

Short Stature And Obesity: A Broad Range Of Diagnosis

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Marie-Laure Frelut is a Pediatrician. She became involved in the field of childhood obesity in the 1990s when she had to run an inpatient unit for severely obese adolescents.

Short stature: A single definition but a population based assessment

Half of the population has by definition a size below average, 25 % below the 25th centile of reference growth curves and 3 % below the third centile. The 25th centile or – 2 standard deviations (SD) in height is a commonly accepted definition of short stature. Major differences in height are noticeable among populations around the world making the choice of the reference curves critical (*see corresponding chapter*). Height velocity decreases from birth onward. The rate is typically of 25 cm/year during the first year, then an average 10 cm/year from age 1 to 4 years. Growth which further slows is linear between the age of 6 and 11 and of about 5 cm per year with little difference between boys and girls. Pubertal growth spurt will increase size by 8 to 10 cm year in girls. Later pubertal onset in boys (usually by 1 to 2 years) enhances prepubertal growth duration. The greater amplitude in boys (3-5 cm more than female growth spurt) gives rise to an average 12.5 cm difference in adult height between the sexes. The final height is reached at the end of puberty, when lower limbs epiphysis are fused. Age of onset of puberty is a key determinant of final height. Pubertal stage and age of occurrence have to be taken into account in order to analyze a given height and estimate target height. Puberty develops often early in overweight girls and later in boys than in lean counterparts. Target height (TH) can be roughly estimated from the parents' ones provided they do not differ by more than 20 cm (cf table 1)¹.

Table 1: Estimation of a child target height (TH, in cm):

TH for girls: $(\text{father's height} + \text{mother's height} - 13) / 2$
TH for boys: $(\text{mother's height} + \text{father's height} + 13) / 2$

A short stature is indicative of a limitation of bones growth. Many reasons may underpin this phenomenon: hormonal deficiency, nutritional deficiency, abnormal responsiveness of the bones to growth factors and drugs. The impact of the individual's genetic background ranges from being the unique cause to being a minor contributor to short stature. The association between obesity and short stature is an apparent paradox which demonstrates that energy intakes are not the single necessary contributor to adequate growth. In this chapter, we shall examine from a clinical point of view the causes that may link an excess energy intake and fat storage to a poor size.

Growth Regulation: Hormones And Nutrition Interaction

Growth is dependent on several hormones and nutrition. Growth hormone (GH) is released by the anterior pituitary in discrete pulses that increase during childhood until puberty, under the control of hypothalamic GH releasing hormone (GHRH), ghrelin an orexigenic hormone released by the stomach and insulin growth factor 1 (IGF1). GH and IGF1 actions are ubiquitous. IGF1 exerts a potent negative feedback on GHRH secretion. GH may act directly or require to be mediated by IGF1. Eighty per cent of IGF1 is synthesized by the liver and circulates bound mainly to IGF binding protein 3 (IGFBP3) and an acid labile subunit (ALS) which together enhance its stability and half-life. GH has little direct action on bone

contrary to what occurs in muscles. Circulating IGF1 and locally secreted IGF1 through endocrine and paracrine actions allow long bone growth. IGF1 action on cell proliferation is mediated by signal transduction cascades after GH and IGF have bound to cell surface receptors. Thyroid hormones, parathyroid hormone (PTH) also play key roles in bone growth and maturation process. As a consequence, a short stature may reveal several genetic defects.

GH does not only influence linear growth. It promotes lipolysis and prevents lipogenesis and together with IGF1 plays a key role in preadipocytes proliferation, differentiation and senescence. Insulin receptor on the cells membranes can bind IGF but with a much lower affinity than they do with insulin. Thyroid hormone has multiple actions, including stimulation of thermogenesis and hence increase energy expenditure and in children the stimulation of growth.

GH And Obesity

In healthy adults a strong inverse relationship exists between the amount of GH secreted, visceral adipose tissue and the amount of ectopic fat deposition, notably in the liver and muscles. In obese person both spontaneous and stimulated GH secretions are blunted. The mass of GH secreted per burst is decreased but burst frequency is unaffected. Weight loss restores GH responsiveness. Data in children and adolescents are scarce. Obese adolescents have similar serum fasting IGF1 concentrations and lower baseline, peak and area under the curve GH (expressed in Log) than their lean counterparts². IGF1, IGF binding protein 3 (IGFBP-3) serum concentrations were similar in a group of prepubertal lean and obese controls whereas IGFBP-1 was lower in obese children³. Insulin itself has growth stimulation properties. As a consequence, obese children tend to exhibit higher linear growth velocities than lean counterparts until the end of puberty. The lack of transient increase in growth velocity, a short stature in association to overweight or obesity and a decreased growth velocity should all draw the attention since both of them may reflect hormonal deficiency or abnormal responsiveness to growth factors. Additional but transient growth spurt linked to obesity starts with its onset and stops at the end of puberty when bone plates are fused.

