Overweight and obesity in children and adolescents with endocrine disorders

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Obesity has become a serious medical condition where many factors can contribute to excess weight gain. The most common type of childhood obesity is simple obesity, which is due to gene-obesogenic environment interaction. Only a minority are due to pathological causes. Secondary causes of obesity, while less common, include these: genetic syndromes, drug-related obesity, as well as endocrine disorders (hypothyroidism, Cushing's syndrome, growth hormone deficiency, hypogonadism, pseudohypoparathyroidism type Ia, insulinoma, hypothalamic obesity and polycystic ovary syndrome). Given that some conditions may be treatable, physicians must be aware of obesity due to endocrinopathies and distinguish them from simple obesity, and treat them properly. Although rare among children, early detection of the endocrine cause of obesity leads to reduced morbidity and, in some cases, reduced mortality in these individuals. The aim of this review is to summarize the current findings on obesity-related endocrinopathies in children (illustrated by clinical examples), highlighting aspects of pathogenetic mechanisms, genetics, the clinical diagnosis, growth, body mass index and possible therapeutic approaches. Early detection and correction of endocrine obesity is of paramount importance for obese children who could benefit from timely diagnosis and an improved management of obesity as many disturbances related to obesity can be reversed at the early stage, if weight loss is achieved.

Key words: secondary obesity, hypothyroidism, growth hormone deficiency, Cushing's syndrome, hypogonadism, pseudohypoparathyroidism type Ia, insulinoma, hypothalamic obesity, polycystic ovary syndrome

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INTRODUCTION

Obesity is defined as an excessive accumulation of adipose tissue in the body. The worldwide epidemic of childhood obesity is caused by an obesogenic environment. Observational studies have shown that childhood obesity and concurrently the prevalence of metabolic complications, which include dyslipidemia, hepatic steatosis, hypertension, and type 2 diabetes mellitus, are increasing. There is growing evidence supporting the importance of obesity in childhood and adolescence for the development of obesity and cardiovascular diseases in adulthood[1,2].

A balance between total energy intake and energy expenditure is necessary to maintain appropriate body weight. Energy intake is determined by food availability and individual eating behaviour. Energy expenditure is divided into basal metabolic rate, energy expended in activity and thermic effect of food. The development of overweight and obesity occurs when energy intake exceeds energy expenditure (positive energy balance) (ref.[2,3]).

The reasons for obesity range widely. The most common type of childhood obesity is simple obesity, where, in addition to multiple genetic factors, disturbed eating behaviour and a lack of physical activity play an important role.

There are numerous disorders including genetic syndromes and underlying endocrine disorders that can present with obesity, however, endocrine diseases are believed to compromise only a small minority of paediatric patients referred for evaluation of obesity[4]. Of particular relevance, in the presence of severe obesity in a child under 3 years of age, a genetic-endocrinological etiology must always be ruled out[2].

Obesity and overweight can correspond to the real endocrine alterations arising from disturbances in the hypothalamic-pituitary-endocrine axes. These include hypothalamic changes, hypothyroidism, Cushing's syndrome (CS), hypogonadism and growth hormone deficiency (GHD). Further, obesity may be also a feature of polycystic ovary syndrome (PCOS), insulinoma and pseudohypoparathyroidism type Ia (PHP Ia) (ref.[3,5,6]). The pathophysiological concept for the development of obesity vary in according to the primary endocrine alterations on energy balance, adipose, and other tissues[7]. However, since appropriate therapy of these conditions generally resolve obesity, they are frequently considered. Endocrinopathies resulting in obesity can present with an insidious course or with typical clinical features seen in these endocrine disorders. They usually respond to conventional therapy, which should be instituted promptly upon diagnosis to avoid disease progression.

The aim of this review is to pinpoint pathophysiological mechanisms responsible for the development of obesity in childhood and clinical, diagnostic and management issues specifically related to endocrinopathies as well as other relevant factors such as growth's patterns and BMI (body mass index) charts leading to the diagnosis of these conditions on the bases of evidence available in the litera-

Table 1. Differential diagnosis of endocrine causes of overweight and obesity in children and adolescens; typical clinical features of endocrinopathies and biochemical diagnosis.

