Review Article

Endocrine check-up in adolescents and indications for referral: A guide for health care providers

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ABSTRACT

The American Academy of Pediatrics recommends that young people between the ages of 11 and 21 years should be seen annually by their pediatricians, since annual checkups can be an important opportunity for health evaluation and anticipatory guidance. Parents of infants and young children are accustomed to regularly visiting a pediatrician for their child's checkups. Unfortunately, when children reach the teen years, these annual checkups may decrease in frequency. In routine check-ups and medical office visits, particular attention should be paid to the possibility of a developmental or endocrine disorder. Early diagnosis and treatment may prevent medical complications in adulthood and foster age-appropriate development. Our purpose is to acquaint readers with the concept, based on current scientific understanding, that some endocrine disorders may be associated with a wide range of deleterious health consequences including an increased risk of hypertension and hyperlipidemia, increased risk of coronary artery disease, type 2 diabetes, significant anxiety and lack of self-esteem. Understanding the milestones and developmental stages of adolescence is essential for pediatricians and all other health providers who care for adolescents. Treating adolescents involves knowledge of a variety of medical, social and legal information; in addition, close working relationships must be established within the adolescent's network to create an effective care system. In summary, we underline the importance of a periodic endocrine checkup in adolescents in order to identify endocrine problems early and develop an approach to treatment for those patients who need help during this time. Indications for endocrine referral for professional and other healthcare providers are also included. These lists are clearly not intended to be comprehensive, but will hopefully serve as a guide for specific clinical circumstances.

Key words: Adolescent medicine, check-up, endocrine disorders, health care

Introduction

Adolescent medicine is a medical subspecialty that focuses on the care of patients who are in the period of development generally ranging from 10 to 20 years. Worldwide there are now 1.2 billion young people aged 10–19 years, who form 20% of the global population.[1]

Adolescence is a period of great change physiologically, psychologically and socially. During puberty, the body achieves its maximum potential in terms of fitness, physical strength and reproductive capacity. Guiding adolescents through this period is a challenge for parents as well as clinicians. This has increased the public health interest in health promotion, early detection and preventive health care for adolescents.[2-4]

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The American Medical Association's Guidelines for Adolescent Preventive Services (GAPS) recommend that all teens between the ages of 11 and 21 should receive annual routine visits. General assessments include the following: Medical and psychosocial history, measurements (such as height, weight, and blood pressure), sensory screening (vision and hearing), developmental and behavioral assessment, physical examination, immunizations, anticipatory guidance (in such areas as injury prevention and nutrition counseling), dental referral and laboratory tests (such as blood work or a urinalysis).[5]

Even though annual checkups including three complete physical examinations—one each during early (11-14 years), middle (15-17 years) and late (18-21 years) adolescence—are recommended, adolescents are thought to be infrequent users of health services.[6-9]

It appears that little attention has been focused on growth and endocrine disorders in adolescents.[10,11] Hormonal problems affecting growth or sexual development can have significant effects on an adolescent's physical and emotional well-being.

The purpose of this article is to present a practical approach to a teen well-care endocrine check-up for pediatricians and family doctors, based on personal experience and resources reported in the literature. Indications for endocrine referral for professional and other healthcare providers are also included. These lists are clearly not intended to be comprehensive, but will hopefully serve as a guide for specific clinical circumstances.

Short Stature

Human growth depends on a complex interaction between nutritional, environmental and hormonal factors and by a large number of different genes.[12]

Growth is an essential and integral component of adolescent assessment. Growth velocity expressed in cm/yr and height standard deviation score (HSDS) are a sensitive index of an adolescent's health because decelerating growth rate and/or short stature (SS) may be the first indication of a disease state.[12,13]

SS is arbitrarily defined as height below 3rd percentile or two standard deviations below the mean for that age and sex. A growth velocity outside the 25th to 75th percentile range may be considered abnormal. Serial height measurements over time documented on a growth chart are a key in identifying abnormal growth.

Potential diagnoses include familial SS, constitutional delay of growth and puberty, occult systemic diseases (pulmonary, renal or gastrointestinal disease), endocrinopathies and genetic disorders.

There are several factors that one must consider in the evaluation of SS, including genetic potential for growth, rate of growth, and pattern of growth. A comprehensive history and physical examination can help differentiate abnormal growth patterns from normal variants and identify specific dysmorphic features of genetic syndromes. History and physical examination findings should guide laboratory testing. javascript: A graded diagnostic approach, with a careful history, physical examination and targeted laboratory and radiologic evaluation, is recommended in order to determine the etiology and guide treatment. Bone age (BA) is particularly useful in children and adolescents with SS, tall stature, early or late puberty, and congenital adrenal hyperplasia (CAH). Especially in delayed puberty, growth rate is better compared with bone age than chronological age. The assessment of skeletal maturity is always recommended as part of routine workup for both diagnostic and prognostic purposes at first presentation of a child with SS.[14]

As subtle skeletal dysplasias can underlie SS, close collaboration with pediatric radiologists is essential to exclude dysplasias or other bone disorders.

