A 4-day-old, 35-week-gestation male infant with intrauterine growth restriction is referred to you for evaluation and management of mixed hyperbilirubinemia. His mother is being treated with thyroxine after thyroid ablation 5 years ago for Graves disease. Delivery was vaginal and uncomplicated. After birth, the infant is found to be symmetrically growth restricted with marked hepatosplenomegaly, petechiae, icterus, and small anterior fontanel (0.5 cm diameter). Tachypnea and tachycardia are also present. He is vigorous and no congenital anomalies are present. Stools are pale white in color. Laboratory and radiology investigations available include the following:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>Markedly elevated</td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>Markedly elevated (33% of total)</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Moderately elevated</td>
</tr>
<tr>
<td>Transaminases</td>
<td>Minimally elevated</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Elevated</td>
</tr>
<tr>
<td>γ-glutamyl transferase</td>
<td>Normal</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Elevated</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>Elevated</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>Elevated</td>
</tr>
<tr>
<td>Platelets</td>
<td>Low</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Low</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Normal</td>
</tr>
<tr>
<td>Galectose-1-phosphatidyl transferase activity</td>
<td>Normal</td>
</tr>
<tr>
<td>α1-antitrypsin</td>
<td>Normal</td>
</tr>
<tr>
<td>Sweat chloride</td>
<td>Normal</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>High</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>Low</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Mild cardiomegaly, diminished vascularity</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Mild pulmonary hypertension</td>
</tr>
<tr>
<td>Abdominal sonogram</td>
<td>Normal, gallbladder present, no dilatation of hepatic ducts, biliary sludge, or choledochal cyst</td>
</tr>
<tr>
<td>Bacterial cultures</td>
<td>No growth</td>
</tr>
<tr>
<td>Viral serologies and cultures</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Of the following, the study that is MOST likely to confirm the diagnosis in this infant is:

1. **ABCB11 gene mutation analysis (lymphocytes)**
2. Cytomegalovirus culture (urine)
3. Fumarylacetoacetate hydroxylase activity (lymphocytes)
Jagged-1 gene mutation analysis (lymphocytes)

thyroid-stimulating antibody concentration (serum)

You selected 1, the correct answer is 5.

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The presence of thyroid-stimulating antibodies in the infant in this vignette will confirm the diagnosis of congenital hyperthyroidism. Maternal Graves disease, high thyroxine concentration, and low thyroid-stimulating hormone concentration raise suspicion about congenital hyperthyroidism as the cause for the clinical findings in this infant. Intrauterine growth restriction, cardiomegaly associated with congestive heart failure, hepatosplenomegaly, small anterior fontanel, petechiae, goiter, proptosis, hyperkinesis, diarrhea, and poor growth are reported in neonates with this disorder.

Infants born to mothers receiving antithyroid medications, such as propylthiouracil, may become biochemically and clinically hyperthyroid during the first weeks after birth as the antithyroid medications are metabolized. In contrast, infants born to mothers whose thyroid gland has been ablated may become hyperthyroid in utero because of the ongoing production and transplacental passage of thyroid-stimulating antibodies by the mother, as occurred in the infant in this vignette.

Cholestatic jaundice is an unusual finding in congenital hyperthyroidism. Although the mechanism is unclear, the cholestasis improves with treatment and recovery from hyperthyroidism. Immaturity of bile formation and flow in neonates is reflected by impaired hepatic uptake of bile salts (the primary stimulus for bile flow), smaller bile salt pool size, and lower rates of absorption in the ileum (versus the adult). These deficiencies are described by the term physiologic cholestasis (or physiologic hypercholanemia) of infancy. It is likely that pituitary hormones affect bile synthesis and flow because of the association of cholestasis with hypopituitarism. However, the specific effect of pituitary hormones, specifically thyroxine, on bile metabolism is yet to be determined.

It could be conjectured that the taurine conjugated bile acids and precursors that predominate in the fetus, rather than the glycine conjugates that predominate in the older child and adult, may be overproduced in response to the hypermetabolic response to high thyroxine concentrations. These taurine-conjugated bile acids may then accumulate because of immature bile metabolism in the neonate and impair the metabolic and cellular functions of the hepatocyte.