Figure 1: Height growth velocity increase during obesity development in a girl.
Note the decrease in height velocity with puberty despite increasing obesity

A short stature associated to obesity should lead to suspect either an early nutritional defect which has blunted normal growth, endocrine disturbance or genetic disease affecting the hormonal cascade stimulating growth or long bone responsiveness.

The Late Consequences Of Early Malnutrition

GH and IGFs secretion are under nutritional control. Undernutrition *in utero* and during the first 2 years of life is a major determinant of both stunting of linear growth and subsequent obesity and associated complications. In a cohort of Uruguayan children under 5 years, the risk of overweight was almost multiplied by 3 (OR: 2,4, 95 % CI 1.6-3.5) in stunted infants whereas maternal short stature below 1,5 m enhanced the risk of low birth weight but not of obesity⁴. Pregnancy in adolescence which slows and stunts the girl's growth enhances the risk of poor perinatal outcome and its later consequences⁵. A

prospective study performed in five birth cohorts in South America, Philippines and South Africa showed that a higher birth weight is associated with an adult body mass index (BMI) greater than 25 kg/m² (OR 1.28, 95 % CI 1.21-1.35) and reduced likelihood of short adult stature (OR 0.49, 95 % CI 0.44-0.54). Faster linear growth raise the likelihood of overweight during childhood (age 2 years OR 1.24, 95 % CI 1.17-1.31, mid childhood OR 1.12, 95% CI 1.06-1.18)⁶.

Short Stature, Obesity And Digestive Tract Disease

Obesity associated to short stature shows that energy requirements are more than covered. It does not strangely preclude gastro intestinal diseases associated to macronutrients malabsorption such as celiac disease. A recent review reports several cases of obesity at the time of diagnosis of celiac disease. Reduced growth velocity despite overweight or obesity can be part of the feature of this still poorly understood condition. Recurrent abdominal pain and family history of celiac disease were the main features that led to the diagnosis. Overweight and obesity may worsen while growth velocity increases in some children and adolescents after the introduction of a gluten free diet⁷. In some children and adolescents overweight and obesity are present at the time of diagnosis of inflammatory bowel diseases. Reduced growth velocity and impaired final height are another consequence of these diseases. To the best of our knowledge, their combination has not been yet reported⁸.

Obesity of hormonal origin

Hypothyroidism

Historical forms of hypothyroidism resulted in dwarfism with severe mental retardation, hypotonia and increased fat accumulation. Worldwide campaigns of iodine supplementation under the umbrella of the World Health Organization and neonatal screening for congenital hypothyroidism in many countries have resulted in a near total disappearance of this major form of the disease. Early hormonal replacement results in most cases in normal growth pattern. In older children, especially when diagnosis is set beyond the age of 5 years, stature and excess weight gain are among the commonest consequences of thyroid hormones deficiency in association to mental retardation⁹. The commonest cause of hypothyroidism in older children and adolescents is the Hashimoto's lymphocytic thyroiditis which typically combines a goiter, a significantly increased TSH, low fT4 and total T4 and the presence of anti -thyroperoxidase (TPO) and anti -thyroglobulin (TG) antibodies.

Obese adolescents with severe obesity have mildly elevated concentrations of fT3 which should not be misinterpreted as hypothyroidism but result from an increased rate of transformation of fT4 to fT3 (*see corresponding chapter*). Mild TSH increase may also be observed, however obesity cannot be attributed to these moderate abnormalities which usually resolve after weight reduction and do not require hormonal treatment¹⁰.

Growth Hormone Deficiency

GH plays a pivotal role in growth and adipose tissue metabolism. GH deficiencies therefore result in a decreased growth velocity associated to an excess fat mass ranging from a mild overweight to obesity.

GH and IGFs deficiency covers a wide range of diagnosis since any step in the cascade from hormone and IGF synthesis to action into target cells may be involved¹¹. Many syndromes are described that range from severe dwarfism to short stature. Most of them are not in their classical form associated to overweight or obesity. However the increasing prevalence of overweight and obesity may change the clinical picture. The lack of sufficient GH causes a characteristic appearance with truncal obesity, immature cherubic face and maxillary hypoplasia. Before the age of 2 years, growth is more dependent from IGFs so that GH deficiency usually has little expression on height.