	Clinical features	Biochemical diagnosis
Hypothyroidism (severe, primary)	**myxedema; weight gain; obesity; growth retardation**; goitre; fatigue; inactivity; impaired school performance; delayed puberty; irregular menstrual cycle; cold intolerance; hair loss; dry skin; constipation; bradycardia; hypotension; pericardial effusion	• high level of TSH • low level of fT4
Cushing′s syndrome	**rapid weight gain; central obesity; growth retardation**; moon face; purple striae; bruising; dorsal/subclavicular fat pads; pseudo-precocious puberty; delayed puberty; amenorrhea; hirsutism; hypertension; glucose intolerance; osteoporosis; depression; sleep disturbance	• high urinary free cortisol excretion • loss of serum cortisol circadian rhythm • failure of serum cortisol to suppress during LDDST • detectable or elevated ACTH → central etiology of CS • suppressed ACTH → adrenal etiology of CS
Growth hormone deficiency	**central obesity; growth retardation**	• GH stimulation tests (maximum stimulated GH level <20 mIU/L) • low level of IGF-I • possible associated anterior pituitary hormone deficiencies (TSH, ACTH, LH, FSH)
Hypogonadism	**central obesity**	• LH, FSH, testosterone, estradiol
Pseudohypoparathyroidism type Ia	**symptoms of AHO: obesity**; round faces; short stature; subcutaneous calcifications; brachydactyly; shortened fourth metacarpals and metatarsals sometimes mental defects or cataract	• hypocalcemia • hyperphosphatemia • high level of PTH • elevated level of TSH • decreased level of fT4
Hypothalamic obesity	**weight gain; obesity** ← results from damage to the ventromedial hypothalamus	• possible hypopituitarism, central diabetes insipidus
Insulinoma	**weight gain**; fasting hypoglycemias with neuroglycopenic and autonomic symptoms	• hyperinsulinism → increased level of insulin and C-peptide at the time of hypoglycemia
Polycystic ovary syndrome	**central obesity**; hirsutism; acne; irregular menstrual cycle; amenorrhea; signs of metabolic syndrome (hypertension, acanthosis nigricans)	• hyperandrogenism • metabolic syndrome (dyslipidemia, glucose intolerance)

ture. We systematically searched the literature assessing endocrine conditions causing obesity in children from databases MEDLINE, EMBASE, Web of Science and COCHRANE Library.

Table 1 provides an overview of endocrine causes of overweight and obesity in children and adolescents.

HYPOTHYROIDISM

Evidence suggests that hypothyroidism is responsible for obesity. However, there is a lack of clarity regarding linking them causally[8]. Chronic lymphocytic thyroiditis (CLT) is the most common cause of acquired primary hypothyroidism[9]. Severe and long-lasting primary hypofunction of the thyroid gland with typically high levels of TSH (thyroid-stimulating hormone) and existing low level of fT4 (free thyroxine) leads to the development of overweight and obesity[1,3,6].

From the pathophysiological point of view, reduced basal metabolism with a decrease in energy expenditure and myxedema with deposition of mucopolysaccharides in the subcutaneous tissue and water retention may be involved in the development of obesity[1,3,5,6,10]. El Amrousy et al suggested that insulin resistence (IR) and leptin levels are increased in hypothyroid children and adolescents; more in those with obesity. IR is not related to leptin and adiponectin levels, however, leptin and adiponectin levels correlate well with BMI in hypothyroid children and adolescents with obesity[11]. Several studies suggest that even a slightly elevated serum TSH might be important in determining an excess of body weight and it can be considered a risk factor for overweight and obesity[12].

The most typical features of severe hypothyroidism are myxedema, progressive BMI, growth retardation, goitre, fatigue, inactivity, impaired school performance, delayed puberty, irregular menstrual cycle in girls, cold intolerance, hair loss, dry skin, constipation, cardiac symptomatology with bradycardia, hypotension and pericardial effusion[1]. Fig. 1a,b demonstrates myxedema before and during the treatment with levothyroxine.

