



# HHS Public Access

Author manuscript

*Pediatr Ann.* Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:

*Pediatr Ann.* 2014 September ; 43(9): e218–e224. doi:10.3928/00904481-20140825-08.

## Screening for Hormonal, Monogenic, and Syndromic Disorders in Obese Infants and Children

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### Abstract

The prevalence of pediatric obesity in the United States is nearly 17%. Most cases are “exogenous”, resulting from excess energy intake relative to energy expenditure over a prolonged period of time. However, some cases of obesity are “endogenous”, associated with hormonal, genetic, or syndromic disorders such as hypothyroidism, Cushing’s syndrome, growth hormone deficiency, defective leptin signaling, mutations in the melanocortin 4 receptor, and Prader-Willi and Bardet-Biedl syndromes. This article reviews the hormonal, monogenic, and syndromic causes of childhood obesity and identifies critical features that distinguish “endogenous” obesity disorders from the more common exogenous obesity. Findings that raise suspicion for endogenous obesity include onset in infancy, lack of satiety, poor linear growth, dysmorphic features, and cognitive dysfunction. Selection and interpretation of appropriate laboratory tests and indications for subspecialist referral are also discussed.

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Disclosure: The authors have no relevant financial relationships to disclose.



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With a prevalence of almost 17% in the United States, pediatric obesity is a challenge for the general pediatrician.<sup>1</sup> Most cases are exogenous, resulting from excess energy intake relative to energy expenditure over prolonged periods.<sup>2</sup> Less commonly, pediatric obesity is attributable to hormonal or genetic disorders. Whereas children with exogenous obesity may require screening for type 2 diabetes, fatty liver disease, and dyslipidemia, those with suspected endogenous obesity require additional testing to identify the cause and to make appropriate referrals to subspecialists. This article explores the hormonal, monogenic, and syndromic causes of childhood obesity, identifying critical features that necessitate testing or referral (Tables 1–4; Figure 1).

Determining the etiology of pediatric obesity requires a detailed history, including age at onset and speed of weight gain, pubertal onset and rate of progression, cognitive development, and parents' and siblings' heights, weights, and pubertal onset. Identifying a family history of obesity or an endocrine disorder, particularly thyroid disease, is helpful.

Careful examination of the growth chart is critical because several hormonal and genetic disorders reduce linear growth velocity. Physical examination findings vary, but dysmorphic features and/or cognitive dysfunction should increase suspicion for an endogenous etiology.<sup>2</sup>

## HORMONAL AND STRUCTURAL DISORDERS

Hypothyroidism can reduce growth velocity and promote water retention and fat deposition; thus, many (but not all) hypothyroid children have an increased body mass index.<sup>2</sup>

Hypothyroidism alone does not cause severe obesity, and most pediatric patients have limited weight loss after beginning treatment.<sup>3</sup> Children with hypothyroidism may fatigue easily, feel cold or depressed, sleep more, and develop dry skin or constipation.<sup>3</sup> A family history of autoimmune thyroid disease is important given the strong genetic component of the disease. Goiter should raise immediate concern but is not necessary for the diagnosis.

When considering hypothyroidism, the authors recommend checking thyroid-stimulating hormone (TSH), free T4 (fT4), and total or free T3 levels. Children with primary hypothyroidism have normal or low fT4 and T3 and high TSH; those with central (hypothalamic or pituitary) hypothyroidism have low fT4 and normal or low T3 with normal or low TSH. In contrast, children with exogenous obesity commonly have normal or mildly elevated TSH (4.5 to 7 mIU/mL) with normal fT4 and elevated T3<sup>2</sup>; this is because leptin, a hormone produced by white adipose tissue, stimulates TSH secretion and peripheral conversion of T4 to T3 (Figure 2).<sup>2,4</sup> Because Hashimoto's thyroiditis is the most common cause of pediatric hypothyroidism, thyroid antibodies should be measured in children with hypothyroidism or goiter. Children with hypothyroidism require treatment with levothyroxine and referral to pediatric endocrinology for ongoing management.

