Secondary causes of obesity in children and adolescents

Gordana Stipančić[1,2], Marija Požgaj Šepec[1]

[1]University department od Pediatrics, University Hospital Center Sestre milosrdnice, Zagreb, Croatia, [2]Dental School of Medicine, University of Zagreb, Zagreb, Croatia

Correspondence:
  gordana.stipancic@zg.t-com.hr
  Tel.: + 385 1 3787 818
  Fax.: + 385 1 3768 284

Aim of this paper is to present an overview of the major disorders associated with obesity. An increasing number of children and adolescents are overweight or obese. In developed countries, the incidence of overweight and obesity exceeds 30%. The obesity mostly results from exogenous causes, when energy intake exceeds consumption for an extended period of time. In a considerably smaller number of children and adolescents, the cause is secondary. Great attention is paid to the epidemic of exogenous obesity while secondary causes of obesity often remain unrecognized and untreated. The child can be obese due to a genetic disorder such as a mutation of the leptin gene, or the leptin receptor or melanocortin-4 receptor genes. If the obesity is the consequence of a hormonal disorder, the possibility of aetiological treatment that leads to healing is considerably higher. The most common underlying disorders are hypothyroidism, growth hormone deficiency or Cushing's syndrome. Obesity is often an integral part of syndromes such as Prader-Willi or Bardet-Biedle. In most cases of monogenic obesity treatment is based on lifestyle changes and limited caloric intake. **Conclusion** – It is important to recognise the disease as early as possible, in order to restrain the unhealthy increase in body mass that causes a number of associated disorders which dramatically affect the patient's duration and quality of life. Secondary obesity should be considered in a child who, besides being obese, displays short stature or a reduced growth rate, delayed psychomotor development, facial dysmorphia, cryptorchidism, hypogonadism or a vision or hearing impairment. In the process of recognising the disease, the primary paediatrician plays an important role and then participates in the treatment providing support to the child and family.

Introduction

Over the last fifty years, the incidence of overweight and obesity has been increasing in all races and ethnic groups not only in adults, but also in children and adolescents. In 2014, 17% of American children and adolescents between the ages of 2 and 19 entered the statistic as obese, and if associated with the percentage for overweight, the number increased to 31.8% (1). Newer data are encouraging because they suggest a certain stabilisation of the number of obese individuals, and some observations have shown a reduction of the obesity frequency in children under the age of 5 (1).

Children >2 years and adolescents are overweight if their body mass index (BMI) is >85 but <95 percentile, and obese if their BMI is >95 percentile for age and gender using the revised 2000 CDC curves. Chil-

dren younger than 2 years are obese if their weight-for-length is >97.7 percentile according to the WHO curves (2). Extreme obesity is defined by a BMI of ≥120% for the 95th percentile, or >35 kg/m². According to recent guidelines, this would be grade 2 obesity, while grade 3 obesity is defined by a BMI >140% for the 95th percentile or >40 kg/m² (1). There are indications that it is extreme obesity of grade 2 and 3 that is increasing in girls of all ages and boys over 12 years (1, 3). Most overweight or obese children are exposed to increased energy intake and lower energy consumption for extended periods of time, the obesity being exogenous.

Children with exogenous obesity are endangered by a series of metabolic disorders such as type 2 diabetes, dyslipidaemia, fatty liver disease and prehypertension/hypertension, and in adulthood have an increased risk for cardiovascular disease. Screening is primarily aimed at detecting these complications. In a small number of children overweight or obesity are caused by hormonal or genetic disorders, or the obesity is only one part of the clinical characteristics of a syndrome, in which case we talk about endogenous or secondary obesity. According to the experiences of endocrinology departments in the tertiary service, the frequency of secondary obesity is less than 1% (4). The aetiology of the disorder should be established by screening, which will also determine the therapeutic approach. Furthermore, treatment will primarily include an appropriate and restricted diet; aetiological treatment is rarely available, with the exception of endocrine diseases in which the treatment of the basic disorder also regulates the body mass.

This paper aims to present an overview of the major disorders associated with obesity.