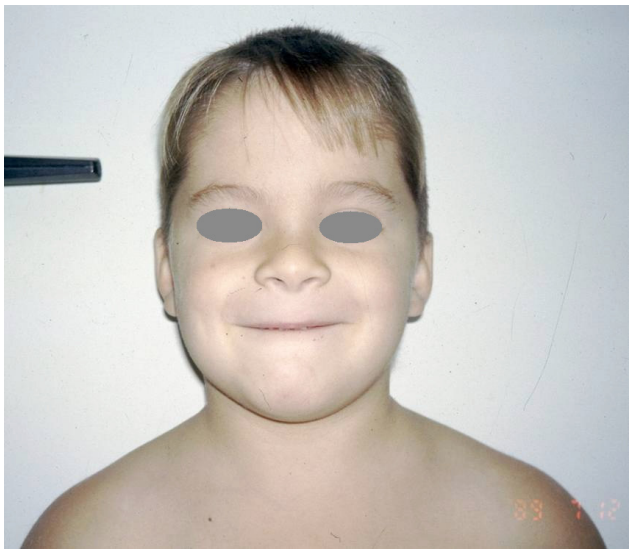

Fig. 1a. Myxedema in 7-year-old patient with severe primary hypothyroidism in the atrophic form of CLT before the treatment with levothyroxin.
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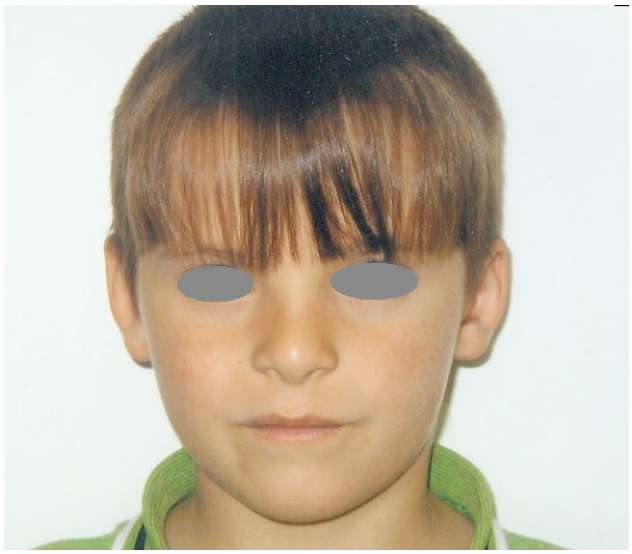

Fig. 1b. Regression of myxedema in 7-year-old patient with severe primary hypothyroidism in the atrophic form of CLT during the treatment with levothyroxin.
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CUSHING'S SYNDROME

Cushing's syndrome is frequently included in the differential diagnosis of obesity and weight gain. The most frequent form of CS in children over 5 years of age is ACTH (adrenocorticotropic hormone) producing pituitary microadenoma (Cushing's disease), with the predominant occurrence in puberty and adolescence[13-15].

From the pathophysiological point of view, weight gain is caused by endogenous hypercortisolism leading to increased lipogenesis not only in the facial area, but also in the abdominal tissue (central obesity), and to hyperphagia[1,3,5,6]. In CS, an interaction with thyroid and growth hormones also plays an important role in addition to an increased adipocyte differentiation and adipogenesis[10]. Furthermore, the highly expressed 11 β-hydroxysteroid-dehydrogenase-1 in omental adipose tissue is believed to enhance the local effect of cortisol on adipose tissue by converting inactive cortisone to active cortisol[16].

In children, attention should be focused on key features of CS such as growth failure with decreased linear growth, as a consequence of the impairtment of GH secretion by hypercortisolism, weight gain and a change in facial appearance with the development of the so-called moon face (Fig. 2). Other typical symptoms frequently presenting in pediatric patients include pseudo-precocious puberty in both sexes, hirsutism in pubertal girls due to excessive adrenal androgen secretion and pubertal delay or arrest caused by suppression of the hypothalamic-pituitary-gonadal axis due to hypercortisolism. Other possible symptoms of CS include purple striae (Fig. 2), which are almost never present before the age of 5–7 years, bruising, fungal infections, hypertension, glucose intolerance, osteoporosis and, rarely, depression and sleep disturbance[1,13,15,17]. While the most common findings in prepu-