The presence of intrauterine growth restriction, coagulopathy, and elevated liver function results, including the conjugated fraction of bilirubin, is consistent with a number of congenital infections, including cytomegalovirus, toxoplasmosis, human immunodeficiency virus, parvovirus B19, and herpes simplex. Absence of maternal or placental evidence of congenital infection usually prompts a search for the other common and easily evaluated causes for neonatal cholestasis, especially if early recognition and treatment are important to reduce morbidity. The causes of neonatal cholestasis include:

- biliary atresia (most common)
- other obstructive biliary tract disorders (such as choledochal cysts, paucity of bile ducts)
- inherited disorders (such as a₁-antitrypsin deficiency, cystic fibrosis)
- bacterial infections (such as sepsis and urinary tract infections)
- galactosemia
- hypothyroidism
- idiopathic hepatitis

If clinical or laboratory studies are inconclusive or suggestive of other diagnoses, additional
evaluation is indicated for other inborn errors of metabolism (such as tyrosinemia, fructosemia, peroxisomal disorders, progressive familial intrahepatic cholestasis, bile salt synthetic defects, congenital hemochromatosis), endocrinopathies (such as hypopituitarism, hyperthyroidism), syndromes (such as Alagille syndrome), and toxic exposures (such as drugs, parenteral nutrition).

*ABCB11* gene mutation analysis determines the presence of mutations in the gene responsible for progressive familial intrahepatic cholestasis type 2 (PFIC2). The *ABCB11* gene is responsible for the activity of the bile salt export pump located on the canalicular membrane of the hepatocyte. Like progressive familial intrahepatic cholestasis type 1 (*PFIC1*, mutation of the *ATP8B1* gene), *PFIC2* is inherited in an autosomal recessive pattern and the spectrum of disease can be variable. However, severe cholestasis with pruritus, malabsorption, greasy stools, and failure to thrive may present in the first months after birth. If untreated, cirrhosis, hepatic failure, and death may occur during infancy or early childhood. The diagnosis is usually determined on clinical and laboratory findings with low or normal concentrations of g-glutamyltranspeptidase (GGT). In most disorders that cause cholestasis, GGT is elevated. Cholestasis with hyperthyroidism is one of the few disorders associated with normal or low GGT, as in the infant in this vignette.

Isolation of cytomegalovirus (CMV) from fibroblast tissue cultures of urine or saliva is the standard reference method to determine the presence of CMV. Modifications of the tissue culture method by the addition of monoclonal antibodies to CMV-specific early antigens (shell vial assay, microtiter plate immunofluorescent antibody assay) may allow diagnosis to be established within 24 hours. Such modifications have shown high sensitivity and specificity. DNA hybridization methods are reliable but limited if the titer of virus is less than $10^3$ infective doses per milliliter. The polymerase chain reaction amplification method for detecting CMV in many tissue or body fluid specimens is highly sensitive and specific. A modification for use of dried filter paper specimens is also available for retrospective diagnosis. Detection of antigenemia using CMV-specific monoclonal antibodies is also available but sensitivity and specificity are not superior to other methods. Serologic analysis of the immune response to CMV is complicated by individual variations in development of IgG and IgM antibodies and lower sensitivity and specificity than viral culture methods.

A diagnosis of tyrosinemia type 1 is confirmed by measurement of fumarylacetoacetate hydroxylase activity in lymphocytes, erythrocytes, or liver biopsy specimens. A presumptive diagnosis is determined by the onset in early infancy of hepatic failure, hepatomegaly, hemorrhage, vomiting, hypoglycemia, Fanconi-like syndrome (normal anion gap acidosis, hyperphosphaturia, hypophosphatemia), mixed hyperbilirubinemia, and elevations of serum transaminases and a-fetoprotein (even in cord blood specimens suggesting in utero liver dysfunction). These findings usually are precipitated by an intercurrent illness and catabolic state. Increased plasma tyrosine and methionine concentrations and elevated serum and urine succinylacetone and succinylacetone are diagnostic. Tyrosinemia type 1 is rare (1:110,000 live births) outside Quebec, Canada (1:1,846 live births), transmitted in an autosomal recessive fashion, treatable with 2-(nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione and liver transplantation, and carries a high risk of hepatocellular carcinoma (37% of cases).