Obesity caused by endocrine disease

Although hormonal disorders which occur in endocrinopathies cause obesity in only a small number of children, they are of great importance because it is possible to treat the aetiology and achieve a cure.

Hypothyroidism is a consequence of reduced thyroid hormone production or secretion. It is rarely a matter of reduced peripheral tissue sensitivity to thyroid hormone activity. In the absence of thyroid hormone, the metabolism of most body tissues decreases. The cause can be thyroid disease (primary hypothyroidism) or pituitary and hypothalamic disease (secondary or tertiary hypothyroidism). Children with hypothyroidism complain of fatigue, have difficulty learning and sleep heavily. Their hair is sparse and dry and the skin dry and exfoliated. Hypothyroidism significantly slows down the growth rate and causes retention of water and fat tissue, which contributes to an increase in the BMI, but just by a few kilograms or 1-2 BMI units (5). The body mass increase is primarily due to increased capillary wall permeability, resulting in water retention (6). Therefore, after therapy introduction the fluid loss alone will trigger a noticeable initial weight loss. Due to reduced energy consumption, greater fat storage is achieved (7). Since children with hypothyroidism have reduced linear growth, the BMI can be increased although weight-for-age does not exceed the 95th percentile (5). Therefore, in every obese child with a reduced linear growth rate a screening for hypothyroidism should be performed by determining fT4, T3 and TSH. Children with primary hypothyroidism will have normal or reduced fT4 and T3 and high TSH. Those with central hypothyroidism have reduced fT4, normal or reduced T3 and normal or reduced TSH. In contrast, children with exogenous obesity mostly have normal or slightly elevated TSH (4.5 to 7 mIU/mL) with normal fT4 and elevated T3 as a result of the action of leptin secreted by white fatty tissue, which promotes TSH secretion and peripheral T4 conversion into T3 (8, 9). Hashi-

moto thyroiditis is the most common cause of hypothyroidism in hypothyroid children or children with goitre, and therefore thyroid peroxidase and thyroglobulin antibodies should be determined. Confirmation of a diagnosis of hypothyroidism will enable levothyroxine therapy initiation that leads to linear growth rate acceleration, primarily improving body composition and eliminating obesity.

Growth hormone (GH) deficiency has to be considered in children with short stature (height <2.5 SD), in children with a growth rate <2 SD and/or when the child's height is <1.5 SD of the midparental height. Muscle mass and tone are reduced, there is a centripetal distribution of fat and a moderate body mass increase. If the GH deficiency is congenital, the child has an infantile appearance, dentition is delayed and the voice is high. Bone age and puberty are late. A history of hypoglycaemias and prolonged jaundice in the neonatal period and a micropenis support the suspicion of congenital GH deficiency (8, 10). In children with primary or exogenous overweight, 24-hour GH secretion, maximal nocturnal GH secretion and GH response to different pharmacological stimuli are reduced. Therefore, the interpretation of pharmacological test results in children with overweight is difficult. However, in children with overweight or obesity, the growth rate is normal or increased, bone age is concordant or advanced, and the concentration of insulin-like growth factor I (IGF I) and its binding protein 3 (IGF BP 3) is normal or increased. On the other hand, all of these parameters (growth rate, bone age, IGF I and IGF BP3) are clearly decreased in GH deficiency. Therefore, when a reduction of linear growth associated with increased body mass is present, GH deficiency should be considered (4, 8). In those with proved GH deficiency, substitution therapy with recombinant human GH will accelerate growth and alter the body composition.

Cushing's syndrome in children is very rare, and most commonly iatrogenic as the consequence of glucocorticoid therapy of malignant or rheumatic diseases. However, in rare cases it may be the result of a pituitary or adrenal gland tumour. Ectopic secretion of ACTH is exceptional in children and adolescents (11). Adiposity caused by hypercortisolism is associated with a reduction in the growth rate (growth almost ceases). This clinical sign has to be the main reason for hypercortisolism screening. Unlike in adults, whose adiposity is predominantly centripetal, involving the trunk and fatty tissue pad on the neck, in children the adiposity is mostly generalised. Physical examination will reveal a round face with red cheeks, hirsutism, acne and purple striae. Increased glucocorticoid levels increase gluconeogenesis, and thus insulin secretion and insulin resistance, simultaneously inhibiting lipolysis and stimulating lipogenesis (12). Therefore a glucose tolerance disorder, hypertension, headache, hyperphagia, emotional instability and depression are often concomitant. In the case of simple obesity, hypercortisolism may also be present, making it difficult to distinguish it from Chushing's syndrome (8). This can be managed by monitoring the daily cortisol rhythm, with the most relevant and lowest level at midnight, and by means of the dexamethasone suppression test.

