Delayed Puberty

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Metella Dei and Francesca Pampaloni

Abbreviations

AMH	Anti-Mullerian hormone
CD	Coeliac disease
CDGP	Constitutional delay of growth and puberty
CSF	Cerebrospinal fluid
DP	Delayed puberty
FHH	Functional hypogonadotropic hypogonadism
FSH	Follicle stimulating hormone
GD	Growth hormone deficiency
Gh	Growth hormone
GhRH	Growth hormone releasing hormone
GnRH	Gonadotropin hormone releasing hormone
HH	Hypogonadotropic hypogonadism
IGD	Isolated Gh deficiency
IGF-1	Insulin growth factor-1
KS	Kallmann syndrome
LH	Luteotropic hormone
PRL	Prolactin
SSRI	Selective serotonin reuptake inhibitors
TIDA	Tuberoinfundibular dopamineagonists

M. Dei, M.D. (✉)
Italian Society of Pediatric and Adolescent Gynecology, Florence, Italy
e-mail: meteldei@alice.it

F. Pampaloni, M.D.
Pediatric and Adolescent Gynecology Unit, Careggi Hospital, Florence, Italy
e-mail: pampa@virgilio.it

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2.1 Definition and Pathogenesis

We define a delayed puberty (DP), warranting a diagnostic evaluation, as:

1. Lack of breast development by age 13
2. Lack of menarche by age 15 in the presence of secondary sexual characteristics
3. Lack of menarche 4 years after the beginning of breast development (thelarche)

These criteria, based on two standard deviations from normal range of pubertal timing of European Caucasian girls, can be, in the clinical practice, extended also to African girls (whose pubertal development starts earlier) and to Asian girls. The presence of clues of specific conditions (malnutrition, poor growth, reduced sense of smell, cyclic pelvic pain, androgen excess) can suggest the need of an earlier evaluation.

As the first menstrual bleeding is the endpoint of the maturation of genital organs and of various endocrine systems, the failure to undergo menarche could be secondary to:

– Genital malformations as genital tract outflow obstructions or Mullerian Agenesis (or Rokitansky, Kuster, Hauser, Mayer syndrome) described in Chap. 3
– Primary gonadal failure, present in more than 25% of girls with lack of physiological sexual development (see Chap. 4)
– Secondary gonadal failure due to antineoplastic therapy or, rarely, to autoimmune processes
– Deficiency of gonadotropin production, the specific topic of this chapter

Impaired gonadotropin release is linked to a wide variety of underlying conditions leading to delayed or absent puberty (Table 2.1). Recent genetic studies have demonstrated a significant overlap between CDGP and GD and among different forms of HH, so our classification will probably change in the next years.

Considering the relative frequencies of the various etiologies, we estimate that more than 30% of female subjects with DP have a constitutional delay; functional hypogonadisms now account for almost 40% (for the increasing incidence of eating disorders in very young girls). The remaining subjects are affected by other causes.

2.1.1 Hypogonadotropic Hypogonadism

HH includes various congenital deficiencies of GnRH production, not involving other pituitary tropins. In Table 2.2, the well-defined syndromes in female subjects are summarized.

The Kallmann syndrome (KS) is the association of isolated hypogonadotropic hypogonadism (HH) and reduced or absent smell sense: the association provides evidence that the dysfunction of GnRH neurons activity is related to their impaired migration during intrauterine life from olfactory area to hypothalamus. The prevalence of Kallmann syndrome is rare (1:50,000 in females) and related to mutations