Alagille syndrome is diagnosed with *Jagged-1* mutation analysis. Eighty-eight percent of affected individuals have abnormalities in the *Jagged-1* gene. Fluorescence in situ hybridization for microdeletions of chromosome 20p12 will detect another 7% of affected patients and mutation analysis of the *NOTCH2* gene in present is 1% of affected individuals. Alagille syndrome is inherited as an autosomal dominant disorder and is characterized by:

- Chronic cholestasis
- Peripheral branch pulmonary stenosis and other cardiac defects
- Paucity of bile ducts (beginning in childhood)
- Butterfly vertebrae and other skeletal abnormalities
- Characteristic facies (broad forehead, deep-set eyes, triangular facies)
- Eye abnormalities (posterior embryotoxon = prominent Schwalbe ring in the anterior chamber of the eye)
References:


**American Board of Pediatrics Content Specification(s):**

Identify the effect of maternal immunologic disease with transplacental passage of immunoglobulins and its treatment on the fetus

Understand the relationship between fetal and maternal thyroid physiology

Understand the differential diagnosis, evaluation, and approach to management of mixed forms of jaundice

Recognize the effects on the fetus of maternal endocrine disorders (other than diabetes mellitus) and their management

Identify the etiology and clinical manifestations of congenital hyperthyroidism

Know the laboratory features and treatment of congenital hyperthyroidism

Understand the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids

Understand the diagnostic criteria of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Ebstein-Barr virus, and varicella virus

Know the various laboratory and radiographic techniques to diagnose metabolic and familial causes of cholestasis in the neonate
Of the following, the outcome MORE likely to be found later in life in the infant in the vignette than in infants with normal growth is:

1. growth hormone deficiency
2. insulin resistance
3. mental retardation
4. short stature
5. subcutaneous adiposity

You selected 5, the correct answer is 2.

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The metabolic syndrome, although variably defined, is composed principally of insulin resistance, hyperinsulinemia, visceral adiposity, dyslipidemia, and systemic hypertension. Ischemic heart disease and overt type 2 diabetes mellitus may develop. Systemic inflammation, hypercoagulability, and endothelial dysfunction are also observed in the spectrum of this disorder. About 20% to 30% of adults are affected and the prevalence is increasing. Teenagers are also being diagnosed with the metabolic syndrome at an alarming frequency. Because morbidity and mortality during adulthood are substantial, research and development of strategies to prevent or treat associated pathophysiologic aberrations are receiving emphasis by neonatologists and internal medicine specialists alike.

Multiple metabolic and physiologic abnormalities underlie the metabolic syndrome. Insulin resistance and abnormal adipose tissue metabolism are common, but not essential, features (Figure 1).

Figure 1: Pathogenic mechanisms contributing to the metabolic syndrome (adapted from Batsis et al [2007])
A large body of epidemiologic and animal model evidence indicates that low birthweight, especially presenting as intrauterine growth restriction (IUGR) as in the infant in this vignette, is associated with a high risk for developing the metabolic syndrome and its complications. The risk for metabolic syndrome in small-for-gestational-age infants during young adulthood is low (2.3%) but is sixfold higher than in those who were appropriate for gestational age (0.4%). Landmark studies have demonstrated associations between low birthweight and obesity, hypertension, hypertriglyceridemia, cardiovascular disease (myocardial infarction, stroke), impaired glucose tolerance, and type 2 diabetes mellitus.

It is important to recall that size at birth is a poor proxy for IUGR. Small size is associated with many causes, not all of which may have implications for adult disease. For example, infants whose birthweights are lower than the 10th percentile on growth grids are often constitutionally small but do not have IUGR. These normal-growth but small infants may not be at higher risk for adult morbidity than those born with IUGR. Additional research is needed to clarify which populations of infants born “small” are at risk for “adult” diseases.

The underlying mechanisms for later development of metabolic syndrome in infants with IUGR are unclear. These mechanisms likely involve fetal programming of metabolic pathways and organ development in response to limited nutrient/oxygen delivery and pathologic insults (Figure 2).