A comprehensive physical examination should be performed by an experienced clinician to reveal critical information pertaining to the cause of the adolescent's decelerating growth (HSDS decline) or SS.

Failure to thrive (FTT) describes retarded growth in height and weight, whereas SS involves comparison of adolescent's height to that of a reference group or to his or her own height across time. To identify either condition in adolescents, the family physician should focus on accurate measurement of length/height and weight as well as careful plotting and assessment of the rate of linear growth and weight gain based on Centers for Disease Control and Prevention charts. Identification of the etiologies of FTT and SS is complex, requiring consideration of such factors as birth weight, prematurity, and familial height. FTT can result from inadequate caloric intake, inadequate caloric absorption or excessive caloric expenditure/ineffective utilization.[15]

Criteria for referral

A primary health care professional who has a high index of suspicion regarding a possible pathology should discuss his/her concerns with a specialized health care professional.

The abnormal growth findings suggesting the need for referral to a pediatric endocrinologist are:

- Height below 3rd percentile or 2 SD for age and sex
- Crossing two major percentile lines (upward or downward), for example, going from above 75th percentile to below 50th percentile on a height chart
- Growth velocity is consistently below the 25th percentile over 6-12 months of observation
- The adolescent is significantly shorter than expected for family (>1.5 SD below mid-parental height)
- The adolescent is growing poorly, associated with headaches or vision changes.

Tall Stature

Tall stature is defined as a height that is two standard deviations above the mean for age and sex (greater than the 95th percentile). It is important to distinguish tall patients who are otherwise healthy from those who have underlying pathology.[16]

A comprehensive history should be obtained for the evaluation of tall stature. The areas of emphasis are the same as for SS. Subjects with constitutional tall stature have a normal upper-to-lower body segment ratio and arm span, whereas most children with Klinefelter syndrome have an increased arm span and eunuchoid proportions (i.e. disproportionately long limbs with an arm span exceeding the height by 5 cm).[16]

Criteria for referral

Signs and symptoms of an adolescent with a potential excessive growth disorder are:

- Height greater than the 95th percentile
- Accelerated growth velocity for age
- Projected height over midparental height by more than 8.5 cm
- Multiple syndromic or dysmorphic features: Abnormal facies, midline defects, body disproportions
- Advanced bone age by more than two standard deviations.

Obesity

Obesity can be defined as generalized or localized fat mass accumulation as a result of energy disbalance caused by the interplay of genetic and environmental factors.[17-19] The prevalence of obesity in children and adolescents has increased dramatically in the past three decades, not only in the developed countries, but also in the less developed areas.[17-19]

Although several classifications and definitions for overweight and obesity are available, the most widely accepted is the World Health Organization (WHO) criteria based on BMI. Under this convention for adults, grade 1 overweight (commonly called overweight) is a BMI of 25-29.9 kg/m^2; grade 2 overweight (commonly called obesity) is a BMI of 30-39.9 kg/m^2 and grade 3 overweight (commonly called morbid obesity) is a BMI equal to or greater than 40 kg/m^2.[20-23]

The Endocrine Society Clinical Practice Guidelines based on expert opinion recommend that a child be diagnosed as overweight if the BMI is at the 85th percentile but less than the 95th percentile for age and sex, and as obese if the BMI is at the 95th percentile for age and sex.[24] Experts suggested that severe obesity should be defined as BMI ≥ 99th percentile or BMI ≥ 1.2 times the 95th percentile, this latter corresponds to the definition of severe obesity in adults (class 2, BMI ≥ 35 or approximately 1.2 times the BMI 30 cut-off point).[25] Accumulating evidence suggests that severe obesity in childhood is associated with an adverse cardiovascular and metabolic profile, even compared with obesity and overweight.[25-27]

Waist circumference (WC), measured in the midline between iliac crest and the inferior part of the last rib, is the most simple and representative anthropometric index that estimates intra-abdominal fat (visceral fat), besides central obesity and cardiometabolic risk. Nevertheless, waist circumference measurements in children and adolescents are not currently recommended. Reference values that identify risk over and above the risk from the BMI category are not available.[20] The increase in abdominal fat has been associated in children and adolescents with metabolic syndrome components, namely arterial hypertension, hypertriglyceridemia, low HDL-C, hyperglycemia, and hyperinsulinemia, with a strong correlation to insulin resistance.[25-27]