Table 2.1 Pathogenesis of hypogonadism

Hypogonadotropic hypogonadism (HH)	Kallmann syndrome
	Isolated gonadotropin deficiency
	Charge syndrome
	Leptin deficiency
Organic CNS pathologies	Congenital hypopituitarism (complete or partial)
	Congenital hypogonadotropic hypogonadism
	Midline cerebral and cranial malformations
	Empty sella syndrome
	Iron overload secondary to hemoglobinopathies, aplastic anemias, juvenile hereditary hemochromatosis
	Sarcoidosis, granulomatous infections (tuberculosis), Langerhans cell histiocytosis
	Autoimmune hypophysitis
	Rathke's pouch cysts
	Arachnoid, dermoid, or epidermoid cysts
	Obstructive hydrocephalus
	CNS tumors
	Repercussions of trauma, surgery, vasculopathies
	Long-term effects of antineoplastic treatments
Hyperprolactinemia	Prolactinoma or other pituitary adenomas
	Pituitary stalk lesions
	Drugs affecting prolactin secretion
Gh deficiency (GD)	Isolated
	Syndromic (Noonan syndrome, Prader–Willi syndrome)
Constitutional delay of growth and puberty (CDGP)	
Functional hypogonadotropic hypogonadisms (FHH)	Eating disorders
	Strenuous physical activity
	Coeliac disease (CD)
	Chronic diseases
	Endocrinopathies (Cushing syndrome, 21α hydroxylase deficiency, hypothyroidism)
	Long-term corticosteroid treatment
	Endocrine disrupters

Table 2.2 Hypogonadotropic hypogonadism

	Associated defects	Known involved genes
Kallmann syndrome	Hypo-anosmia; infrequently cleft palate, synkinesis, unilateral kidney agenesis, hearing defects	ANOS1, FGFR1, FGF8, PROK2, PROKR2, WDR11, CHD7, NELF, HS6ST1, SOX10, SEMA3A, FEZf1
Isolated hypogonadism		GnRHR, GnRH1, FSHb, FGFR1, GPR54/KISS1R, KISS1, TAC3/TACR3, NR5A1, PIN1, NNKB, NKR3 (FGFR1, FGF8, PROKR2, CHD7, WDR11)
Charge syndrome	Coloboma, cardiac malformations, atresia choanae, external genital hypoplasia, ear anomalies, growth anomalies	CHD7
Leptin deficiency	Obesity, immunological deficiency	LEP, LEPR

of different genes; it is mainly sporadic; sometimes familiar transmissions X linked or autosomic recessive or autosomic dominant have been documented. Consequently, the phenotype is also variable concerning olfactory ability, secondary sex characteristics development and associated defects. The possibility of a late recovery of hypogonadism has been described in few cases [1].

For the diagnostic workup, it should be kept in mind that the self-evaluation of smell is generally unreliable except in subjects who admit anosmia; so it should be investigated with a selection of essential oils or scented papers or with specific standard kits. In KS the growth is linear, without spurts, exceeding the average for chronological age and inappropriate for bone age, with a prevalent increase of arms and legs, because the physiological pubertal shift between legs and trunk increase doesn't take place.

Isolated hypogonadism includes various diseases with different stages of pubertal delay without other functional (even if small impairment in olfactory ability is sometimes present) or somatic defects and with normal brain imaging. The underlying genetic mutations are various and overlapping with alterations in genes involved also in KS [2].

The CHARGE syndrome (Coloboma, Heart defects, Choanal atresia, Retarded growth and development, Genital abnormalities, Ear anomalies) is a rare association, mainly sporadic of several anomalies related in more than 60% of cases to CHD7 gene mutation. The hypogonadism may result from the same migration defects of KD and is associated with growth, coloboma of iris and sometimes of retina, choanal atresia, internal and external ear abnormalities, and heart malformations. Cranial nerve defects with problems with breathing and feeding, orofacial clefts, defective sense of smell, vestibular abnormalities, hearing loss, and genital hypoplasia are also common.

The association between hypogonadotropic hypogonadism and leptin deficiency or leptin receptor anomalies entails, in typical forms, obesity and a higher prevalence of infections for an associated T cell functional anomaly; actually leptin mutations have been described even in subjects mildly overweight or normal and with normal immunologic defenses.