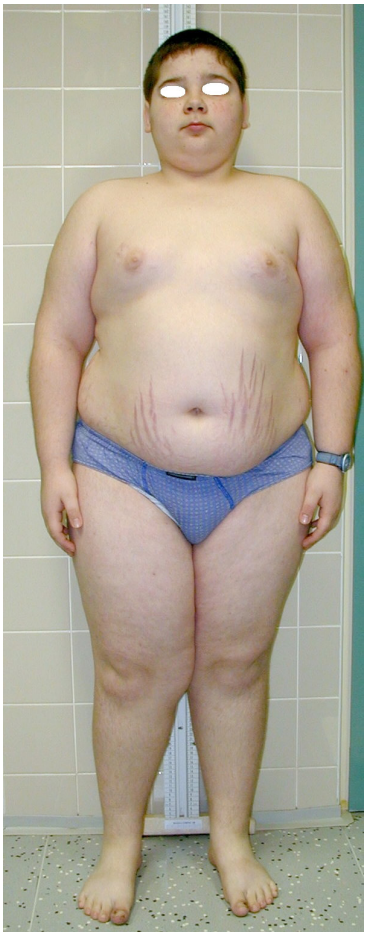

Fig. 2. 11-year-old patient with typical picture of CS, including obesity, purple striae, moon face, pseudopuberty and growth retardation from 9 years of age.
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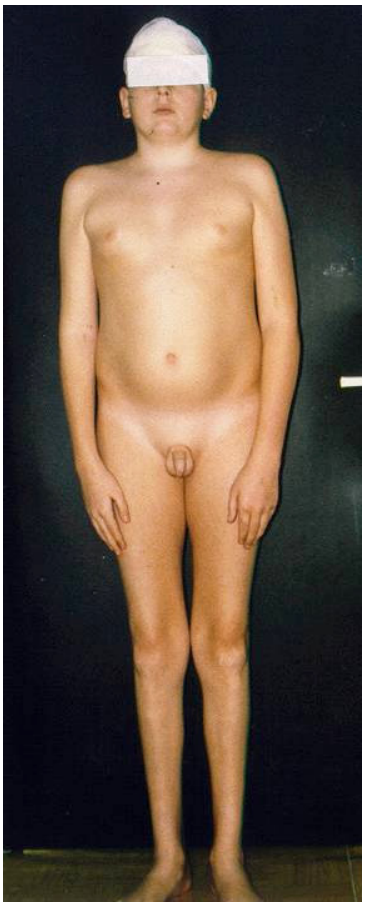

Fig. 3. 15-year-old patient with panhypopituitarism due to a Rathke's cleft cyst. Typical change in body composition with an excess of adipose tissue in the trunk area and with a loss of muscle mass due to severe growth hormone deficiency and central hypogonadism.
From archive of the Department of Paediatrics, Charles University in Prague, Faculty of Medicine in Pilsen.

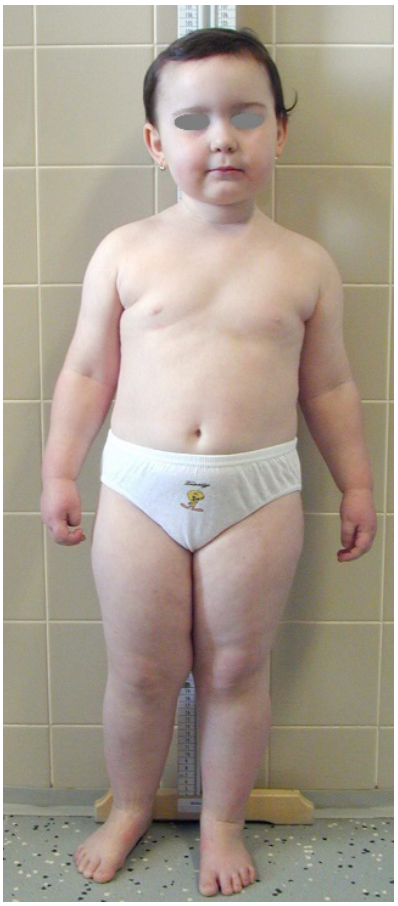

Fig. 4. 3-year-old girl with PHP Ia. Typical AHO fenotype with obesity and a round face.
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bertal pediatric patients include rapid weight gain, obesity, and decreased linear growth, the most common findings in postpubertal pediatric patients are rapid weight gain, dorsal/subclavicular fat pads, and amenorrhea[18].

The diagnosis of CS is based upon the confirmation of high urinary free cortisol excretion, loss of serum cortisol circadian rhythm and failure of serum cortisol to suppress during a low-dose dexamethasone suppression test (LDDST). A detectable or elevated ACTH level indicates a central etiology of CS; a suppressed ACTH level reveals an adrenal cause[1,13,17].