Hypothalamic obesity may develop due to inherited malformations, traumas, tumours or granulomatous and inflammatory processes of the hypothalamic region. 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. Trauma or malformation may affect peripheral feedback signalling, including cholecystokinin, glucagon-like peptide, grelin, insulin and leptin. These peptides pass

the blood-brain barrier and, under normal conditions, regulate the appetite by binding to their receptors in the hypothalamus (13). If this function is absent, for example, leptin will not produce the sensation of satiety, resulting in hyperphagia and significant progressive weight gain even with the introduction of dietary restrictions. Patients with hypothalamic obesity are also exposed to other endocrinopathies such as GH deficiency, hypothyroidism, or premature or delayed puberty and diabetes insipidus due to the absence of pituitary function stimuli. This form of obesity occurs in approximately 50% of children treated surgically due to craniopharyngioma (14, 15).

Monogenic obesity and obesity presented as part of a syndrome

Excessive body mass and obesity are usually primary or a consequence of a long-term imbalance between energy intake and consumption. It is the result of various environmental and genetic factors, with the concomitant involvement of multiple genes, and therefore considered a polygenic disorder (polygenic-induced disease). The human genome map contains at least 253 loci associated with obesity as well as 127 candidate genes, which have been proved for all chromosomes except for chromosome Y (5, 16).

The most striking examples for the role of genetics in weight control are evident in conditions induced by mutations of a single gene, which cause severe (grade 3) obesity. Many syndromes that include damage to a single gene or part of a chromosome present with obesity as one of the clinical characteristics, but the affected patients usually seek medical attention for other reasons, because more organ systems are involved. To date, several genetic disorders have been clearly identified, but only one of them (leptin deficiency) is aetiologically treatable. In most

disorders, the cause of obesity is still poorly understood (5, 16). About 7% of children with severe obesity probably have an underlying chromosomal disorder and/or genetic mutation (17).

Monogenic disorders that cause obesity

In the last twenty years, by studying leptin and related signal pathways involved in the regulation of appetite and energy balance, significant progress has been made in understanding the pathogenesis of obesity. Inactivating mutations of particular genes encoding the included proteins are responsible for monogenic forms of obesity, which account for 3-4% of severe obesity beginning at an early age (5, 18).

The whole process of appetite and energy balance control begins with the activation of leptin and its binding to the receptor on the hypothalamic neurons. Its anorexigenic role is manifested through proopiomelanocortin (POMC), the cocaine- and amphetamine-regulated transcript (CART) and the melanocortin system. Neurons involved in the POMC/CART signal pathway synthesise the melanocyte-stimulating hormone α (α-MSH), which, through melanocortinic receptors 3 and 4 (MC3R and MC4R), participates in appetite regulation and energy consumption, reducing appetite and increasing energy consumption. The group of orexigenic hormones includes neuropeptide Y (NPY) and proteins related to agouti-peptide (AgRP), which inhibit melanocortin receptors (17).