2.1.2 Organic CNS Pathologies

Gonadotropin deficiency can be present in congenital diseases involving the production of other pituitary hormones, linked to mutations of genes encoding transcription factors involved in the ontogenesis of pituitary gland or of hypothalamus-pituitary axis. The diagnosis is usually made during infancy and a definite cytogenetic testing is very important in order to plan the follow-up needed to prevent clinical outcomes related to late onset deficiencies [3]. Rare congenital midline cerebral and cranial malformations, i.e., septo-optic dysplasia or absence of septum pellucidum with optic hypoplasia, are associated with endocrine pituitary dysfunction. More frequent is the empty sella syndrome, characterized by cerebrospinal fluid filling the sella; as a result, the pituitary gland is often compressed and

flattened. Empty sella may occur as a primary disorder because of an herniation of the arachnoid through a defect in the diaphragma sellae or as a secondary disorder due to damage to the pituitary itself, for instance as long-term consequence of surgery, radiation therapy, or of autoimmune hypophysitis. In most cases empty sella is asymptomatic; in adolescents could be associated with endocrine abnormalities: Gh and gonadotropin deficiency or hyperprolactinemia.

The pituitary gland is characterized by a very high blood flow (0.8 mL/g/min) and therefore is very exposed to overload phenomena especially iron overload. A pituitary injury may arise, in spite of the progress of chelation therapy, as a consequence of iron deposition in reticuloendothelial cells in subjects with hemoglobinopathies (thalassemia, hemolytic or aplastic anemias), who need transfusion therapy (transfusional hemosiderosis). The iron overload increases gradually reducing the pituitary volume and function; chronic hypoxia and ineffective erythropoiesis contribute to the endocrine impairment often involving also the growth hormone production. A significant iron overload in pubertal age is rare in subjects affected by hereditary idiopathic hemochromatosis [4]: in this disease, the deposition is mainly at parenchymal level but very slow and endocrine repercussions appear in older age. The history of relatives affected by the disease, the tiredness, the elevation of liver enzymes and ferritin, and the transferrin saturation of more than 45% address to a more detailed study including genotype.

Neurosarcoidosis and Langerhans cell histiocytosis are uncommon in adolescence; pituitary tuberculous infiltration has been described in adolescents living in other countries. Autoimmune hypophysitis is an inflammation of the pituitary gland due to the attack of T lymphocytes against secreting pituitary cells, sometimes secondary to systemic diseases, infections, or immunomodulating treatments. It occurs more commonly during and shortly after pregnancy, but it is described also in adolescence. Autoimmune damage of the pituitary gland results in the deficiency of various tropins and often diabetes insipidus. Autoantibodies against pituitary (APA), sometimes against hypothalamus (AHA) and thyroid gland, can be detectable. Specific mutation of CTLA-4 gene can predispose to this disease.

The Rathke's pouch is embryologically an ectodermic evagination at the roof of the developing mouth that gives rise to the anterior pituitary; its posterior wall remains as intermediate lobe of the gland. Fluid-filled cysts can arise from the expansion of remnants of this formation. They are generally asymptomatic, but sometimes exert compression on adjacent pituitary tissue and distortion of the pituitary stalk. Arachnoid cysts are probably derived by congenital splitting of the arachnoid layer with accumulation of CSF within this potential space and usually located in the middle cranial fossa. The majority of arachnoid cysts are asymptomatic, but sometimes their gradual enlargement produces a mass effect resulting in either direct neurological or endocrine dysfunction or distortion of normal CSF pathways.

A chronic obstructive hydrocephalus may be derived from a congenital stenosis at or below the level of the aqueduct of Sylvius, connecting the third to fourth ventricle (often on genetic basis), or from compression gradually exerted by a colloid or an arachnoid cyst on the third ventricle located on the diencephalon of the

forebrain between the right and left thalamus. It may cause a distension of the periventricular or medial basal hypothalamus disrupting the physiological release of GnRH; sometimes hypothyroidism and anomalies of Gh secretion are associated. In congenital aqueduct stenosis, the presence of symptoms of increased intracranial pressure (headache, nausea, vomiting, papilledema) is very rare and the situation is mainly asymptomatic.