BMI is an important screening tool, but it must be integrated with other information in the health assessment, such as detailed medical history and physical examination. Patients can present with several signs and symptoms that may indicate obesity-related risk or syndromes and for which further evaluation is indicated. These include: SS/developmental delay, acanthosis nigricans, excessive acne, hirsutism, violaceous striae, goiter, hepatomegaly, pubertal delay and/or true hypogenitalism (micropenis in male, labia minora hypoplasia in girls), small hands and feet, and polydactyly.[17,28]

SS with obesity suggests a syndromic or hypothalamic cause. Slowing in growth velocity in conjunction with weight gain indicates an endocrine cause such as hypothyroidism, hypercortisolism or growth hormone deficiency.[16,17]

Acanthosis nigricans on physical examination is a sign of insulin resistance. A personal or family history of type 2 diabetes mellitus or gestational diabetes mellitus or the presence of hypertension should also be sought in the evaluation.[25-27]

Criteria for referral

The abnormal findings in an obese teen suggesting the need for referral to a pediatric endocrinologist are:

- Children with BMI ≥ 95th centile
- Rapid changes in BMI
- Height below the 10th percentile, or if the subject is unexpectedly short for the family, or if there is a reduced growth velocity
- Presence of precocious or delayed puberty or hypogenitalism
- A significant learning disability
- Symptoms/signs suggestive of an endocrine or genetic problem
- Serious comorbidity related to weight (e.g. insulin resistance and type 2 diabetes; symptoms of obstructive sleep apnea; orthopedic conditions; elevated liver enzymes; psychosocial morbidity; vitamin D and iron deficiency)
- Concomitant drug use.

Hirsutism

Hirsutism is a disorder of excess growth of terminal hair in androgen-dependent areas, which include the chin, upper lip, chest, breasts, abdomen, back and anterior thighs. Hirsutism is the most commonly used clinical indicator of hyperandrogenism.[29-33]

It is well known that there are racial variations in hair growth patterns. For example, Japanese women tend to have less body and facial hair than their non-Asian counterparts, whereas European women are more likely than other ethnic groups to present with hirsutism.[34]

Hirsutism should not be confused with hypertrichosis, which is defined as a diffuse increase in vellus (fine) hair growth. Terminal hair can be distinguished clinically from vellus hair primarily by length (i.e. >0.5 cm), coarseness, and pigmentation. In contrast, vellus hair generally measures <0.5 cm in length, is soft and non-pigmented.[29,30]

Virilization, defined as the development of male characteristics in women, that is of rapid onset is generally a more ominous sign, suggesting the presence of an androgen-secreting ovarian or adrenal tumor.[31,32]

The prevalence of hirsutism is dependent on the ethnic and racial origin of the population under study but it also depends, to a certain degree, on the method used to diagnose hirsutism. An estimated 2% to 8% of women in the general population are hirsute.[34]

Patients who have clinical evidence of androgen excess should be queried regarding the age of onset of symptoms, rate of progression, time of exacerbation, menstrual history, medical history and medications. A family history of endocrine disorders also should be identified or ruled out.[35,36]

Excess body and facial terminal hair growth is measured semiquantitatively using a scoring system such as that of Ferriman and Gallwey (FG).[37] FG evaluated 9 "hormonal" sites in 161 women aged 18–38 and reported that a score above 5 was found in 9.9%, above 7 in 4.3% and scores above 10 in only 1.2% of women tested.[37,38] A total score >8 is considered hirsute based on the 95th percentile of the data originally collected by FG, although some experts recommend a score of 6 or greater.[34,37] As with any subjective scoring system, interobserver agreement varies. In addition, there are no separate diagnostic levels in adolescents.[34,39]

Rapid onset of hirsutism or virilization suggests an androgen-secreting tumor, whereas gradual onset of symptoms at puberty suggests polycystic ovary syndrome (PCOS), the most common underlying cause of hirsutism.[31-33]

The symptoms of PCOS vary with age, race, weight, and medications, adding to the challenges of accurate diagnosis. Adolescents are diagnosed with PCOS using the same criteria as adults; no formal diagnostic criteria have been established in adolescents. In the absence of a consensus for this age group, the NIH criteria for the diagnosis of PCOS are suggested.[40]

Other conditions share common features and need to be considered in the differential diagnosis. These include the non-classic form of CAH, Cushing syndrome, hyperprolactinemia, hypothyroidism, use of anabolic steroids and valproic acid and virilizing tumors.[40]

Practically, pediatricians should evaluate for PCOS in any girl presenting with menstrual irregularity over 2 years after menarche, hirsutism, refractory acne, or obesity, especially when patients with any of these features had premature pubarche and a family history of metabolic syndrome or obesity.

Criteria for referral

The following symptoms and signs in hirsutism are associated with an endocrine disorder and should alert the clinician to this possibility:

- Presence of virilization or if the total testosterone or DHEAS level is above twice the upper limit of normal or if there are signs of Cushing's disease
- Irregular menses, amenorrhea
- Short stature
- Rapid onset of hirsutism
- Elevated blood pressure.