Growth hormone deficiency (GHD) should be considered in children with short stature (height more than 2.5 SD below mean), growth deceleration (height velocity more than 2 SD below mean), and/or height more than 1.5 SD below mid-parental height.<sup>5</sup> This differentiates GHD from constitutional delay, in which growth rate after age 2 years is typically normal. Muscle mass and tone may be diminished, and there is often accumulation of abdominal fat; weight gain is maintained or mildly increased, distinguishing GHD from failure to thrive.<sup>6,7</sup> Children with congenital GHD may have immature facies, underdeveloped nasal bridges, frontal bossing, delayed dentition, and high-pitched voices.<sup>8</sup> Bone age and pubertal progression are delayed<sup>7</sup> unless there is concurrent precocious puberty, which may occur in children with central nervous system lesions. A history of microphallus or hypoglycemia, hepatic dysfunction, or unexplained jaundice in the neonatal period should raise suspicion for congenital GHD.<sup>8</sup>

The diagnosis of GHD is difficult because the low basal GH levels in children with GHD may not differ from those in normal children.<sup>5</sup> Insulin-like growth factor1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) are useful screening tests but may be difficult to interpret in children with systemic disorders causing growth failure.<sup>5</sup> Both IGF-I and IGFBP-3 are usually low in GHD but may also be reduced in malnourished children with underlying gastrointestinal, hepatic, or renal disease.<sup>5</sup> Primary disorders of weight gain (failure to thrive) are more commonly associated with mild reductions in IGF-1 and normal

IGFBP-3. Children with exogenous obesity usually have normal or increased growth velocity, normal or advanced bone age, and normal or increased IGF-1 and IGFBP-3.<sup>2</sup> Children with suspected GHD should be referred to a pediatric endocrinologist for additional testing and are typically treated with daily subcutaneous growth hormone injections.

Most cases of pediatric Cushing's syndrome are iatrogenic, due to prolonged glucocorticoid exposure.<sup>9</sup> However, some children with Cushing's syndrome have tumors of the pituitary or adrenal gland. Like GHD, children with glucocorticoid excess demonstrate growth failure despite continued (and often excessive) weight gain (Figure 3).<sup>9</sup> Physical examination may be notable for moon facies; facial plethora; hirsutism; acne; central (truncal) obesity; bruising; and broad (more than 1 cm), hemorrhagic, violaceous, and/or atrophic striae.<sup>9</sup> In contrast, striae in exogenous obesity are typically thin and pink. Children with glucocorticoid excess may have hypertension, glucose intolerance, headaches, hyperphagia, emotional lability, depression, and anxiety.<sup>9</sup> The bone age is delayed in children with isolated glucocorticoid excess but may be normal or even advanced in patients who produce excess androgens as well as glucocorticoids.<sup>10</sup> Many clinical manifestations of exogenous obesity mimic those of Cushing's syndrome; thus, diagnostic testing is obligatory and may include measurement of 24-hour urinary-free cortisol excretion, dexamethasone suppression test, and/or salivary cortisol testing to assess diurnal rhythm.<sup>9</sup> Concern for Cushing's syndrome should prompt referral to pediatric endocrinology.

Hypothalamic obesity is usually associated with a central nervous system injury or structural lesion involving the hypothalamic-pituitary region and/or the third ventricle; examples include supra/parasellar brain tumors, hypothalamic surgery, or central nervous system radiation.<sup>2</sup> Leptin cannot signal satiety to the damaged hypothalamus, resulting in severe or atypical hyperphagia and dramatic weight gain even in the setting of caloric restriction.<sup>2,11</sup> Patients with hypothalamic obesity also have fatigue and decreased energy expenditure and are at risk for other endocrinopathies, including GHD, hypothyroidism, precocious or delayed puberty, and diabetes insipidus.<sup>2,11</sup> Behavioral counseling and pharmacologic agents have limited success in controlling weight gain.<sup>12</sup> Nevertheless, pediatricians should refer these patients to endocrinology for evaluation of hypothalamic-pituitary function and possible pharmacotherapy.