GROWTH HORMONE DEFICIENCY

Growth hormone deficiency (GHD) is either congenital or acquired; it can be isolated or accompanied by deficiency of other pituitary hormones. Congenital causes of hypopituitary states include a pituitary morphogenesis disorder (e.g. septo-optic dysplasia) or a pituitary cell differentiation disorder (e.g. *PROP1* gene defect) with combined pituitary hormone deficiency. Acquired causes include midline brain tumors (e.g. commonly craniopharyngioma), infections (e.g. meningitis), radiotherapy, infiltrative disorders (Langerhans cell histiocytosis) or brain trauma[1].

GH plays a significant role in the regulation of energy expenditure, body composition, bone mineral density, lipid metabolism and cardiovascular function. GH stimulates lipolysis and proteosynthesis. GHD leads to a change in body composition with decreased muscle mass and increased truncal fat deposition, so that these children appear obese, but their BMI ranges may be normal (Fig. 3). Untreated severe GHD is accompanied by an increased cardiovascular risk; therefore severe GHD treatment must continue, with a reduced dose of GH, even after the growth has stopped[1,3,5,6]. However, the pathophysiologic role of GH in obesity is yet to be fully understood[19].

HYPOGONADISM

Hypothalamic hypogonadism and PCOS are two conditions where reproductive function appears to directly relate to excess weight[20]. Sex hormones support the mobilization of visceral fat and affect proteosynthesis and bone

mineral density. Some authors provide evidence that sex hormone deficiency leads to a change in body composition with a loss of muscle mass and the development of visceral obesity, including metabolic syndrome and the associated cardiovascular risk[3].

PSEUDOHYPOPARATHYROIDISM TYPE IA

Patients with PHP Ia develop early-onset obesity. This syndrome is typically associated with short stature, obesity, brachydactyly, and subcutaneous calcifications. PHP Ia is an autosomal dominant disease due to maternal transmission of a mutation of the *GNAS1* gene, leading to an inability to activate adenylyl cyclase and, therefore, causing target-organ unresponsiveness to multiple hormones, including parathyroid hormone (PTH), TSH, luteinizing hormone, follicle-stimulating hormone and GHRH (growth hormone-releasing hormone). PTH resistence typically leads to hypocalcemia, hyperphosphatemia with a paradoxically high PTH level and TSH resistence to primary hypothyroidism, usually with mildly elevated TSH up to 10 mIU/L and decreased fT4 level[3,6].

PHP Ia patients have a classical presentation, known as Albright hereditary osteodystrophy (AHO), characterized by round faces, obesity (Fig. 4), short stature, subcutaneous calcifications (Fig. 5), shortened fourth metacarpals and metatarsals (Fig. 6); sometimes mental defects or cataract may be present. Paternal inheritance of the *GNAS1* gene mutation leads to the AHO alone without hormonal resistence being called pseudopseudohypoparathyroidism (PPHP) (ref.[3,6,21]). Because pathogenic mutations may manifest with obesity alone, screening of children with severe obesity for *GNAS* deficiency may allow early diagnosis, improving clinical outcomes, and melanocortin agonists may aid in weight loss[21].

From the pathophysiological point of view, the cause of the early development of obesity from infancy is a disorder of the melanocortin receptor type 4 (MCR4) of the anorexigenic axis, when physiological post-receptor signalling is impaired due to a malfunction of the α-subunit of the G-protein. Physiological activation of MCR4 leads to reduced food intake and increased energy expenditure, so that patients with PHP Ia have a reduced basal metabolism and suffer from hyperphagia[21]. Shoemaker et al indicated that children with PHP Ia have decreased rest energy expenditure compared with the obese controls, and that may contribute to the development of obesity in these children. These subjects may also have abnormal diet-induced thermogenesis in response to a high-fat meal[22]. These findings may allow for targeted nutritional or pharmacologic treatments in the future.