In children between 6 and 11 years old, at a time when growth is linear, GH deficiency should be suspected if IGF1 serum concentration is <100 ng/ml in a child from 6 to 11 years old: GH deficiency is severe when IGF1 serum concentration is below 30 ng/ml, marked between 30 and 50 ng/ml and to be confirmed between 50 and 100 ng/ml. Other associated hormonal deficiencies of hypothalamic or pituitary origin have to be detected. At the time of puberty, an associated delay in a girl (lack of breast development at the age of 12 years, ongoing puberty at a slow pace, no menstruation at the age of 14.5 years, require to suspect a more complex disorder of the hypothalamic pituitary axis. In boys, delayed puberty onset is often associated to overweight.. However, in both sexes, a MRI should be performed in order to rule out midline brain tumor mostly a craniopharyngioma. Other findings include an abnormal or ectopic pituitary gland or the enlargement of the pituitary stalk, findings that require careful specialized investigations by experienced teams^{12, 13}. Clinical phenotypes reported in relation to abnormal GHR, STAT5b, IGF1, IGF-ALS and IGF1-R genes seldom include obesity. Precise diagnosis and management and of such patients rely on straight cooperation between specialized pediatric endocrinology and genetics teams^{11, 14}.

Pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) and Albright hereditary osteodystrophy (AHO) are rare, heterogeneous, related inherited disorders with a genetic component. Their prevalence is estimated at 0.8/100 000. Genetic defects lead to organs resistance to parathyroid hormone (PTH). The PTH receptor is coupled to the stimulatory G protein (Gs), thereby activating cAMP formation. This finding allowed the distinction between different subtypes of the disorder and the association to other hormonal defects sharing the same Gs (TSH, GH) could be partly clarified. However, in about 20 to 30% of the patients, no GNAS mutation, the gene causing the disease, is present. Epigenetic defects and previously unidentified inactivating mutation of the gene were identified. The typical phenotype includes obesity, short stocky build, round face, short thick neck, short metacarpals (especially the 4th and 5th). IQ is decreased in 50-70 % of the cases. Bone age advance contrasts with the retardation found in GH deficiency. Calcification in the subcutaneous tissue, kidneys and brain are common. Biological features include high PTH, low calcemia and hyperphosphatemia. Calcitriol and calcium administration require careful management. Patients suffering PHP Ia, where mutations are inherited from the mother, suffer multiple hormone resistance including PTH, TSH, FSH, LH and GHRH which have to be regularly assessed and monitored. Follow-up also includes weight monitoring¹⁵.

Cushing syndrome or obesity induced metabolic disorder?

Cushing syndrome is a rare severe entity with an incidence of about 5 children per million per year. The

most common cause of endogenous Cushing syndrome in children is corticotrophin (ACTH) overproduction from the pituitary, called Cushing disease. Cushing disease which accounts for about 75 % of all Cushing syndromes in children over 7 years is mostly due to a pituitary microadenoma. In younger children, adrenal causes of Cushing syndromes (adenoma, carcinoma and bilateral micro or macronodular hyperplasia) are dominant. The most common presenting symptom is an insidious weight gain with lack of height gain. Other symptoms include facial plethora, hypertension, hirsutism, delayed pubertal development or amenorrhea. Characteristic skin manifestations include violaceous striae. Diagnosis is challenging and relies on the confirmation of hypercortisolism and the localization and characterization by diagnostic imaging, including catheterization studies by highly specialized teams¹⁶.

Cushing syndrome must be differentiated from increased cortisol responses in common obesity. While plasma cortisol levels appear normal, abdominal obesity associates with increased free urinary excretion and increased cortisol production rates. In adults, local tissue level of conversion of cortisone to cortisol catalyzed by the 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) which is expressed in many tissues and 11 β -HSD2 action in adipose tissue, are thought to mainly explain this observation. Cortisol levels turn back to normal with weight reduction (*see corresponding chapter*)¹⁷.

Skeletal Dysplasia

A majority of the 400 skeletal disorders listed in the nosology of these diseases presents with short stature. However mild forms are seldom diagnosed while in some cases recombinant human GH (rhGH) treatment may enhance the final height. The association to obesity is not yet, to our knowledge, reviewed and the prevalence of the association to overweight or obesity is unknown. Mild forms are not uncommon in obesity units. The diagnosis should be suspected on clinical examination when excess weight gain is not associated to increased height velocity in a subject with short stature or lower growth centile than predicted from parents' heights. Short parents' stature should also draw the attention. Other hormonal deficiencies or short stature from nutritional origin should be ruled out.

Mild skeletal abnormalities are often detected on clinical examination: Madelung's deformity of the forearm, disproportion of the limbs (short proximal segments) lead to suspect a Leri Weill dyschondroosteosis resulting from heterozygous defect of the SHOX (*Short stature Homeobox containing gene*) gene, located in the pseudoautosomal region of chromosome X and Y, which is identified in 58 to 100 % of the patients. The SHOX protein is expressed in the plates of the members' bones. A haploinsufficiency of SHOX gene increases the rate of differentiation of the chondrocytes and hence the rate of fusion of bone plates. Girls with Turner syndrome have dyschondroostosis deformities.