Polycystic ovary syndrome (PCOS) affects 5% to 10% of women, depending on diagnostic criteria.<sup>2</sup> Classic features include irregular menstrual cycles (two years post-menarche), caused by oligo- or anovulation, and hyperandrogenism, which manifests as acne, hirsutism, or alopecia.<sup>13</sup> Excess weight gain occurs in approximately 60% of patients with PCOS and promotes or exacerbates insulin resistance and glucose intolerance.<sup>6</sup> The diagnosis is based on hyperandrogenism and menstrual irregularities in the absence of other virilizing disorders. Free testosterone, adrenal androgens (including 17-hydroxyprogesterone), prolactin, and pelvic/adrenal sonography may be helpful in certain cases.<sup>13</sup> Patients with presumed PCOS should be referred to endocrinology for evaluation and management.

Hyperprolactinemia is associated with obesity because prolactin promotes food intake and weight gain.<sup>14</sup> Pathologic hyperprolactinemia can be caused by prolactinomas, tumors that

damage the hypothalamic-pituitary stalk, septo-optic dysplasia, hypothyroidism, renal insufficiency, medications (particularly antipsychotics), and ROHHAD (rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) syndrome.<sup>15,16</sup> Symptoms vary by etiology but include weight gain, pubertal delay or amenorrhea, hirsutism, acne, and galactorrhea.<sup>14,15</sup> The diagnosis is based on a prolactin level greater than 25 ng/mL.<sup>15</sup> Treatment with dopamine agonists such as bromocriptine or cabergoline may reduce weight and improve insulin sensitivity.<sup>14</sup>

ROHHAD is a recently described heterogeneous syndrome. Hyperphagic obesity typically begins between ages 2 and 4 years, following a period of normal development.<sup>16</sup> The obesity may be associated with decreased growth velocity,<sup>16</sup> mimicking Cushing's syndrome. Hypothalamic and autonomic dysfunction, as well as central hypoventilation, occur months or years later.<sup>16</sup> Symptoms vary and may include vital sign instability, disordered sodium and water regulation, behavior problems, pain hyposensitivity, hypothyroidism, and delayed or precocious puberty.<sup>16</sup> There may be hyperprolactinemia and low levels of IGF-1.<sup>16</sup> Approximately 35% of patients with ROHHAD have neural crest tumors.<sup>16</sup> Detecting central hypoventilation is critical: respiratory failure and cardiopulmonary arrest are common, and approximately 50% of patients require 24-hour ventilation with a tracheostomy.<sup>16</sup>

## MONOGENIC DISORDERS

The features of monogenic and syndromic obesity differ from those of hormonal obesity. Monogenic obesity results from a single gene mutation and includes leptin deficiency, leptin receptor mutations, proopiomelanocortin (POMC) deficiency, preproconvertase deficiency, and, most commonly, melanocortin 4 receptor (MC4R) mutations. These disorders arise from defects in proteins that act in the hypothalamus to control food intake and energy expenditure. Children with such defects develop severe hyperphagia, leading to rapid weight gain in the first year of life.<sup>11,17</sup>

Leptin binds to receptors on POMC/cocaine and amphetamine-related transcript (CART) neurons, which act as sensors of energy balance within the hypothalamus. Disorders in leptin production or action result in severe early-onset obesity, altered immune function due to T-cell defects, and pubertal delay. Linear growth is normal, but adults may be short due to lack of the pubertal growth spurt.<sup>2,18</sup>

Leptin deficiency is rare, identified primarily in those of Pakistani or Turkish descent as a result of consanguinity. On the other hand, mutations in the leptin receptor have been identified in up to 3% of individuals with severe, early-onset obesity. Unlike children with leptin deficiency, who develop hyperphagia at several months of age, infants with leptin receptor mutations become hyperphagic in the first week of life.<sup>18</sup>

POMC is produced by POMC/CART neurons in the hypothalamus. It is cleaved into several peptides, including adrenocorticotrophic hormone (ACTH) and alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH).<sup>19</sup> Individuals deficient in POMC become obese due to lack of  $\alpha$ -MSH, which, in addition to regulating melanin synthesis, inhibits food intake through binding to the MC4R.<sup>11,17</sup> Affected children often have a fair complexion and may present with



adrenal crisis (hypoglycemia, hyponatremia, hypotension) during infancy due to ACTH deficiency.<sup>20</sup>