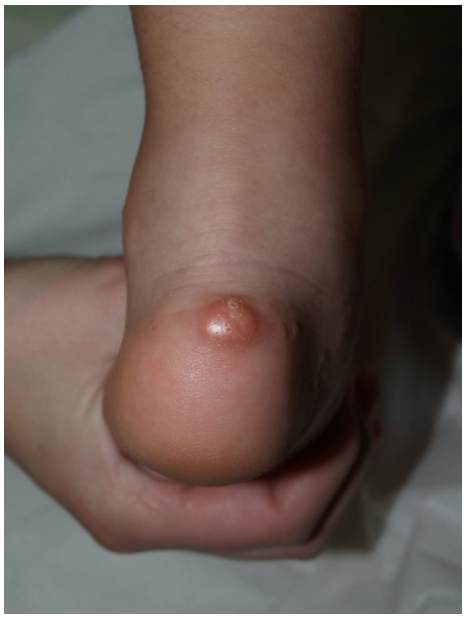

Fig. 5. Calcifications on the heel in PHP Ia patient.
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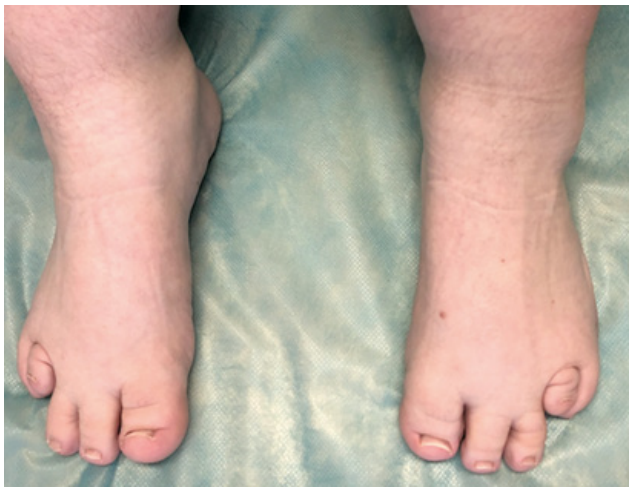

Fig. 6. Shortened fourth metatarsals in PHP Ia patient.
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HYPOTHALAMIC OBESITY

Hypothalamic obesity is a rare disorder caused by a variety of insults, including congenital malformations, trauma, tumors, intracranial infections, radiotherapeutic intervention, inflammatory processes, vascular problems, surgical damage in the area of the hypothalamus as well as with genetic neurodevelopmental syndromes, such as Prader-Willi syndrome (PWS) or septo-optic dysplasia[23,24]. Hypothalamic obesity develops in approximately 50% of children treated surgically for craniopharyngioma[1,25,26]. Imaging studies have demonstrated a direct correlation between the extent of hypothalamic damage and presentation of obesity in children with acquired hypothalamic damage due to craniopharyngioma[27].

The pathogenetic mechanisms underlying hypothalamic obesity are complex and multifactorial. Weight gain results from damage to the ventromedial hypothalamus, which leads, variously, to hyperphagia, a low-resting metabolic rate; autonomic imbalance; growth hormone, gonadotropins and thyroid-stimulating hormone deficien-

cy; hypomobility; and insomnia. Several hypothalamic cores and areas are involved in the control of appetite and energy consumption. They produce a number of neuropeptides associated with appetite control, including orexigenic peptides such as neuropeptide Y and anorexigenic peptides such as melanocortin. Organic lesions may affect peripheral feedback signalling, including cholecystokinin, glucagon-like peptide, ghrelin, insulin and leptin. These peptides cross the blood-brain barrier and bind to their receptores in the hypothalamus in order to regulate appetite. Loss of this function leads to hyperphagia and progressive weight gain[28]. Hypothalamic obesity is often associated with other endocrinopathies such as GHD, premature or delayed puberty and central diabetes insipidus[1,3,5]. Identifying etiological factors contributing hypothalamic obesity may lead to multi-faceted interventions targeting hyperphagia, insulin resistance, decreased energy expenditure, sleep disturbance, hypopituitarism and psychosocial morbidity[28].

INSULINOMA

Insulinoma (nesidioma) in children and adolescents is an extremely rare disease characterized by tumoral excessive insulin secretion, manifesting clinically by frequent, especially fasting, hypoglycemias, associated with neuroglycopenic and autonomic symptoms. Early diagnosis of insulinoma is obviously important for ensuring proper treatment and preventing serious adverse neurological consequences and permanent damage symptoms[29].