Examination of the parents should note their own stature and detect limbs abnormalities that become more evident at the end of childhood and during puberty. X-rays of the forearms and wrists should be performed in parents and children. A typical picture is bowing and shortening of the radius, prominence of the ulnar head and palmar and ulnar deviation leading to a pyramidal configuration of the carpal bones. Some patients benefit from hrGH treatment. This underlines that patients with short stature with or without obesity require appropriate investigations and management by pediatric endocrinology reference units¹⁸.

Some rare syndromes

The prader willi syndrome

The Prader Willi syndrome (PWS) is a rare but severe condition that should be immediately suspected in front of a major neonatal hypotonia with marked feeding difficulties during the first months of life, short hands and feet and other morphological and behavioral abnormalities (table 2). The clinical diagnosis should be confirmed by genetic testing which evidences the loss of paternal alleles in 15q11.2-13 region in 65 to 75 % of the individuals. Other mechanisms include a maternal uniparental disomy of chromosome 15 in 20 to 30 % of the individuals and an imprinting defect of the paternally inherited chromosome 15 in 1-3% of the patients. The study of the methylation of the DNA will diagnose 99% of the PWS without distinction among the molecular classes that have to be further studied. GH deficiency together with hypogonadism is a feature of the PWS. Hypogonadism which is manifested in both sexes causes incomplete and delayed puberty. Whether GH deficiency should be treated in this very special condition is a matter of debate despite recent approval by FDA and EMA. Appropriate early specialized cares and parental support and counseling have improved the outcome in many patients who may avoid obesity¹⁹.

Table 2: Prader Willi syndrome (adapted from ¹¹)

Clinical diagnosis requires 5 points (at least 4 of them major) below 3 yrs of age; 8 points (at least 5 of them major at 3 yrs of age and older.

Prader Willi syndrome	
Prevalence : 1/10 000 -1/30 000	
Consensus diagnostic criteria	
Major criteria (1 point each)	Minor criteria (1/2 point each)
Neoanatal/infantile hypotonia and poor suck	Decreased fetal movements and infantile lethargy
Feeding problems and failure to thrive as infants	Typical behavioral problems
Weight gain at 1-6 years; obesity; hyperphagia	Sleep apnea
Characteristic dysmorphic facial features	Short stature for family by 15 years
Small genitalia; pubertal delay and insufficiency	Hypopigmentation for the family
	Small hand and feet for height
	Narrow hands, straight ulnar border
	Esotropia, myopia
	Thick, viscous saliva
	Speech articulation defects
	Skin picking

Pubertal delay, short stature and associated overweight or obesity may be relevant for an ovarian insufficiency such as a Turner syndrome (X0).

Clinicians should carefully monitor growth of overweight and obese children as they do in their lean counterparts and be aware of the differences to be observed.

The Bardlet-Biedl Syndrome

The Bardlet Biedl syndrome (BBS) is a genetic disorder in which ciliary functions are altered in the cells. Six major features are the hallmark of the disorder: obesity, retinal degeneration, hypogonadism, polydactyly, renal dysfunction and mental retardation. Minor features may be present: neurological impairment, craniofacial abnormalities, cardiovascular abnormalities, hepatic defect, anosmia, defect in thermosensory and Hirschsprung disease. Its prevalence ranges from 1/160 000 in Northern Europe to /13 500 in Kuwait. Fourteen different genes have been identified. In about 20% of the cases the genetic defect is still unknown. The discovery of genetic overlaps with several other ciliary diseases is enhancing the understanding of this group of pathology and obesity: BBS proteins seem to play key roles in energy metabolism, fat storage and regulation of appetite²⁰.

Obesity and short stature may be part of otherwise well characterized syndromes such as Turner syndromes in girls, X-Fragile syndromes. Obesity is also a common feature of several other diseases with intellectual disabilities, the cause of which is often unknown. Several websites describing rare diseases are helpful in order to identify obesity related syndromes.

Idiopathic Short Stature

Idiopathic short stature means that no cause is yet evidenced (not that a cause does not exist) within families where the child usually has at least one short parent. Mild Leri Weill dysostosis, undiagnosed abnormal genetic expression of the GH axis are reported by several recent papers. Because rhGR administration has been shown to enhance final height in some (but not all) patients, wrists X-rays should be more often performed since they bring information on bone age and bone morphology. Pediatricians dealing with obesity should not hesitate to seek help from reference pediatric endocrinology units in order to ensure adequate exploration and treatment²¹.

A short stature or the lack of increased height gain velocity associated to obesity should draw the attention of pediatricians and lead to careful precise physical examination followed by selected investigations in specialized pediatric endocrinology units.

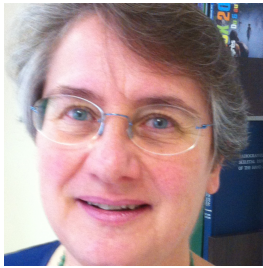
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