Proprotein convertase 1 is the enzyme responsible for processing POMC into its end products. A defect in this enzyme limits the ability to process prohormones and neuropeptides into functional proteins involved in metabolism, including POMC, insulin, and glucagon. Affected children have early-onset obesity but may present with reactive hypoglycemia and diarrhea from an associated enteropathy.<sup>2,20</sup>

Mutations in the MC4R are the most common mutations identified in children with nonsyndromic, early-onset obesity<sup>21</sup>; the prevalence in such cases is as high as 6%.<sup>17</sup> Children with MC4R mutations become hyperphagic during infancy and accumulate fat rapidly, along with an increase in lean body mass, a feature that differentiates this disorder from other causes of monogenic obesity such as leptin or leptin receptor deficiencies. Linear growth acceleration is thought to result from hyperinsulinism.<sup>17</sup>

## SYNDROMIC DISORDERS

In contrast to monogenic disorders, the development of obesity in syndromic conditions typically occurs after infancy. Examples include Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, Albright's hereditary osteodystrophy, and WAGR (Wilms' tumor, aniridia, genitourinary anomalies, and retardation) syndrome. These syndromes are characterized by cognitive impairment, dysmorphic features, and anomalies of major organs.

Prader-Willi syndrome (PWS), caused by functional absence of the paternal allele of 15q11-13, affects one in every 15,000 to 30,000 births.<sup>2,11</sup> Birth weight is normal or slightly low, and infants fail to gain weight, often requiring tube feedings, due to hypotonia and poor suck.<sup>11,22</sup> Following a period of limited catch-up weight gain from 6 to 18 months, children develop an insatiable appetite, resulting in obesity by age 6.<sup>22</sup> The relatively high levels of ghrelin in children with PWS may contribute to hyperphagia and excess weight gain because ghrelin has been shown to stimulate food intake in adults.<sup>2,11</sup> Physical features include small hands and feet and dysmorphic facies characterized by almond-shaped palpebral fissures and a downturned mouth with a thin upper lip.<sup>22</sup> Affected children often have a fair complexion and suffer from developmental delay, delayed puberty, and poor linear growth secondary to growth hormone deficiency.<sup>2,22</sup> Growth hormone replacement improves body composition in children with PWS and has beneficial effects on linear growth. Diagnosis of PWS is made through methylation studies.<sup>2</sup>

Bardet-Biedl syndrome is a heterogeneous autosomal recessive disorder caused by a defect in one of 15 genes involved in ciliary function.<sup>2,23</sup> The prevalence of this group of disorders is one in 13,500 to 160,000 individuals depending on geographic location.<sup>24</sup> Energy dysregulation is thought to arise from defective leptin activity.<sup>23</sup> Classic features include early-onset obesity, cognitive impairment, delayed puberty, renal anomalies (calyceal clubbing, parenchymal cysts, vesicoureteral reflux, hydronephrosis), post-axial polydactyly, and rod-cone dystrophy.<sup>25</sup> Hearing loss, diabetes mellitus, and congenital heart disease may also occur.<sup>23</sup> Complications from morbid obesity and renal disease are the most common causes of mortality.<sup>2,19</sup>

Alström syndrome (AS) is a rare autosomal recessive disorder affecting fewer than one in every 1,000,000 people. It is caused by a mutation in *ALMS1*, resulting in defective ciliary function. Children typically develop obesity by age 5 years. Like children with Bardet-Biedl syndrome, children with AS have visual impairment and sensorineural hearing loss, although the incidence of deafness is higher in those with AS and typically occurs in the first decade of life. Another distinguishing feature is the high incidence of type 2 diabetes, which occurs in up to 70% of individuals by age 20 years.<sup>26</sup> Other endocrinopathies include growth hormone deficiency, hypertriglyceridemia, pubertal delay, and hyperandrogenism. AS is also associated with renal anomalies and cardiomyopathy, the most common cause of mortality in affected individuals.<sup>26</sup>