Puberty and Menstrual Cycles

Puberty is the end-point of a complex series of developmental events. A multitude of factors appear to affect the timing and tempo of pubertal development, including environmental influences.[41]

The assessment of sexual maturity in girls is based on both growth of pubic hair and the development of breasts, starting ages between 8 and 13 years. The first easily detectable sign of puberty is usually the appearance of breast buds, although pubic hair sometimes appears earlier. The first reliable sign of puberty in males, starting ages between 9 and 13.5 years, is an increase in the size of the testes. Next, pubic hair appears, along with progressive enlargement of the penis. The complete change from preadolescent to adult anatomy requires about 3 years, in both males and females.[41]

Precocious puberty (PP) is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Depending on the presence of central activation of the hypothalamic-pituitary-gonadal axis, PP may be classified as gonadotropin dependent, also known as true or central PP (CPP), or gonadotropin independent, also known as pseudo-PP or peripheral PP (PPP). The prevalence of CPP is about 10 times higher in girls than in boys, with an estimated register-based population prevalence in Denmark of approximately 0.2% in girls and below 0.05% in boys.[42,43]

Delayed puberty is defined as the absence of onset of puberty by >2 SD later than the average age, that is, >13 years in females and >14 years in males. Delayed puberty may be idiopathic/familial or due to a number of general conditions resulting in undernutrition. The absence of puberty may also be due to gonadal failure (elevated gonadotrophin levels), or due to impairment of gonadotrophin secretion.[44]

The age of menarche is determined by general health, genetic, socio-economic and nutritional factors. The mean age of menarche is typically between 12 and 13 years. Normal menstrual flow lasts about 4 days (plus or minus 2-3 days). It produces a total blood loss of 30-80 ml (about 2-8 tablespoons), and occurs normally every 28 days (plus or minus 7 days). The maturation of the hypothalamic-pituitary-ovarian axis occurs slowly in the first 18 to 24 months after menarche in the adolescent female. Anovulatory cycles may last up to 5 years.[45,46]

Oligomenorrhea may be defined as menses occurring less frequently than every 35 days. The commonest cause of oligomenorrhea is PCOS, and other causes include temporary disturbances of menstrual cycle control, body weight (obesity or underweight) and hyperprolactinemia as well as developing causes of secondary amenorrhea.[46]

Secondary amenorrhea is the absence of menstruation for 6 months or a length of time equal to three previous cycles after a previous episode of uterine bleeding. Any cause of secondary amenorrhea may also cause primary amenorrhea. Possible causes can include moderate or excessive exercising, eating disorders such as anorexia nervosa or extreme diet, physical or psychological stress, premature ovarian failure, anatomic defects, tumors, and genetic or hormonal problems.[46]

The term "abnormal uterine bleeding" (AUB) is taken to mean excessively heavy, prolonged or frequent bleeding of uterine origin which is not due to pregnancy or to recognizable pelvic or systemic disease.[47]

The four key evaluations for menses should be cycle regularity, frequency of menstruation, duration, and volume of menstrual flow. An international expert group has recommended abolition of such terms as "menorrhagia," "metrorrhagia" and "dysfunctional uterine bleeding", and replacement with much simpler terms to specifically cover cycle regularity, frequency, duration and heaviness of bleeding episodes, and to acknowledge a significant change in pattern for individual women.[48]

Many methods have been described for quantifying blood loss. One criterion is menstrual periods requiring frequent pad/tampon changes, soaking more than 1 every 1-2 hours.[48]

In clinical practice, a pictorial blood loss assessment charts have been shown to be simple and quick to use and can be particularly useful in the monitoring of therapy.[49] Most cases in adolescents are secondary to anovulation; however, structural pathology must be excluded.

Any adolescents complaining of abnormal vaginal bleeding should be assessed. The evaluation includes family, personal history and clinical examination, in particular:

- Sexual maturity rating
- Signs of systemic disease or genetic abnormalities
- Androgen excess
- Thyroid dysfunction
- Presence of galactorrhea
- Hemodynamic stability, signs of a bleeding disorder and its underlying causes in subjects with AUB.

Criteria for referral

The abnormal findings suggesting the need for referral to a pediatric endocrinologist are:

- Subjects with PP. Due to the risk of overlooking rapid progressive PP as well as the risk of misdiagnosing intracranial and other underlying pathologies, this approach should also be applied to girls with early breast development (from 7 to 8 years)
- Girls who have not started breast enlargement by age 13 and boys who have not started testicular enlargement by age 14 are by definition delayed and need to be evaluated and appropriately managed
- Girls with no menses by age 16 in the presence of normal secondary sexual development or 14 years in the absence of secondary sexual development or no menses >4 years after onset of breast development
- Menstrual cycles >90 days representing the 95th percentile for interval length even in the first gynecological year
- Menstrual cycles >35 days after 3 years of gynecological age
- Any cause of secondary amenorrhea
- Frequent pad/tampon changes or AUB associated with anemia, hirsutism, acne or goiter.

