Potent regulator of metabolic rate
- Essential to most organ systems
- Necessary for normal growth
- Normal levels required for neurodevelopment

**Thyroid Embryonic Development**

- Starts at pharyngeal floor
- Diverticulum forms that descends caudally
- Fetus dependent upon transplacental transfer of thyroxine (T4) in first trimester
- By 11-12 weeks gestation, fetal thyroid able to concentrate iodine and synthesize T4
- Infants with complete thyroid agenesis will have preserved levels secondary to maternal transfer

**Hypothalamic-Pituitary Axis**

**Laboratory Detection**

- ELISA (linked immunosorbent assay) is used for the quantitative measurement of T4 for all
- T4 values in the lowest ten percentile are retested for T4 and additionally for TSH
- TSH is quantitatively measured by time-resolved fluoroimmunoassay
- Specimens with T4 below 2 standard deviations of the assay batch are retested for T4 as well as tested for TSH

**Congenital Hypothyroidism**

- Mandated screening in NYS was initiated in 1978 as radioimmunoassays for thyroxine and thyrotropin became available that were sufficiently sensitive and specific for use on dried blood specimens.
**Congenital Hypothyroidism**

- Between 1978 and 2002, 3082 cases in NYS
- Screening enables detection of infants with primary as well as secondary and tertiary hypothyroidism.

**Importance of Congenital Hypothyroidism Newborn Screen**

- Unrecognized congenital hypothyroidism leads to mental retardation
- Remains one of the most common preventable causes of mental retardation worldwide
- Despite the critical importance of TH on multiple organ systems, especially the brain, most infants with CH appear normal at birth
- Thyroid therapy started within 2 weeks of age can normalize cognitive development

**Untreated Congenital Hypothyroidism Symptoms**

- Poor feeding
- Failure to wake for feeding
- Hoarse cry
- Apnea
- Bradycardia
- Poor growth
- Developmental delays

**Congenital Hypothyroidism**

- ~85% sporadic and due to thyroid dysgenesis
  - Agenesis
  - Hypoplasia
  - Ectopy
- ~10% dyshormonogenesis
  - Inborn errors of hormone synthesis
  - Usually autosomal recessive
- Central hypothyroidism
  - Secondary
  - Tertiary

**Untreated CH**

- Large posterior fontanelle
- Delayed closure of anterior fontanelle
- Macroglossia
- Hoarse cry
- Umbilical hernia
- Goiter
- Hypotonia
- Prolonged jaundice
Case #1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Analyte</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Thyroxine</td>
<td>&gt;6 ug/dl</td>
<td>Low level of thyroxine</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Thyroid Stimulating Hormone</td>
<td>&lt;20 uIU/ml</td>
<td>&lt;20 uIU/ml</td>
</tr>
</tbody>
</table>

Case #1 Recommendations

- Repeat lab samples of T4, free T4 and TSH

Case #1 Results

- Repeat labs DOL #28 (9/17/XX)
  - Free T4: 1.11 ng/dl (0.8-3.1)
  - TSH: 2.86 uIU/ml (0.8-10)
  - T4: 11.16 ug/dl (8-16)
- Differential:
  - Transient hypothyroxinemia
  - Central Hypothyroidism
  - TBG deficiency
- Assessment: Transient hypothyroxinemia now normal thyroid function
- Plan: No further endocrine follow-up

Fetal and Neonatal Thyroid Parameters
Case #2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Analyte</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Thyroxine</td>
<td>&gt;6 ug/dl</td>
<td>Screen Negative</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Thyroid Stimulating Hormone</td>
<td>&lt;20 uU/ml</td>
<td>Slightly elevated level of TSH</td>
</tr>
</tbody>
</table>

• Repeat T4, free T4 and TSH

Case #3

<table>
<thead>
<tr>
<th>Condition</th>
<th>Analyte</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Thyroxine</td>
<td>&gt;6 ug/dl</td>
<td>Low level of Thyroxine, possible TBG deficiency</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Thyroid Stimulating Hormone</td>
<td>&lt;20 uU/ml</td>
<td>&lt;20 uU/ml</td>
</tr>
</tbody>
</table>

• Recommend repeat T4, free T4, TSH, TBG
Case #3

- Results DOL #23 (7/16/XX)
  - Free T4: 1.5 ng/dl (0.8-3.1)
  - T4: 6.2 ug/dl (8-19)
  - TSH: 2.53 mIU/l (1.7-9.1)
  - TBG: 12.8 mcg/ml (14.8-32.9)
- Assessment: **TBG deficiency**
- Plan: no treatment

Case #4

<table>
<thead>
<tr>
<th>Gender</th>
<th>Accession No.</th>
<th>Date Received</th>
<th>Submitter Code</th>
<th>Date of Birth</th>
<th>Specimen Date</th>
<th>Date Reported</th>
<th>Physician</th>
</tr>
</thead>
</table>

- **Condition** Analyte Reference Range Result
  - Hypothyroidism Thyroxine >6 ug/dl 3.4 ug/dl
  - Hypothyroidism Thyroid Stimulating Hormone <20 uU/ml 180 uU/ml