Albright's hereditary osteodystrophy is caused by a mutation in *GNAS1*, leading to a defect in the alpha subunit of G proteins ( $G_{\alpha_s}$ ) coupled to transmembrane receptors. Genomic imprinting in tissues including the kidney, thyroid, pituitary somatotropes, gonads, and chondrocytes results in wide phenotypic variability. Excess weight gain may occur during infancy and is thought to arise from  $G_{\alpha_s}$  deficiency in imprinted regions of the hypothalamus.<sup>27,28</sup> Round facies, brachydactyly, metacarpia of hands and/or feet, and heterotopic ossifications are classic characteristics.<sup>28</sup> Other features include early-onset hypothyroidism without goiter due to TSH resistance, short stature from a defect in growth hormone–releasing hormone (GHRH) action, and pubertal delay due to TSH, GHRH, and gonadotropin resistance. Pseudohypoparathyroidism, characterized by hypocalcemia and hyperphosphatemia despite high levels of PTH, may also occur.<sup>2</sup>

WAGR syndrome, characterized by Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation, is another disorder that may be associated with both obesity and cognitive impairment.<sup>21</sup> It is caused by a deletion on 11p14.1, located near the gene responsible for brain-derived neurotrophic factor (BDNF) production. BDNF is regulated by nutritional status and MC4R signaling and is expressed in the hypothalamus, where it facilitates neuronal proliferation, survival, and differentiation. Interestingly, the majority of patients with WAGR and BDNF deletions are obese; in contrast, the rate of obesity in those without BDNF deletions is comparable to that of the general United States population.<sup>2</sup>

Genome-wide association studies have identified other genetic variants thought to predispose to obesity. Many are associated with intellectual disability or developmental delay, demonstrating the critical role of affected genes in maintaining neurologic function and energy balance. Of particular interest are variants on chromosome 1 and the short arm of chromosome 16 (1q21.1, 16p11.2, and 16p12.1 microdeletions). In addition to obesity and developmental delay/intellectual disability, these genetic variants have been associated with autism, schizophrenia, and cardiac and renal anomalies.<sup>29</sup> Continued advances in the field may uncover additional genes implicated in obesity, promoting our understanding of the complex nature of this disorder and leading to the discovery of new obesity-related syndromes.