Considering the tumors affecting the hypothalamic-pituitary region, craniopharyngioma is a dysontogenic lesion arising, near the pituitary stalk, from the epithelial nests of craniopharyngeal duct or of Rathke's pouch. The prevalence is about 1:50,000 subjects. It is a capsulated tumor, with slow evolution but with a tendency to invade surrounding structures and to recur after resection. At the beginning of its growth symptoms are uncommon, so the diagnosis is often delayed when the pressure on the optic tract or on the pituitary gland causes impaired vision, growth and pubertal delay, obesity, insipid diabetes or when an intracranial hypertension has been established. Vomiting in the morning and pathological rate of growth are generally the early manifestations of the disease [5]. Pituicytoma arising from pituitary parenchyma or germinoma and teratoma growing from germ cells inclusions can also involve the sella region as well as neoplastic lesions coming from adjacent structures.

Traumatic brain injuries can lead to acute endocrine changes but also both temporary and permanent alterations of pituitary function in the long term: the most common are Gh deficiency and alterations of puberty. We estimate that 3 months after the trauma about 35% of children and adolescents display pituitary secretion abnormalities and 30% after 12 months. A spontaneous recovery is possible, but permanent deficiencies have been documented [6]. A deficiency in gonadotropin secretion can be the long-term effect of treatments (mainly radiation) of leukemia and brain tumors even if therapeutic procedures with less impact on endocrine function are increasingly under study.

2.1.3 Hyperprolactinemia

An hyperprolactinemia is infrequently a cause of delayed puberty. A prolactin excess can be related to a PRL secreting (or Gh secreting) adenoma or to other intracranial pathologies (chordoma or other neoplasia) causing a pituitary stalk interruption or dislocation (pseudo-prolactinoma). The compression on the stalk may impair the function of TIDA (TuberoInfundibular DopAmine) neurons that physiologically inhibit the secretory activity of PRL cells. An hyperprolactinemia can also be associated to hormone deficiencies secondary to pathologies damaging the hypothalamus-pituitary region, as already mentioned. A prolactin excess related to primary hypothyroidism, linked to TSH secreting cells hyperplasia, has also been described. Increased prolactin concentrations as a consequence of drug intake, especially psychiatric drugs (Table 2.3), are more frequent; so a pharmacological anamnesis is always mandatory.

Table 2.3 Hyperprolactinemic drugs

Antipsychotic	Haloperidol, Chlorpromazine, Thioridazine, Thiothixene	
	Risperidone, Paliperidone, Sulpiride, Amisulpride, Molindone, Zotepine (Olanzapine, Clozapine)	
Antidepressants	Tricyclic	Amitriptylin, Desipramine, Clomipramine, Amoxapine
	SSRI	Sertraline, Fluoxetine, Paroxetine
Prokinetics		Metoclopramide, Domperidone
Opiates		Morphine
H_2 antagonists		Cimetidine, Ranitidine
Others		Physostigmine, antineoplastic drugs

In subjects with prolactinoma, the history and the symptomatology can be insignificant: the linear growth is generally normal, neurological symptoms mostly absent, and galactorrhea is rare in this age group.

2.1.4 Gh Deficiency

Isolated Gh deficiency (IGD) can be acquired (as result of trauma, infection, radiation therapy, or tumor growth), or congenital on genetic basis: the genes coding for Gh (Gh1), its receptor (GhRHR) and Ghrelin receptor (GhSR) are the most commonly involved; less often mutations of transcription factors active in pituitary development are involved. However, known mutations explain only a small percentage of clinical cases (several GD are diagnosed as idiopathic); moreover, genotype–phenotype correlation is not univocal and is variable over time. Subjects with GD may present with insufficient growth velocity and delayed growth spurt, considering their chronological age. Slow tooth eruption and poor nail growth can be present in the history. In subjects with previous diagnosis of IGD and under treatment the pubertal timing is generally normal.

Noonan syndrome is a heterogeneous genetic disorder, typically evident at birth, characterized by a wide spectrum of physical features: abnormalities of head and face, skeletal and vascular malformations, heart defects, delay of growth and puberty. The incidence is 1:1500 subjects. The Prader–Willi syndrome is a genetic disorder affecting 1:30,000 births due to the missed expression of genes imprinted on the chromosome 15. The girls affected display growth and sexual development delay and obesity secondary to hyperphagia. The hypogonadism can be related to a central defect with late menarche (about 20 years); a primary gonadal defect can also be present.