Goiter

Goiter is an abnormal enlargement of thyroid. The prevalence of goiter, diffuse and nodular, is dependent on the status of iodine intake of the population. In general, in iodine sufficient countries the prevalence of clinically palpable goiter is less than 4%.[50]

Common causes of thyroid enlargement include simple (diffuse) goiter, autoimmune disease (ATD), thyroid nodules and iodine deficiency.[51]

ATD affects approximately 2% of the female population and 0.2% of the male population.[52] Its overall prevalence peaks in adulthood; it is also the most common etiology of acquired thyroid dysfunction in pediatrics. It is more common in females and usually occurs in early to mid-puberty.[52-55]

Two types of ATD have been reported in the literature: Hashimoto's disease (goitrous form) and atrophic thyroiditis (non-goitrous form). Both are characterized by circulating thyroid autoantibodies and varying degrees of thyroid dysfunction, the only difference being the presence or absence of goiter.[52,55]

It is well established that the risk of ATD is higher in individuals with chromosomal abnormalities such as Turner syndrome, Klinefelter syndrome and Down syndrome. There is also an increase in association with other ATDs (type 1 diabetes) and celiac disease.[52,55] ATD may be associated with a euthyroid state, hypothyroidism or hyperthyroidism.[52,55]

Graves' disease is much less common in childhood than in adults. Although it can occur at any age in the pediatric range, it is most common in adolescence.[52]

Thyroid nodules are rare in adolescents, with a prevalence rate of 0.05 to 1.8%. Seventy percent of the nodules occur alone and are two or three times more frequent among females.[55,56]

Single or multiple nodules may be toxic such as seen with the diffuse hyperplasia of Graves' disease, hypersecreting adenomata, or autoimmune thyroiditis where areas of induration may be palpable. Nodules palpated within the parenchyma of the gland may be cystic (benign or malignant), neoplastic benign adenomas, local malignant carcinoma, or secondary metastases.[55,56]

Clinical evaluation begins with a detailed patient history and careful thyroid palpation. Most patients present with an asymptomatic mass discovered by a physician on routine neck palpation or by the patient during self-examination.[56-58]

Thyroid examination

A careful examination should record the size, shape and consistency of the gland.

Goiter grading is based on the criteria endorsed by the WHO/United Nations Children Fund/International Council for Control of Iodine Disorders,[57,58] which is as follows:

- 0 = no palpable or visible goiter
- 1 = a mass visible in the neck that is consistent with an enlarged thyroid that is palpable or visible with neck in extended position but not in neutral position. It also moves up in the neck on swallowing
- 2 = a swelling in the neck that is visible in neutral position and is consistent with an enlarged thyroid when the neck is palpated.

The characteristics of thyroid enlargement may help in the formulation of a suspected disease:

- Diffuse goiter: Graves' disease, Hashimoto's thyroiditis, endemic goiter
- Single node: Cyst, benign tumor
- Multinodular goiter: Iodine deficiency.

The validity of the clinical method of estimating goiter size has already been challenged by the development of thyroid ultrasonography, which is now an accepted reference test or gold standard for the diagnosis of thyroid enlargement.[59]

Criteria for referral

Abnormal findings indicating the need for referral to a pediatric endocrinologist are:

- Abnormal thyroid function tests
- Palpable nodules or asymmetry
  a. Firm or immobile; fast growing
  b. Associated with voice change
  c. Seen in a patient with a family history of thyroid cancer
  d. Appeared after radiation or exposure to radioactive fallout
  e. Associated with lymph node swelling in the neck
  f. Associated with palpable tumor elsewhere
- Goiter increasing in size and/or causing discomfort.

Pubertal Gynecomastia

Pubertal gynecomastia (PG) occurs in up to 65% of adolescent boys. Its appearance occurs within a year of age of peak height velocity (PHV) when the boy is usually at Tanner stage 3 for pubic hair and his testicular volume is between 8 and 10 ml.[60-62] Gynecomastia usually is a benign enlargement of the male breast as a result of proliferation of the glandular component and is mainly attributable to imbalance between free androgens and free estrogens. The coincidence of PHV and PG suggests also a causal relationship between the two events and a role of insulin-like growth factor-I (IGF-1).[62]

A family history of gynecomastia has been elicited in 58% of subjects with persistent pubertal gynecomastia. In adolescents, PG regresses in few weeks–months.[60-62]

The physical examination should include evaluation of height and weight, and examination of the breasts, genitals, liver, lymph nodes, and thyroid. Most commonly PG is bilateral, although unilateral symptoms can occur and are usually left sided. Palpable, firm glandular tissue in a concentric mass around the nipple areolar complex is most consistent with gynecomastia. Increases in subareolar fat are more likely pseudogynecomastia.