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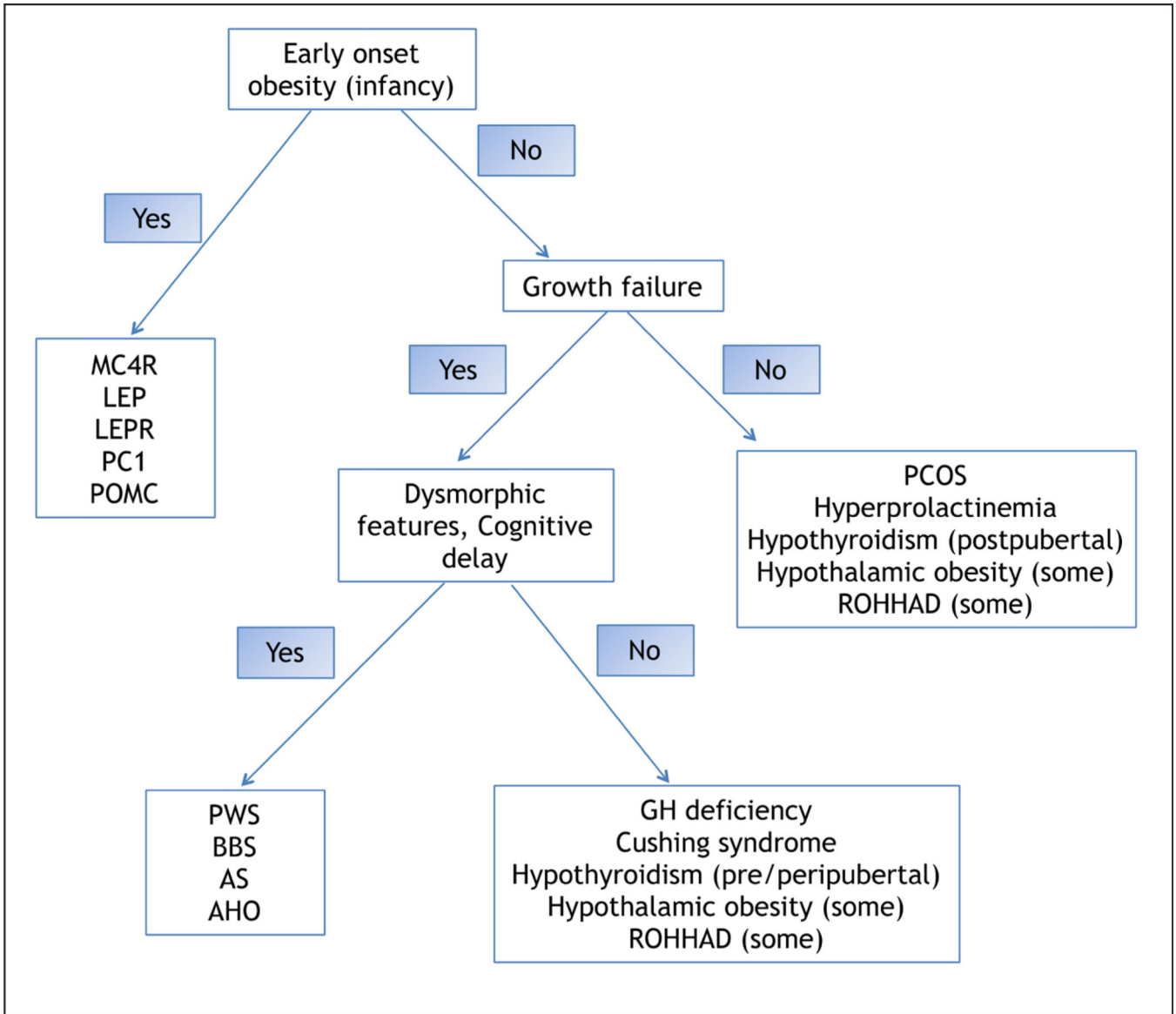
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