Figure 2: The thrifty phenotype hypothesis (reprinted with permission from Fernandez-Twinn and Ozanne [2006])
The “thrifty phenotype” hypothesis describes in utero programming of fetal metabolic systems and physiologic adaptations in response to life-threatening maternal stress, infection, undernutrition, placental dysfunction, and exposure to alcohol and tobacco. After birth, these metabolic and physiologic adaptations then become a liability during times of nutrient excess.

Changes in the hypothalamic-pituitary-adrenal axis are hypothesized to play a pivotal role in fetal adaptations but oxidant stresses also likely play important roles. The combination of increased fetal catabolism and subsequent metabolic reprogramming causes growth restriction. Specific findings in affected infants include reduction in pancreatic beta-cell mass and function; growth hormone hypersecretion (induces insulin resistance); abnormal muscle, liver, and fat development (visceral rather than subcutaneous adiposity); changes in adrenal and neuroendocrine production; and reduction in glomerular number. Genetic and epigenetic changes occur and account, in part, for risk transmission through subsequent generations of offspring. Insulin resistance, hypertension, visceral adiposity, and other findings of the metabolic syndrome result. As the infant grows, occult physiologic and metabolic abnormalities exist but overt signs and symptoms may only become apparent or be triggered during the teenage years and adulthood.

An interesting parallel has been described between full-term infants with IUGR and extremely preterm infants. Both experience undernutrition during the last “trimester” of fetal life. The preterm infant fails to grow during the first weeks after birth because of limited nutrient intake and medical illness. During this time, low concentrations of insulinlike growth factor 1 (IGF-1), an important regulator of growth, stimulate excessive secretion of growth hormone. The adrenal hormone axis is often upregulated because of stress and, combined with a large supply of growth hormone, causes insulin resistance. The addition of exogenous glucocorticoids exacerbates these pathophysiologic phenomena. In the presence of overnutrition and inhibition of important adipocyte metabolic pathway components (such as beta3-adrenoreceptors), fat is preferentially deposited in visceral sites within the mesentery and abdomen rather than in subcutaneous sites. This gives infants the appearance of truncal obesity with relatively thin extremities. Protein supplementation to raise IGF-1 levels has the potential to reduce growth hormone hypersecretion and insulin resistance. Supplementation with very-long-chain polyunsaturated fatty acids (such as eicosapentaenoic acid and docosahexaenoic acid) has been found to reduce production of proinflammatory mediators that also cause insulin resistance. Additional protein and very-long-chain fatty acid supplementation are promising interventions to mitigate the evolution of the physiologic impairments that may lead to the metabolic syndrome in recovering preterm infants and full-term infants with IUGR.

Although there are conflicting reports, infants who are born at term and severely growth
restricted are found to have IQs similar to those of infants with normal growth. Nevertheless, such infants with IUGR are at higher risk for school failure because of behavioral disorders (especially attention deficit disorder) and learning disabilities. In contrast, preterm infants with severe IUGR have higher rates of cognitive, motor, and neurologic deficits than preterm infants without IUGR. Interestingly, such infants have lower rates of cerebral palsy.

Growth patterns in infants with IUGR vary with the cause of the growth restriction. Infants with moderate IUGR and uncomplicated medical courses, such as the infant in the vignette, usually reach normal height. In comparison, infants with severe IUGR are frequently shorter and lighter through adolescence.

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References:


Fernandez-Twinn DS, Ozanne SE. Mechanisms by which poor early growth programs type-2 diabetes, obesity and the metabolic syndrome. *Physiol Behav.* 2006;88:234-243


NY Acad Sci. 2006;1092:138-147
Vuguin PM. Animal models for small for gestational age and fetal programming of adult disease. Horm Res. 2007;68:113-123

American Board of Pediatrics Content Specification(s):

Recognize that there may be a period of catch-up growth in SGA infants
Understand the differences in body composition between SGA, LGA, and AGA infants
Know the nutritional requirement before and during pregnancy and the impact on fetal growth and development
Understand the complications and management of fetal growth restriction