The presence of varicocele has also been strongly associated with gynecomastia.[63]

Criteria for referral

Any case of gynecomastia should be referred in order to diagnose pubertal gynecomastia and to exclude pathological causes as:

- An underlying endocrinopathy
- Klinefelter syndrome, partial androgen insensitivity, 11-beta hydroxylase deficiency or 17-ketosteroid reductase deficiency, hypogonadism or hyperprolactinemia
- Tumors
- Testicular tumor (Leydig cell tumors may secrete estrogen)
- Adrenal tumors may secrete estrogen and estrogen precursors, causing a similar disruption in the estrogen-to-testosterone ratio. These tumors can be detected by elevated serum dehydroepiandrosterone sulfate levels
- Human chorionic gonadotropin (hCG)-secreting tumors as testicular germ cell tumors, liver, gastric or bronchogenic carcinomas
- Systemic disorders, such as liver disease or renal failure
- Iatrogenic gynecomastia (ask about drug intake).

Hypocalcemia

Hypocalcemia is one of the most common disorders of mineral metabolism seen in children and can be a consequence of several different etiologies.[64,65] These include a failure of secretion or action of parathyroid hormone, disorders of vitamin D metabolism and abnormal function of the calcium sensing receptor. Hypocalcemia can also occur as a result of low levels of magnesium. Anticonvulsant drugs have hypocalcemic effects, with mechanism that differs depending upon the class of drugs considered.[66-68]

Hypocalcemia is defined as a total serum calcium concentration less than 2.1 mmol/l (8.5 mg/dl) in children. Although hypocalcemia is most commonly observed among neonates, it is frequently reported in older children and adolescents, especially in pediatric intensive care unit (PICU) settings.[64,65]

Adolescents with hypocalcemia may exhibit no symptoms, especially in the beginning stages, but symptoms emerge as the condition becomes more severe. The most common symptom of hypocalcemia is tetany. Muscle weakness, fatigue, numbness and tingling of the hands, lips and feet, muscle cramps and frank carpopedal spam are common

complaints. Papilledema, cataracts, basal ganglia calcifications and dental changes may occur with chronic hypocalcemia. Patients rarely may have congestive heart failure.[64,65]

Once hypocalcemia has been confirmed and the panel results are available, the result must be interpreted in their physiologic context. The differential diagnosis of hypocalcemia based on serum PTH level is as follows: [64,65,69]

Normal PTH
- Abnormality of the calcium-sensing receptor.

Undetectable or low PTH
- Hypoparathyroidism
- Hypomagnesemia.

Raised PTH
- Pseudohypoparathyroidism
- Vitamin D deficiency
- Impaired vitamin D metabolism
- Chronic renal failure.

Hypocalcemia may be an asymptomatic laboratory finding or a life-threatening metabolic disturbance. Acute hypocalcemia can result in severe symptoms that may require rapid admission to hospital and correction. The goals of treatment for hypocalcemia are to detect and treat a low calcium level promptly by using an intervention that provides the fastest rise in calcium to a safe level.

Criteria for referral

Any case of hypocalcemia should be referred because a definitive diagnosis requires a systematic approach and eventually further testing at a specialized centre.

Hypercalcemia

Primary hyperparathyroidism (HPT) is a disorder of calcium homeostasis. It is rare in pediatric population (age <18 years) and is usually caused by a single parathyroid adenoma (65%).[70-74]

Primary HPT should be included in the differential diagnosis of all cases of hypercalcemia.

Parathyroid adenoma (PA) has an incidence of 2–5 per 100,000 children.[70] Elevated levels of intact parathyroid hormone (iPTH) lead to persistent hypercalcemia. PA commonly involves the inferior parathyroid glands.

Common causes of hypercalcemia include William's syndrome, idiopathic infantile hypercalcemia, malignancy, and toxicity with drugs like thiazides and vitamin A.[75-79]

Other causes of HPT include MEN type I and less often a manifestation of MEN type II. Children with asymptomatic and mild hypercalcemia are likely to have familial hypocalciuric hypercalcemia (FHH).[75-79]

Subcutaneous fat necrosis, granulomatous disorders, hypervitaminosis D, malignancies, adrenal insufficiency, hyperthyroidism, hypothyroidism and limb fracture with immobilization are rare causes of HPT.[71,73,76]

The diagnosis of hypercalcemia is often delayed due to subtle clinical symptoms until the complications emerge and are related to the severity and rate of change of the serum calcium level.[73,76]

A progression of symptoms has been observed:
- General malaise, fatigue, gastrointestinal complaints, weight loss
- Polyuria, polydipsia, renal colic, constipation, epigastric pain, anorexia, nausea, vomiting
- Lethargy, confusion, psychosis and coma.