Leptin (LEP) and Leptin Receptor (LEPR) Deficiency - LEP is a product of adipocytes in fatty tissue and its level increases with increased amounts of fatty tissue. It is bound to LEPR in the arcuate nucleus and other parts of the brain. Hunger acutely lowers the level of LEP, which strongly stimulates

appetite and reduces energy consumption. Recovery of leptin levels leads to changes in the activity of the brain regions involved in controlling appetite and thus reduces food intake. Individuals with a homozygous inactivating mutation of the LEP gene have an excessive food intake and develop severe obesity with very low LEP levels at an early age. The use of human recombinant LEP leads to positive changes in the regulation of appetite and reduction of obesity. Heterozygotes can only be presented with slightly lower levels of LEP (5). Homozygotes for the inactivating LEPR mutation are not clinically distinct from individuals with LEP deficiency, and heterozygotes have a normal phenotype. In children with a LEPR mutation hyperphagia begins in the first weeks of life, and in those with a mutation of LEP after several months. LEP deficiency will also cause frequent infections, mild hypothyroidism and postponed puberty, i.e. hypogonadotropic hypogonadism. LEP application will trigger pubertal development, which proves that in humans LEP is an important factor in initiating puberty (1, 5, 16).

Proopiomelanocortin (POMC) gene mutation - By acting on neurons in the hypothalamus, leptin stimulates the production of POMC, whose cleavage originates from adrenocorticotropic hormone (ACTH), alpha-, beta- and gamma-melanocyte stimulating hormone (MSH), beta-lipoprotein and beta-endorphin. Alpha-MSH regulates appetite and energy consumption by binding to the melanocortin-3 and -4 receptors (MC3R and MC4R) in the arcuate nucleus. Inactivating mutations of POMC prevent its cleavage to alpha-MSH or ACTH. Patients, homozygotes or complex heterozygotes for the POMC mutation, have hyperphagia (probably due to a lack of signals on MC3R and MC4R), red hair (absence of peripheral binding of alpha-MSH to melanocortin-1 receptor) and adrenal insufficiency (insufficient

amount of ACTH to bind to adrenal melanocortin-2 receptor). Therefore, this is a rare form of adrenal gland insufficiency associated with obesity (5, 19).

Prohormone-convertase 1 (PC 1) gene mutation - In a few patients, a mutation of the PC1 gene, an enzyme that cleaves POMC into its metabolically active components and is involved in the emergence of several other hormones, has been demonstrated. Therefore, PC1 deficiency is characterised not only by obesity and adrenal gland insufficiency but also by postprandial hypoglycaemia (due to insufficient cleavage of proinsulin), hypogonadotropic hypogonadism and malabsorption (5, 8).

Mutation of the melanocortin-4 receptor gene (MC4R) - Alpha-MSH affects weight control through MC3R and MC4R. Animal models have shown that MC3R primarily participates in the regulation of nutrition and energy consumption, whereas MC4R has a role in appetite regulation (20). In humans, heterozygous and homozygous MC4R gene mutations located on chromosome 18q22 cause hyperphagia, severe obesity with a high weight gain from the first year of life, hyperinsulinaemia and increased linear growth during childhood. With the increase of fatty tissue there is also an increase in muscle tissue (5). However, leptin and lipid levels, metabolic rate as well as thyroid, adrenal and gonadal functions are normal. Homozygous individuals are more heavily affected, and heterozygotes, with a residual signalling function, have a milder phenotype. In 100% of MC4R gene mutation-affected individuals binge-eating is present, compared to only 14% of such behaviour in non-carrier individuals. Binge-eating implies rapid ingestion of large amounts of food in the absence of hunger at least twice a week. When they reach the age of understanding, those affected develop feelings of discomfort, depression and guilt due to such out-of-con-

trol behaviour. Since binge-eating is the main phenotypic trait of a person with a MC4R gene mutation, MC4R has become a candidate gene for the control of eating behaviour. Hence, it is more likely that binge-eaters are MC4R gene mutation carriers rather than individuals in whom the obesity is the result of constant uncontrolled eating. While binge-eating has so far been considered a psychological phenomenon, the genetic cause of such a condition has now been proved. It appears that the MC4R mutation destroys a signal pathway that leads to feelings of satiety (16, 21). According to previous research, about 2-5% of individuals with early onset of high-grade (severe) obesity are heterozygotes for MC4R gene mutations (22). This is the most common genetic form of childhood obesity. Paediatricians and paediatric endocrinologists should be aware of this and distinguish this group clinically from the PWS group, the latter displaying a reduced height gain along with a reduced amount of muscle tissue (19, 21). In the near future, selective melanocortin receptor agonists could be a therapeutic option for those with mutations in the melanocortin signalling pathway (1).

Brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) gene mutations - BDNF is very important for neuronal development and function. It exerts its effect on food intake and body mass through the TrkB receptor in the leptin signalling pathway, after MC4R. Heterozygosity for BDNF is considered to be responsible for early development of obesity in patients with WAGR syndrome (23). Heterozygous carriers of an inactivating TrkB gene mutation are reported among patients with obesity, psychomotor retardation and convulsions (5, 24).

Transcription factor SIM1 gene mutation - The SIM1 (single-minded 1) gene is located on chromosome 6. It participates in energy homeostasis, probably as a compo-

nent of the melanocortin signalling pathway. Heterozygous carriers of SIM1 mutations share clinical features with MC4R deficiency patients, especially hyperphagia and autonomic dysfunction. In patients with 6q14-q21 chromosome (the region that contains the SIM1 gene) deletion, early hyperphagia and obesity develop, and, to some extent, there is a phenotypic overlap with PWS (17).

Syndromes in which obesity is an important clinical feature

Unlike in monogenic disorders, where obesity begins very early in infancy, in obesity-related syndromes it begins after infancy. Other than obesity, basic syndrome features include dysmorphia, psychomotor retardation and anomalies of certain organ systems (8). They can occur due to gene or larger chromosomal abnormalities. Autosomal or X chromosomes can be affected.

Prader-Willi syndrome (PWS), a rare and complex genetic disorder that affects many organ systems, is a consequence of the lack of expression of paternal genes in the 15q11-q13 region. From the earliest age it causes reduced muscle tone that impairs feeding and development. Due to excessive food intake, severe obesity develops. In spite of the obesity these children lag in growth and are of short stature, there is no sexual development and psychomotor development is also delayed. The disease is characterised by numerous complications, primarily obesity-associated, which significantly impair the quality of life and shorten life expectancy. Early confirmation of the diagnosis by genetic testing and initiation of treatment by multidisciplinary approach are of crucial importance for the course of the disease. First of all, it is necessary to ensure control of food intake and thereby prevent the development of severe obesity and, by applying habilitation measures, to enhance the psychomotor

development of the child (25). In the last few years, growth hormone has been introduced in the treatment, since GH deficiency was recorded in approximately 80% of PWS children. This therapy accelerates growth, improves final height and has a positive effect on body composition, primarily by reducing the amount of fat tissue. Therapy is maintained until the final height is achieved, but its positive effect on the patient's metabolic status persists several years after its discontinuation (26). The appetite regulation disorder in PWS is manifested by the inability to stop eating, repeated food intake soon after the previous meal and consumption of inedible items. This is not a consequence of an increased sense of hunger, but of a lack of satiety because of a hypothalamic disorder and increased stimulation of the ventromedial prefrontal cortex region as a response to food, as evidenced by functional magnetic resonance (fMR) studies (27, 28). Despite the well-known mutation, the product of the affected gene is still unknown. Due to the disorder that most likely primarily affects the hypothalamus, deficiencies of other pituitary and peripheral gland hormones can develop, almost always leading to hypogonadotropic hypogonadism and hypothyroidism or adrenal gland insufficiency (29).

Bardet-Biedl syndrome (BBS) is a heterogeneous autosomal recessive disorder due to mutations in one of the 15 possible genes that control ciliary function. The role of cilia in regulating body mass has been confirmed in mice. Primary ciliary disorders by inactivating mutations of the Tg737 and Kif3a genes in POMC neurons, i.e. the leptin signal pathway, lead to hyperphagia and obesity (30). Classical clinical features include severe early-onset obesity, retinitis pigmentosa, hypogonadism, mental retardation, glucose intolerance, postaxial polydactyly, deafness and kidney disorders (31). Mortality is a consequence of obesity and kidney disease complications.