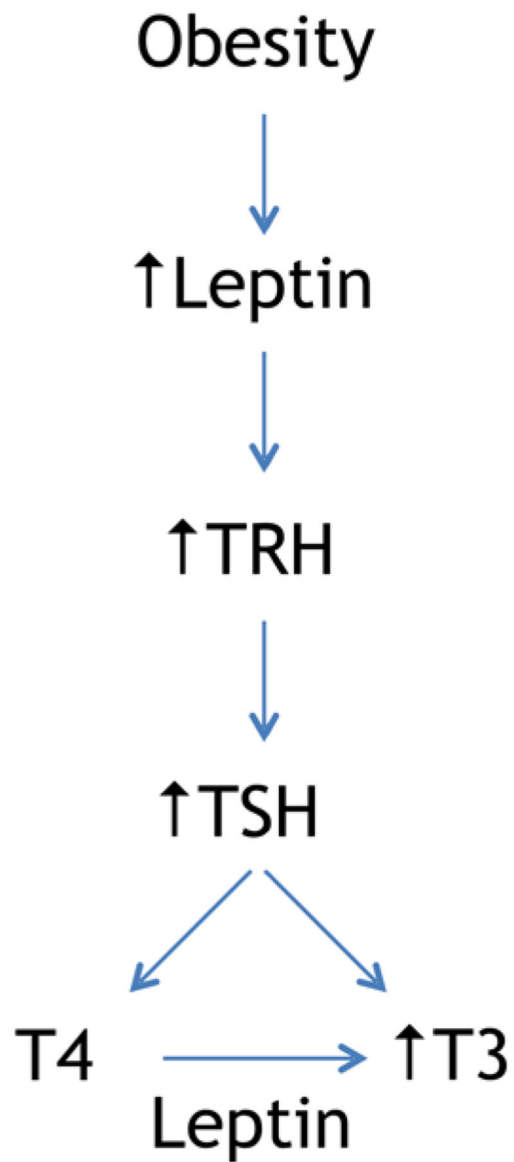
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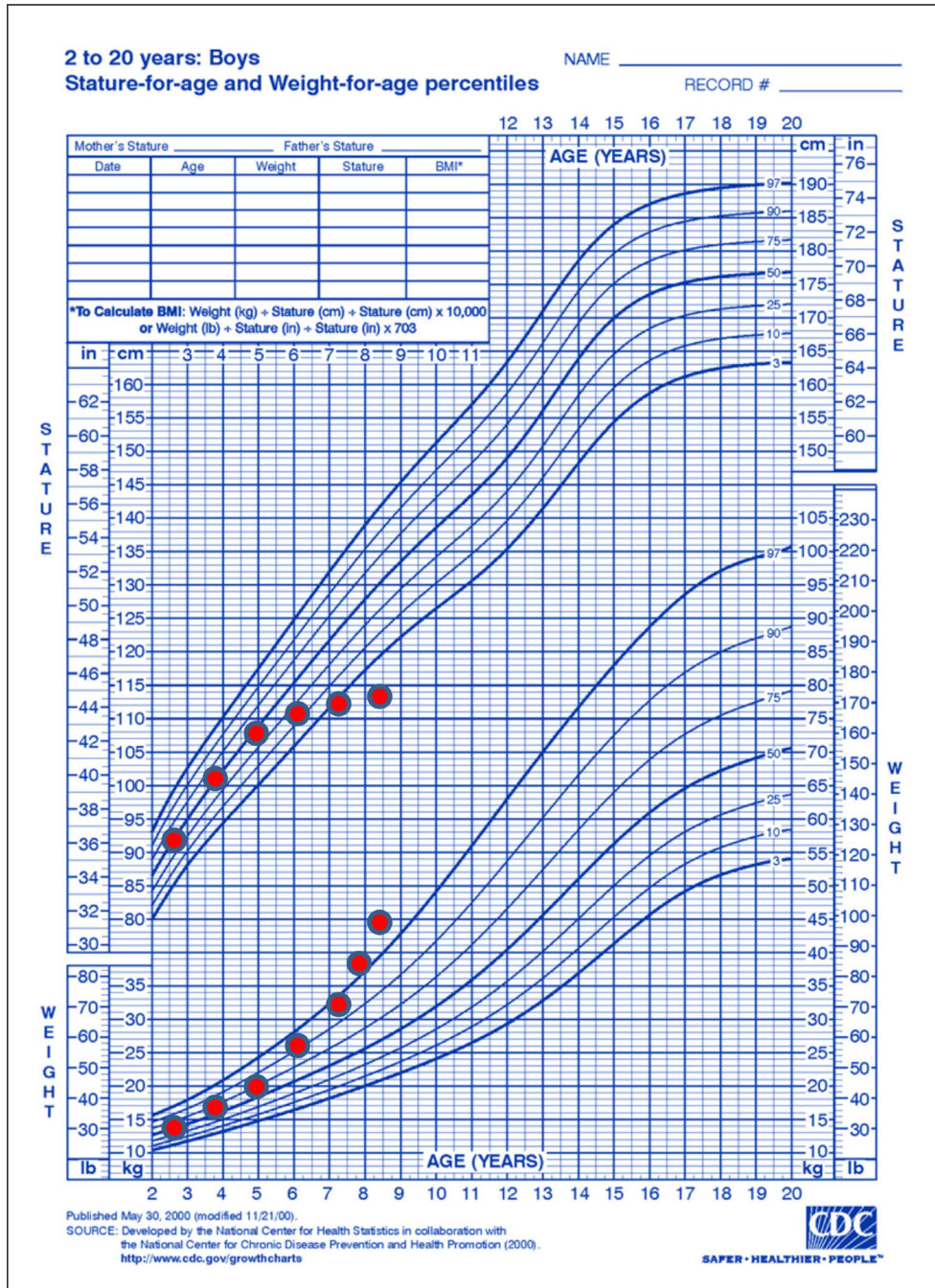