Because HPT in children and adolescents is usually diagnosed late, we should expect advanced clinical signs at the presentation. Nearly all patients (79%) are symptomatic at presentation and end-organ damage (nephrocalcinosis, nephrolithiasis, acute pancreatitis, shortening of QT interval and neuropsychiatric diseases) are observed in 44% of patients.[71-74,80]

For adolescents in whom HPT is suspected, the diagnosis requires an elevated serum calcium level, with simultaneous demonstration of elevated iPTH levels (in 80% to 90% of patients) or within normal limits (in 10% to 20% of patients). A Sestamibi scan of the parathyroid gland can localize the overactive sites.[75,78]

Criteria for referral

Any case of hypercalcemia should be referred in order to make a correct diagnosis and to exclude pathological causes. Adolescents with primary HPT typically have more severe disease than adults.

The need for referral depends on the degree of hypercalcemia and the presence or absence of clinical symptoms. Patients with calcium levels higher than 14 mg/dl should be treated aggressively, regardless of symptoms.

Hypoglycemia

Hypoglycemia most commonly arises in this age group as a complication of type 1 diabetes. Hypoglycemia

in subjects without diabetes is much less common.[81] The causes include: Medications and excessive alcohol consumption; critical illnesses of the liver and kidney; long-term starvation, as may occur in the eating disorders; sepsis; insulin overproduction (insulinoma) and endocrine deficiencies (disorders of the adrenal glands or pituitary gland).[82-84]

Definition of Hypoglycemia

Hypoglycemia is defined by:

- The development of autonomic or neuroglycopenic symptoms;
- A low plasma glucose level (<4.0 mmol/l for patients treated with insulin or an insulin secretagogue); and
- Symptoms responding to the administration of carbohydrate. The severity of hypoglycemia is defined by clinical manifestations.

Symptoms

The adrenergic symptoms usually occur early with a rapid decline in blood glucose and include: Confusion, dizziness, hunger, headaches, irritability, tachycardia, tachypnea, pale skin, sweating, weakness, anxiety. Neuroglycopenic are usually associated with slower or prolonged hypoglycemia.[81,85]

The role of the general practitioner ideally involves initial diagnosis, treatment, coordination of consultant and allied professional care and continuing management.

The goals of treatment for hypoglycemia are to detect and treat a low blood glucose level promptly by using an intervention that provides the fastest rise in blood glucose to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. It is also important to avoid overtreatment since this can result in rebound.[81-83]

Criteria for referral

Once the hypoglycemia has been reversed, doctors should consider referral to endocrinologist/diabetologist.

Hyponatremia

Hyponatremia is one of the most common electrolyte abnormalities encountered in children (mild hyponatremia, serum sodium <135 mEq/l, occurs in ~25% of hospitalized children and moderate hyponatremia <130 mEq/l in ~1%).[86] Hyponatremia can be hypo- iso-, or hyper-osmolar.

Hypo-osmolar (dilutional) hyponatremia is the most common cause and is due to excess water of in comparison to sodium. It is further categorized according to volume status:

- Hypovolemic: Diuretics (selective serotonin reuptake inhibitor, angiotensin-converting-enzyme inhibitors, anticonvulsant, proton pump inhibitor, cytostatics and thiazide diuretic), diarrhea, sweating, salt-wasting nephropathy, peritonitis, pancreatitis, burns
- Euvolemic: SIADH (various causes), adrenal insufficiency, hypothyroidism, psychogenic polydypisia (raves, psychiatric, marathons,)
- Hypervolemic: Congestive heart failure, cirrhosis, nephrotic syndrome and other edematous kidney states.[86-88]

Hyponatremia can also occur in a number of common clinical conditions, including pneumonia, malaria, neuroendocrine disorders and trauma.[89-93] A dilutional hyponatremia, mainly caused by direct stimulation of antidiuretic hormone (ADH) secretion by ecstasy, is among the many side effects of the drug (active substance 3, 4 methylenedioxy methamphetamine, MDMA). Mild hyponatremia is more common in 25% of females attending a rave party and using MDMA compared to males (3%).[94]

Hyponatremia can cause many different clinical signs and symptoms, including neurological symptoms such as headache, confusion, lethargy, fatigue, irritability, spasm, and the most serious, seizures and coma.[95]

Laboratory tests should include serum and urine osmolality and electrolytes. Euvolemic patients should also have thyroid and adrenal function tested.

Criteria for referral

Identifying the cause of hyponatremia can be complex although the history sometimes suggests a cause. The clinical manifestations of hyponatremia depend on the rate of decline of serum sodium. A gradual fall in sodium over several days or weeks can be compensated for by the brain, produces relatively modest morbidity and may be asymptomatic. An acute fall in sodium over 24 to 48 hours produces severe cerebral edema, which can be fatal.[86,95]

Conclusions

During adolescence, children undergo striking physical, intellectual, and emotional growth. Understanding the milestones and developmental stages of adolescence is essential to pediatricians and all other health care providers who treat adolescents.