2.1.5 Constitutional Delay of Growth and Puberty

In more than 60% of cases a familiarity can be demonstrated, with an autosomic dominant transmission. Genetic studies highlighted mutations of GnRH Receptor, GhSR, an endogenous Ghrelin ligand, of genes involved also in IGD, and of genes significant in the pathogenesis of HH. Subjects affected by CDGP have an overall delay in the appearance of sex characteristics, the growth spurt, and the development of internal genitalia of, on average, 2 years and a half, with normal nutritional status. The time span between the thelarche and the beginning of growth spurt is generally reduced; but height velocity is lower than in normal subjects. The current height is in agreement with bone age more than with chronological age.

2.1.6 Functional or Secondary Hypogonadotropic Hypogonadism

Eating disorders are becoming more frequent in preadolescent, considering the trend to a precocious onset of these unhealthy behaviors. Restrictive food intake or selective eating can induce an energy deficiency impairing the normal timing of GnRH neurons activation. Dissatisfaction with their own look and concern about weight can be evident or not. Sometimes, a history of eating disturbances in infancy or of precocious traumatic events is present. Psychopathological traits (anxiety or depression) in the relatives are frequent. A reduced nutritional intake induces a decrease of linear growth and a slowing of pubertal maturation, evident at breast level. Considering body composition a reduced fat deposition and a slow bone mass apposition occur, with a slight increment in fracture risk. The symptoms are related to the mechanisms of adjustment to reduced energy intake (see Chap. 8) and are directly related to the seriousness of the clinical situation. The young athletes undertaking strenuous training programs in peripubertal age may undergo to a period of reduced energy availability for the needs of anabolic processes related to pubertal development, with resulting repercussion on hypothalamus-pituitary-ovarian axis activation. This effect is particularly evident if restrictive eating is associated, sometimes following the esthetic appeal required for certain physical activities, as in gymnasts, dancers, skaters, and wrestlers. From a clinical point of view the prepubertal phase is prolonged, as well as the first stages of puberty development, the growth potential is attenuated, and the relative proportions of lean and fat body mass are modified.

Undiagnosed or untreated coeliac disease (CD) is often associated with pubertal maturation delay and sometimes with growth impairment considering the genetic target. The pathogenesis is multifactorial: in addition to nutrients deficiency and body composition alterations, the involvement of autoimmune processes is now under study. The estimated prevalence of this condition is 1% of population. The hallmark of CD is an immune-mediated enteropathy elicited by gluten in genetic susceptible individuals, but gastrointestinal symptoms can be absent; sideropenic

Table 2.4 Chronic diseases associated with pubertal delay

Chronic liver diseases, alpha1-antitrypsin deficiency, congenital biliary tract atresia
Congenital heart malformations
Chronic inflammatory bowel diseases
Cystic fibrosis
Epilepsy, cerebral palsy
Hemoglobinopathies (thalassemia, sickle cell disease), Fanconi anemia
HIV infection
Insulin-dependent diabetes
Nephrotic syndrome, renal insufficiency
Juvenile idiopathic arthritis
Juvenile LES
Severe chronic asthma

anemia, raised liver enzymes, and autoimmune thyroiditis may be found. The research and the identification of CD in adolescents with faltering growth and delayed puberty are supported by evidence criteria [7].

We estimate that a chronic disease (Table 2.4) affects more than 10% of young people: in a majority of cases the energy deficiency, the metabolic impairment, the changes in body composition, the chronic hypoxia, the opportunistic infections, sometimes the treatments impact on pubertal development slowing it down and delaying menarche. The level of involvement depends on the type of disease, the age of onset, its duration and severity, and on the individual response to therapy [8]. Considering 25% begins under 18 years of age: Crohn disease especially is associated with growth and puberty delay. In adolescents suffering from insulin-dependent diabetes and following intensive insulin therapy in agreement with current guidelines, the improved glycemic entails minimal impact on timing of menarche.