Alström's syndrome (AS) is a rare autosomal recessive disorder due to the mutation of the ALMS1 gene located on chromosome 2p13, which also disrupts ciliary function. In addition to early central obesity like in children with BBS, children with AS also have visual impairment and deafness. Central obesity develops by 5 years of age, and the affected children have acanthosis nigricans and type 2 diabetes more often than children with BBS. Other endocrinopathies include hypothyroidism, primary hypogonadism in boys and GH deficiency. Intellectual development is normal (8).

Carpenter syndrome besides obesity, includes mental retardation, short stature, brachicephalus, polydactyly, foot syndactyly, cryptorchidism, hypogonadism in boys, umbilical hernias and high palate. The RAB23 gene is located on chromosome 6p11. Like in Alström's and Bardet-Biedl's syndromes, this gene mutation also causes an impaired function of proteins involved in the ciliary body important for intercellular communication in mammals. The disorder also seems to disrupt communication between the neurons involved in the leptin signal pathway, crucial for energy homeostasis (31).

Cohen's syndrome is characterised by hypotonia and failure to thrive during infancy, and the central obesity develops in mid-childhood. The clinical features include microcephaly, mental retardation, cryptorchidism, small hands and feet with long, thin fingers as well as marked central incisors. The COH1 gene, whose mutation causes these disorders, is located on chromosome 8q22 and encodes a transmembrane protein with a still unknown function (32).

Albright's hereditary osteodistrophy involves a phenotype with short stature and obesity, along with a shortening of the 4th metacarpal bone as well as pseudohypoparathyroidism type 1a (PHP 1a) and pseudopseudohypoparathyroidism (PPHP). In case of PHP 1a with hypocalcaemia and mental

retardation, hypothyroidism can develop due to TSH resistance and delayed puberty or hypogonadism due to gonadotropin resistance (8). The responsible GNAS1 gene is located on chromosome 20q13.2. Patients have an inactivating mutation in the stem cells involving the α-subunit of the widespread stimulating G protein, which is a component of many hormone receptors involved in the adenylate-cyclase signal pathway. The aetiology of obesity in PHP 1a may be partially associated with a reduced signal transmission through receptors that include the α-subunit of Gs-proteins, and are also found in the leptin signal pathway (33).

WAGR syndrome includes Wilms tumour, aniridia, genitourinary tract abnormalities and mental retardation, while obesity is present only in some patients. The syndrome is caused by a deletion on chromo-some 11p11.4, near the gene responsible for BDNF production. BDNF is regulated by nutritional status and included in the leptin signal pathway in the hypothalamus where it stimulates the production, differentiation and survival of neurons, but also body mass regulation. Most WAGR syndrome patients with the deletion which includes BDNF are obese, unlike those with no deletion, in whom the frequency of obesity is consistent with that in the general population (8, 23).

Clinical evaluation and treatment of secondary obesity

In children with a suspicion of secondary obesity, determination of the aetiology requires obtaining a careful and thorough history as well as a detailed physical examination (Table 1).

Table 1. Clinical presentation in secondary forms of obesity			
Cause	Short stature/ decreased height velocity	Delayed psychomotor development	Other clinical features
Endocrinologic diseases			
Hypothyroidism	Yes	No	Fatigue, constipation, dry skin and hair
GHD	Yes	No	Centripetal obesity, infantile appearence, microakria
CS	Yes	No	Round face with red cheeks, acne, striae, hirsutism, hypertension
HO	Yes	No	Signs of increased intracranial pressure and hypopituitarism
Syndroms			
Prader Willi	Yes	Yes	Hypotonia, small hands and feet, hypogonadism
Bardet-Biedel	Yes	Yes	Polydactyly/sindacty, retinitis pigmentosa, hypogonadism, kidney disorder
Alstrom	Yes	No	Blindness, deafness, acanthosis nigricans, type 2 diabetes
Carpenter	Yes	Yes	Polydactyly/ leg sindactyly, cryptorhism, hypogonadism in boys
Cohen	Yes	Yes	Microcephaly, long thin fingers, marked central incisors
AHO	Yes	Yes	Short 4th and 5th metacarpal bone round face, hypocalcaemia
WS	Yes	Yes	Wilms tumour, aniridia, genitourinary tract abnormalities
Monogenic defect			
LLR	No	No	Secondary hypogonadism, tendency towards infections
POMC	No	No	Adrenal insufficiency, red hair
MC4R	No	No	Accelerated growth, hyperinsulinism

GHD=Growth hormone deficiency; CS=Cushing's Syndrome; HO=Hypothalamic obesity; AHO=Albright's Hereditary Osteodistrophy; WS=WAGR syndrome; LLR=Leptin-leptin receptor; POMC=Proopiomelanocortin; MC4R=Melanocortin-4 receptor.