Insulinomas are associated with obesity in 18–39% of individuals. Weight gain in these patients is related to excessive energy intake in order to avoid hypoglycemia, and to an increased lipogenesis due to insulin overproduction[3,5]. Bonfig et al. presented a case of delayed diagnosis of an insulinoma in a 15 year-old boy. The patient suffered from recurrent hypoglycemic seizures and gained 54 kg in weight[30].

POLYCYSTIC OVARY SYNDROME

PCOS is the most common endocrine disorder in young reproductive-aged women. PCOS is frequently associated with obesity and impairs reproductive health[20,31].

Although the pathophysiology of PCOS remains unclear, several underlying mechanisms have been proposed. Firstly, elevated androgen concentrations combined with an irregular menstrual cycle, such as oligomenorrhea or secondary amenorrhea. Secondly, the higher levels of insulin due to insulin resistence are key components[6]. The presence of clinical and/or biochemical hyperandrogenism is an essential criterion for diagnosing PCOS including hirsutism, acne or alopecia, and signs of insulin resistance, such as acanthosis nigricans. The diagnosis of PCOS among youth is based on clinical characteristics, measurements of hormones and the typical morphology of polycystic ovaries. Pelvic ultrasonography might be helpful for excluding other causes of hyperandrogenism such as tumors. Obesity, especially abdominal, and the metabolic syndrome occur in approximately 60% of patients with PCOS (ref.[6]). More data on pharmacologic therapy for adolescents with PCOS are required.

CONCLUSION

There is increasing recognition of the role that endocrine disorders play in causing obesity in childhood. However, their identification and diagnosis are often delayed. They represent a minority group among overweight and obese children, on the other hand, late diagnosis may be associated with high morbidity and, in some cases, mortality of an individual.

Importantly, the presence of specific clinical symptoms is typical for various endocrinopathies associated with obesity. When examining causes of overweight and obesity, the history, physical examinantion and the evaluation of a child's growth and BMI charts are crucial. Growth retardation and simultaneously progressing BMI ranges or a change in body composition with decreased muscle mass and increased truncal fat deposition are typical symptoms of severe primary hypothyroidism, CS and GHD. Clinical evaluation can lead to suspected endocrinopathy (e.g. cushingoid habitus, myxedema and goitre in hypothyroidism, subcutaneous calcifications and shortened fourth metacarpals and metatarsals in PHP Ia).

We draw attention to atrophic forms of CLT in children without palpable goitre leading to severe symptoms of hypothyroidism including growth disorder and myxedema. Growth retardation and change in facial appearance with development of the moon face are the first symptoms of endogenous hypercortisolism. Early development of obesity from infancy and primary hypothyroidism of unclear etiology should be suspected of PHP Ia. In a child with sudden hyperphagia and progressive weight gain, hypothalamic obesity should be considered and MRI of the brain should be performed. Note that small tumors in this area can first manifest only as an endocrine disorder without presence of intracranial hypertension.

Search strategy and selection criteria

A comprehensive search of MEDLINE, EMBASE, Web of Science and COCHRANE Library was performed to identify potentially relevant studies. The following terms were considered: obesity, endocrine disorders, children, Cushing's syndrome, hypothyroidism, as well as polycystic ovary syndrome, insulinoma, hypothalamic obesity, pseudohypoparathyroidism, hypogonadism, and growth hormone deficiency. Articles were used if they were peer-reviewed and included clinical information about obesity and endocrine causes in children, or if they discussed the use of a therapy to target a specific endocrine pathway. We also searched the reference lists of key articles published during the same period.

ABBREVIATIONS

CS, Cushing's syndrome; GH, Growth hormone; GHD, Growth hormone deficiency; PHP Ia, Pseudohypoparathyroidism type Ia; PCOS, Polycystic ovary syndrome; BMI, Body mass index; CLT, Chronic lymphocytic thyroiditis; TSH, Thyroid-stimulating hormone; fT4, Free thyroxine; ACTH, Adrenocorticotropic hormone; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; IGF-I, Insulin-like growth factor I; LDDST, Low-dose dexamethasone suppression test; PTH, Parathyroid hormone; GHRH, Growth hormone-releasing hormone; AHO, Albright hereditary osteodystrophy; PPHP, Pseudopseudohypoparathyroidism; MCR4, Melanocortin receptor type 4; MRI, Magnetic resonance imaging.

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