Undiagnosed or untreated endocrine diseases can condition pubertal maturation:

- Hypothyroidism implicates reduced linear growth with higher trunk development related to legs and delay in facial bones modifications.
- Cushing syndrome is very rare in prepuberty and can induce growth delay, trend to overweight, skin signs of hypercortisolism (striae, acne, hair growth excess); an episodic cortisol hypersecretion has been described, more difficult to identify.
- The glucocorticoid treatment of congenital adrenal hyperplasia can have an impact on growth and pubertal maturation.

Similar effects can be evident in subjects under extended treatment with glucocorticoids for juvenile LES, idiopathic arthritis, and asthma.

Finally, a mention of the possibility of exposure to endocrine disrupters: lead, dioxins, and polychlorinated dibenzodioxins have been pointed out as possible causes of pubertal delay [9].

2.2 Diagnostic Workup

The diagnostic evaluation of a patient with pubertal delay is easier if history taking, physical examination, and laboratory tests are performed bearing in mind the possible pathogenic spectrum, in order to orient the tests required. So the diagnostic workup here proposed is illustrative and does not include an in-depth analysis of all the diseases underlying a secondary functional hypogonadism. Moreover, few differential diagnoses usually require a follow-up. In Table 2.5, the first-level diagnostic approach is synthetized.

Sitting height reflects the proportion of girl's height that is attributed to the head and the trunk, in relation to legs and is a useful measurement to detect conditions that affect growth in a disproportional manner. In HH, legs growth is typically reduced (and SH/TH ratio is less than 50%) while in growth hormone or thyroid hormones deficiencies it is reduced and SH/TH ratio results increased.

Pelvic ultrasonography, in addition to excluding uterovaginal malformations, offers a first evaluation of ovarian echostructure and biological appraisal of estrogenization. The study of uterine length and/or volume and the ratio of anteroposterior diameters of corpus and cervix are well-known criteria of staging of pubertal maturation. In many cases of functional hypogonadism, pelvic US shows a uterus of normal morphology but reduced volume and ovaries with microfollicles similar to physiological prepubertal period. Pelvic US is also an easy method of follow-up if a CDGP or secondary hypogonadism is suspected.

The bone age, evaluated on a single X-ray of left hand and wrist, is a measure related to pubertal maturation more than to chronological age; for this reason in the majority of conditions linked to pubertal delay it results also delayed [10]. In subjects with CDGP and GD bone age is usually coherent with the mean age corresponding to current height; this coherence is not present in girls suffering from HH who display delayed bone age and increased linear growth considering chronological age. In chronic diseases, bone age is delayed but in agreement with Tanner stage and internal genitalia US development. In functional hypogonadotropic hypogonadism, secondary to energy deficiency, the deviation between bone and chronological age is probably the most significant.

Table 2.5 First-level diagnostic approach

Clinical history	Familiar: pubertal delay, shortness, autoimmune diseases
	Personal: onset of pubertal signs, physical activity, eating habits, headache, visual impairment, gastrointestinal problems, pelvic pain known pathologies, previous or current drugs used, surgery, head trauma
Physical exam	BMI, Tanner stages, eventual dysmorphisms, smelling ability, external genitalia inspection, neurological signs, eventually fundus examination
Auxology	Weight (W), height (H), sitting height (SH) and SH/TH ratio, growth chart, target height (TH)
Imaging	Pelvic US scan, bone age
Laboratory	FSH, LH, PRL, TSH, FT_4, IGF-1 if growth impairment or suspected low energy availability
	Blood tests suggested by history and physical exam