**Figure 1.** Flowchart of classic features of hormonal, monogenic, and syndromic causes of childhood obesity. AHO = Albright’s hereditary osteodystrophy; AS = Alström syndrome; BBS = Bardet-Biedl syndrome; GH = growth hormone; LEP = leptin deficiency; LEPR = leptin receptor mutation; MC4R = melanocortin 4 receptor mutation; PC1 = proprotein convertase 1 deficiency; PCOS = polycystic ovary syndrome; POMC = proopiomelanocortin deficiency; PWS = Prader-Willi syndrome; ROHHAD = rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation.



**Figure 2.** Effects of obesity on thyroid function. TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Figure courtesy of Kelly Mason, MD



**Figure 3.** Growth chart consistent with Cushing’s syndrome. (From US Centers for Disease Control.)

**TABLE 1**

## Distinctive Characteristics of Hormonal Disorders Associated With Excess Weight Gain

<b>Distinctive Findings</b>	<b>Disorder</b>
Microphallus, neonatal hypoglycemia, giant cell hepatitis	GHD, hypopituitarism
Broad (> 1 cm) hemorrhagic or violaceous striae, muscle wasting, osteoporosis, vertebral fracture	Cushing's syndrome
Goiter	Hypothyroidism
Lack of satiety, bizarre feeding behavior, temperature instability, rage attacks	Hypothalamic obesity
Galactorrhea	Hyperprolactinemia
Hypoventilation, temperature instability, pain hyposensitivity, neural crest tumors	ROHHAD

GHD = growth hormone deficiency; ROHHAD = rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation.



**TABLE 2**

Distinctive Characteristics of Monogenic Disorders Associated With Hyperphagia and Infantile Obesity

<b>Distinctive Findings</b>	<b>Disorder</b>
Tall stature	MC4R deficiency
Frequent infections	Leptin deficiency, leptin receptor mutations
Adrenal crisis	POMC deficiency
Diarrhea	Proprotein convertase 1 deficiency

MC4R = melanocortin 4 receptor; POMC = proopiomelanocortin.

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**TABLE 3**

## Distinctive Characteristics of Syndromic Disorders Associated with Childhood Obesity

<b>Distinctive Findings</b>	<b>Disorder</b>
Hypotonia, infantile failure to thrive followed by hyperphagia and weight gain, small hands and feet, pain insensitivity, obsessive compulsive behavior	Prader-Willi syndrome
Visual dysfunction, polydactyly, cardiac/genitourinary/renal anomalies	Bardet-Biedl syndrome
Visual dysfunction, hearing loss, cardiomyopathy, type 2 diabetes	Alström syndrome
Short metacarpals, soft tissue calcification	Albright's hereditary osteodystrophy
Autism, schizophrenia, cardiac/renal anomalies	Chromosome 16p, 1q deletions

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TABLE 4

## Tests Used to Diagnose Genetic/Hormonal Disorders in Obese Children

Test	Expected Result in Hormonal/ Genetic Disorder	Expected Result in Exogenous Obesity
T4, T3, TSH	<i>Primary hypothyroidism:</i> decreased fT4, normal or decreased T3, increased TSH <i>Central hypothyroidism:</i> decreased fT4, normal or decreased T3, normal or decreased TSH	Normal or mildly increased TSH, normal fT4, increased T3
IGF-1, IGFBP-3	Decreased in GHD	Usually in the normal range
ACTH, cortisol 24-h urine-free cortisol Salivary cortisol Diurnal cortisol rhythm Dexamethasone suppression	<i>Cushing's syndrome</i> Variably high cortisol, variable ACTH Increased Increased Abnormal Abnormal	All usually in the normal range
Free testosterone	High in PCOS	Normal or mildly increased
Prolactin	High in prolactinoma, hypothalamic obesity, septo-optic dysplasia, antipsychotic medications, ROHHAD	Normal or low
Polysomnography	Central hypoventilation in ROHHAD	Normal or obstructive sleep apnea
Leptin	Very low/absent in leptin deficiency, high in leptin receptor mutation	High for age, but appropriate for BMI
MC4R sequencing	MC4R mutation	Normal
Methylation analysis	Prader-Willi syndrome	Normal
Parathyroid hormone	Very high in Albright's hereditary osteodystrophy with pseudohypoparathyroidism	Normal if vitamin D sufficient
Chromosomal microarray	16p, 1q deletions	Normal

ACTH = adrenocorticotropic hormone; BMI = body mass index; GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor-binding protein-3; MC4R = melanocortin 4 receptor; PCOS = polycystic ovary syndrome; ROHHAD = rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation; TSH = thyroid-stimulating hormone.