Teens grow and develop at different rates and can experience many concerns or worries about growth and puberty. Physical differences and abnormalities of the genitals can be very distressing to the developing young

person.[96,97] They rarely consult a physician and during a medical visit for other conditions, they do not always feel comfortable bringing up these issues.

Growth and puberty are an essential and integral component of adolescent health assessment. They are a sensitive index of the adolescent's health because SS and delayed puberty may be the first indication of a disease state.

Obesity is one of the most common reasons of adolescent medical consultation. Most cases of obesity are due to eating more than is needed, often in conjunction with a sedentary life style. Primary endocrine (e.g. hyperadrenocorticism, hypothyroidism) or metabolic causes are uncommon. Hypothyroidism should be ruled out as a cause and should be suspected if height growth slows significantly. Increased body weight is one of the earliest signs of Cushing syndrome, with a characteristic redistribution of fat from peripheral to central parts of the body, mainly in the abdominal region.

Obesity represents a potential emerging public health issue, because it is associated with increased morbidity and mortality. The complications include hypertension, hyperlipidemia, increased risk of coronary artery disease, type 2 diabetes, obstructive sleep apnea, degenerative joint disease, gallstones and the Pickwickian syndrome. Prompt diagnosis is essential to optimize therapy, establish healthy diet and exercise habits and prevent potential health risks.

An early age of menarche is a potential risk factor for breast cancer and a low age at male puberty is associated with an increased risk for testicular cancer according to several, but not all, epidemiologic studies.[98,99] Girls and possibly boys who exhibit premature adrenarche are at a higher risk for developing features of metabolic syndrome, including obesity, type 2 diabetes and cardiovascular disease later in adulthood, as are adolescents with PCOS.

The psychological consequences of pubertal delay in boys are noteworthy because there is evidence of emotional distress, poor body image and low self-esteem. These boys are also more likely to be teased or bullied.[99,100]

Oligomenorrhea in the first years of menstrual life is often neglected although nearly 70% of girls with irregular cycles for more than 2 years after menarche continue to have an abnormal bleeding pattern in adulthood and may have PCOS.

Rapid onset of hirsutism or virilization suggests an androgen-secreting tumor, whereas gradual onset of symptoms at puberty suggests PCOS, the most common underlying cause of hirsutism.[33]

Gynecomastia is a frequent concern of boys. In obese boys, the condition may be worsened by pseudogynecomastia. It is rarely related to underlying conditions such as testicular neoplasms, Klinefelter's syndrome, medications or drug use (anabolic steroids or heavy marijuana use).

Goiter is a common clinical condition observed in medical practice. Nevertheless, it is an infrequent cause of medical consultation because it is usually not clinically recognized.

Serum calcium level is still not a frequent screening examination in children and adolescents. For this reason, in contrast to adults, 73–94% of HPT cases in young patients are recognized as a symptomatic, advanced disease with multi-organ changes.

Hypoglycemia most commonly arises in this age group as a complication of type 1 diabetes and acute severe hyponatremia (serum sodium <125 mmol/l) has been associated with serious sequelae, including confusion, hallucinations, seizures, coma and respiratory failure leading to death. Severe hyponatremia can be a leading symptom of acute Addison's disease. It can also occur in patients with secondary adrenal insufficiency in the absence of hypovolemia and dehydration, and it is rapidly corrected by hydrocortisone substitution. The clinical manifestations of hyponatremia depend on the rate of decline of serum sodium. Severe primary hypothyroidism can be associated with an SIADH-like syndrome.

In conclusion, endocrine disorders are encountered in a wide range of clinical situations and by a variety of different clinicians because of the multi-system nature of endocrine disease. Problems seen by pediatric endocrinologists are often quite different from those commonly seen by endocrinologists who care for adults. Endocrine disorders are often chronic and require life-long follow up. The role of the pediatrician is to take any opportunity to assess the adolescent and refer as needed, to educate teens about the importance of regular checkups, to welcome the adolescents' contact with their physician if they are experiencing any concerns about their health or well-being and to recognize abnormalities that warrant referral to a pediatric endocrinologist.

There is a need for stronger links between primary health care, public health and private services to ensure access to adolescent health services. In order to achieve this goal a collaborative and coordinated effort by physicians, health care payers and governments is required.

Health checks appear to improve preventive care although their impact on health outcomes has not been fully demonstrated. Nevertheless, we believe that a pediatric endocrinology checkup can help to make a definitive diagnosis, reduce symptom duration, and decrease morbidity and the social cost of some endocrine diseases. Patients at risk are those likely to derive most benefit from these interventions.

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