The history must establish the onset of obesity and its duration, and whether other family members are also severely obese. In the clinical examination special attention should be paid to body height and weight measurement. The child's height is to be compared with the midparental height; calculating the BMI and setting the BMI value on the percentile curve for age and gender determines the degree of obesity. Attention should be paid to the dysmorphic characteristics and dysfunction of individual organ systems, with an emphasis on psychomotor development. According to age, consideration should be given to the time of puberty onset and its progression.

Clinically, endocrine disorders associated with obesity are primarily manifested by short stature as well as impaired psychomotor development. The crucial features in the clinical picture are growth rate deceleration and development of mostly central obesity. Along with a congenital GH deficiency, in male children small genitals, frequently concomitant with testicular retention, are often observed. All forms of endocrine-induced obesity often result in delayed puberty, i.e. hypogonadotropic hypogonadism, with the exception of primary hypothyroidism, which may also cause premature puberty.

Routine laboratory screening for endocrine diseases such as GH deficiency, hypothyroidism or hypercortisolism is not indicated in all obese children, but only in those that are short in relation to the mean parental height or have a reduced growth rate. However, one should bear in mind that, for example, in Albright's hereditary osteodystrophy, associated with short stature in adolescence, growth can be accelerated in the first 2-3 years of life (1).

Most genetic syndromes are characterised by delayed psychomotor development, short stature and phenotypic features that should help determine their aetiology. Neonatal hypotonia and feeding difficulties should raise the suspicion of Prader-Willi syndrome. Complete development of the clinical characteristics of a syndrome at an older age significantly aggravates the efficiency of treatment measures. Shorter 4th and 5th metacarpal bones point to Albright's hereditary osteodystrophy, as well as to Turner's syndrome in female children, which is also often associated with obesity. Polydactyly and retinitis pigmentosa can suggest Bardet-Biedel's syndrome. Many other syndromes, such as Down's syndrome or fragile X-chromosome, are often associated with obesity as well. Again, emphasis should be placed on the particular features of obesity associated with a MC4R gene mutation, in which children are tall and have normal mental status without any other clinical features.

Screening for monogenic obesity is currently not routinely available. Diagnosis is not performed in all laboratories, and the results are primarily important for genetic counselling, while therapeutic options remain very limited. Generally, genetic analysis is indicated in children with extreme early-onset obesity (before 5 years of age) and a clinical picture indicating a genetic syndrome, and/or the presence of family members with severe obesity (1).

In all patients with secondary obesity it is necessary to carry out a screening for pathological conditions that often accompany the obesity (e.g. dyslipidaemia, hyperinsulinaemia, carbohydrate metabolism disorders, diabetes, hypertension or non-alcoholic fatty liver disease) and, if necessary, apply appropriate treatment. In most syndromes that include obesity there is also a disorder of psychomotor development, which impedes the implementation of therapeutic measures that involve lifestyle changes and nutritional restrictions. In some of the above-mentioned syndromes the associated short stature considerably contributes to the obesity. It is ex-

tremely important to make an early diagnosis of obesity syndromes in order to initiate early lifestyle and dietary changes before the development of severe obesity, when treatment results can hardly be expected. In contrast, treating endocrine-induced obesity is much more successful and leads to its reversion (34, 35).

Conclusion

Secondary obesity is present in a smaller number of obese children. It is especially important to single out children in whom the cause is a hormonal imbalance, because such conditions are treatable. In other forms of secondary obesity it is important to establish the diagnosis early, in order to implement available therapeutic measures and prevent the development of severe obesity as well as consequent complications that can significantly impair the quality and length of life.

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