Case #4

- Repeat T4, free T4, TSH
- Evaluate immediately and start thyroxine replacement

TBG Deficiency

- Incidence in New York of 1:4,900 births
- Most commonly ascribed to an X-linked dominant gene
- Characterized by low T4 and low TBG serum levels and normal TSH
- Mostly male
- Clinically euthyroid
- No Endocrine follow-up needed

Congenital Hypothyroidism Treatment

- With clearly positive screening test, treatment should begin as soon as confirmation levels drawn
- Important to normalize T4 as rapidly as possible
  - Selva et al showed that lower cognitive scores in children whose levels took longer than 2 weeks to correct
  - 11 studies show early treatment (12-30 days) had mean IQ 15.7 points higher than infants started later (>30 days)
Congenital Hypothyroidism Treatment

- AAP recommends initial dose of 10 to 15 mcg/kg/day
  - Usually correlates to 37.5 to 50 mcg daily
  - Selva et al showed 11 IQ points higher when higher ranged used
- Only tablet should be used
  - Liquids with unstable concentrations
  - Crush tablet in small amount of milk
  - Avoid soy formulas
  - Calcium can interfere with absorption

Congenital Hypothyroidism Treatment

- Keep T4 in upper half of normal range
- Keep TSH less than 5 mU/L
- Recommended lab follow-up:
  - 2 and 4 weeks after T4 Rx start
  - Every 1-2 months during first 6 months
  - Every 3-4 months between 6 months to 3 years
  - Every 6-12 months until growth complete

A 6 month old baby whose family has just emigrated from Ecuador is brought to your office by maternal grandmother. Physical examination reveal length at the 5%tile and weight at the 10%tile, HC at the 25%tile, a sallow complexion with jaundice, horse cry, dry skin and large tongue. The anterior fontanelle measures 3x4 cm. You diagnose primary hypothyroidism and start appropriate thyroid hormone replacement therapy. Of the following, the MOST likely long-term outcome in this baby is

A. Adrenal insufficiency
B. Microcephaly
C. Normal adult height
D. Normal intellectual function
E. Precocious puberty

Answer: C

- Intellectual impairment expected
- Height should catch-up
- Adrenal insufficiency and early puberty not expected
- Head size even with late treatment usually normal

Congenital Adrenal Hyperplasia

- Autosomal recessively inherited disorder
- Caused by a deficiency of any of five of the enzymes of cortisol biosynthesis
- 90-95% of CAH cases, the cytochrome P450 21-hydroxylase (CYP-21) is impaired
- Enzyme 21-hydroxylase is necessary for the conversion of 17-hydroxyprogesterone to 11-deoxycortisol
- Failure to produce cortisol causes the anterior pituitary to produce elevated levels of ACTH, which in turn leads to over production of testosterone, causing virilization

Adrenal Steroid Pathway
CAH Neonatal Presentation

- Female infants may present with genital ambiguity
- Untreated, hyponatremia and hyperkalemia can result in shock or death in the neonatal period from an inability to conserve urinary sodium
- Infants may have hypoglycemia, recurrent fever and hypertension

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<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAH</td>
<td>17OH-Prog</td>
<td>&lt;35 ng/ml</td>
<td>17-OHP=53.1 ng/ml, elevated level suggests CAH</td>
</tr>
</tbody>
</table>

Case #5

- Preterm infant 26 week gestation
- Progression normally, normal electrolytes
- Recommended repeat 17-OHP and renin

17OH-P: 189 ng/dl (normal < 360 for 31-35 week gestation), levels at 6 weeks
- Renin: 5.35 mg/ml/h (0.25-5.82)
- Diagnosis: Prematurity
- Treatment: no endocrine follow-up

Case #6

<table>
<thead>
<tr>
<th>Condition</th>
<th>Analyte</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAH</td>
<td>17-OHP</td>
<td>&lt;35 ng/ml</td>
<td>17OHP=407.8 ng/ml, elevated level indicative of CAH</td>
</tr>
</tbody>
</table>

Figure 7-1

- Flowchart showing the diagnostic steps for CAH
Case #6

- Immediately bring infant in for evaluation and treatment
- Assume CAH with salt wasting and treat accordingly until confirmation labs

You are called to see a newborn who appears to be male and has a well developed rugated scrotum without palpable testes. The phallus is 3.5 cm in length, but there is hypospadias extending to the base of the phallus and what seems to be an open urogenital sinus. It is hard to determine weather there is a separate urethral opening. On reviewing the maternal records, you discover that the prenatal amniocentesis obtained because of advanced maternal age showed an XX chromosome pattern. You arrange a complete initial evaluation for a potential disorder of sexual differentiation.

Of the following, the MOST important initial test to obtain for this child is

A. Fluorescence in situ hybridization for sex determining region of the Y chromosome
B. Measurement of serum 17-hydroxyprogesterone
C. Measurement of serum testosterone
D. Pelvic ultrasonography
E. Repeat confirmatory chromosome study

Adrenal Insufficiency Treatment

- Immediate evaluation
- Rapid volume expansion
- Correction of any hypoglycemia
- Administration of corticosteroid
  - Stress coverage 100 mg/m2/dose
- Electrolyte monitoring
- Long term RX: maintenance hydrocortisone and mineralocorticoid replacement

Answer: B

Most common underlying diagnosis in genetic female infants is congenital adrenal hyperplasia

References