Concerning endocrine evaluation, the increase in FSH level is diagnostic of gonadal failure (see Chap. 4); in central deficiency gonadotropin concentrations, especially of LH, are in the lower range, but current assays are not so accurate in the lower detection limits. So a basal plasma determination is generally unable to differentiate between organic deficiency, constitutional delay, and functional impairment. PRL sampling should be performed in the morning but not just after the awakening, in order to avoid misleading increases related to the circadian rhythm of the hormone [11]. It is advised to repeat the assay in case of high levels, together with thyroid hormones and IGF-1 to exclude the involvement of other tropins. If it is available, Polyethylene Glycol (PEG) precipitation should be tested in order to screen the presence of macroprolactinemia, large molecular masses of PRL together with IgG and anti-PRL autoantibodies, with poor biological activity. This phenomenon is however rare in young ages. The 17β estradiol dosage is generally not so significant because it is usually performed with methodology with poor sensitivity in the lower range: the use of integrated measurement (i.e., early morning urinary determination) and of different methodology (liquid chromatography and gas spectrometry) could add more information. The usefulness of follicular activity markers (AMH, Inhibin B) is under study: interesting preliminary data about basal inhibin level with a cutoff 20 pg/mL have been published [12].

Serum levels of Insulin growth factor-1 (IGF-1) in adolescent girls are physiologically related to pubertal stage more than to age, with a peak in late puberty [13]. Very low concentrations (less than two SD for age range) are a marker of congenital or acquired Gh deficiency (as in thalassemia major); in constitutional delay of growth and puberty (CDGP), IGF-1 levels are in agreement with growth and Tanner stage, more than with chronological age. In situation of energy deficiency, such as restrictive eating, an acquired growth hormone resistance with low IGF-1 levels is present. As already mentioned, in subjects with hyperprolactinemia, not related to pharmacological treatment, IGF-1 levels should be investigated in order to identify mixed Gh and PRL secreting adenoma.

Blood tests should include serum creatinine to exclude kidney disease before programming a brain RMI with gadolinium-containing contrast medium and the anti-tissue transglutaminase (tTg) together with the dosage of IgA (to exclude misleading results related to IgA deficiency). IgA endomysial antibodies (EMA) should be required if IgA tTG is weakly positive and the use of IgG EMA, IgG deamidated gliadin peptide (DGP), or IgG tTG should be considered if IgA are deficient.

In a second-level diagnostic workup, we include further tests:

1. To confirm the hypothesis of functional hypogonadism:

   Body impedance analysis (BIA) or total body Dual X Ray absorptiometry (DXA) to assess body composition: a significant reduction in fat mass as a percentage of body weight puts in evidence subject with BMI not so far from the normal range, but with energy deficiency. This evaluation is also useful to estimate the metabolic homeostasis in subjects with chronic diseases. It is mandatory to remind that we do not have standard references values for BIA in peri-pubertal years, even if it has been demonstrated that fat mass increases in

the 6 months before menarche, reaching a plateau after around 1 year [14]. We estimate as 18% of weight the fat mass necessary for the onset of menstrual function, considering that BIA underestimate fat measurement, in comparison to DXA. The use of total body DXA is accurate, but expensive and minimally radiant, so it find an indication when also an evaluation of bone mass deficiency is necessary.

Hormonal markers of reduced energy availability as FT3, insulin, cortisol and leptin (see Chap. 8)

Nutritional tests: folate, zinc, albumin, pre-albumin, transferrin, retinol-binding globulin;

2. To study the possibility of hypothalamus-pituitary organic disease:

   Magnetic Resonance Imaging (MRI) of brain and head with contrast medium (gadolinium) should be performed if headache or neurological sings are present, Kallmann or Charge syndrome are suspected, hyperprolactinemia has been found, a Gh or other tropins deficiency are supposed, the clinical history orients to iron overload and when hypogonadotropic hypogonadism without known etiology is present. The exam can put in evidence the olfactory tract and bulbs hypoplasia (Kallmann and Charge syndrome, septo-optic dysplasia), the presence of obstructive hydrocephalus, pituitary adenoma, empty sella, tumors compressing the stalk or the hypothalamic region, pituitary infiltrates or autoimmune hypophysitis (even if the differential diagnosis with pituitary adenoma is not easy from a radiological point of view);
3. To evaluate the hypothesis of Gh deficiency:

   Gh provocation tests (Insulin tolerance test of GhRH + arginine test);
4. To confirm the option of autoimmune hypophysitis:

   APA, AHA, TPO Ab, TSHR Ab should be tested;
5. To differentiate HH with normal MRI from CDGP

   GnRH test is largely used but the response in the two conditions show great overlap. The choice of GnRH analogue test seems to be diagnostic, but the published data are poor and the cut-off not univocal (LH/FSH ratio increase of 0.7, after 2 or 3 h has been proposed as a confirmation of the possible activation of hypothalamus-pituitary axis). It is useful also to evaluate estradiol production 24 h after the release injection [15]. The response to exogenous kisspeptin as diagnostic test is under study;
6. Genetic testing is useful in hypogonadotropic hypogonadisms, in syndromic diseases or in presence of additional phenotypic features, for diagnosis, prognosis and genetic counselling to siblings.

2.3 Therapeutic Approaches

When a diagnosis of hypogonadotropic hypogonadism has been defined, a puberty induction should start, to promote secondary sex characteristics, internal genitalia growth and function. Current guidelines [16] advise the use of preferably transdermal estradiol starting with low-dose formulations, in order to mimic physiological

puberty [17]. If the diagnosis is evident at about 10 years of age it is possible to start with 0.05–0.07 μg/kg nocturnally, obtained cutting 25 μg/kg patches and advising the use of occlusive dressing if the patch tends to detach. If the girl is older, as usual, the starting dose can be 0.08–0.12 μg/kg (at the beginning only during the night and then with normal change of the patch twice a week) to promote breast development. The dose is slowly increased every 9–12 months. As an alternative percutaneous or oral estradiol can be chosen, using prepared pharmaceutical formulations with equivalent dosages. The progesterone (100 mg per os) or dihydrogesterone, a progestin similar to progesterone from a metabolic point of view, (10 mg per os) should be added for 12 days after at least 2 years of estrogen treatment, when spotting is present or US endometrial thickness well documented (usually with an estradiol dosage of 25 μg/kg/day). In girls with panhypopituitarism deydroepiandrosterone, starting with 15 mg/day, should be added to promote pubarche. After the first menstrual bleeding, the treatment must convert to a hormone replacement therapy, increasing the transdermic estradiol dosage to at least 75 μg and redoubling the dose of progesterone or progestin. Oral therapy with 2 mg of estradiol or with combined natural estrogens and progestin is another option. A serum estradiol assay could be used to check if hormonal concentrations are in the normal range for age. It is also important to remind that in the future fertility will be possible using gonadotropins or GnRH therapy.

In the rare cases of leptin deficiency a treatment with human recombinant leptin may be proposed, starting with low dosages (0.04 mg/kg/day) given by subcutaneous injection at 6 p.m., adjusting the dose in order to achieve circulating level of the hormone in the normal range for age and BMI.

In organic pathology of CNS the definition of the clinical situation and of the best strategy of therapy require a strict cooperation with the neuroradiologist and the neurosurgeon. An operation, to be performed in specialized units, is usually indicated in cases of obstructive hydrocephalus, compressive pathologies, expansive tumors. The use of intraoperative MRI can be a support. Considering the craniopharyngioma, if the neoplasia does not invade the hypothalamus, the treatment of choice is the complete excision of the tumor; if hypothalamic involvement is present, the treatment consists in subtotal resection associated with postoperative radiotherapy. The overall 5 years survival rate is 80%, even if it is associated with marked morbidity (hypothalamic dysfunction, modifications of the neuropsychological profile). The treatment of autoimmune hypophysitis is medical and mostly using corticosteroids, sometimes in association with azathioprin. In all the situations of persistent gonadotropin damage an endocrine therapy of pubertal induction and replacement is indicate, eventually associated with substitution of other inadequate tropins.

In subjects with hyperprolactinemia related to microadenoma or stalk anomalies not secondary to expansive pathology, a treatment with dopamine agonist (cabergoline, bromocriptine) can be started, in order to consent a normal pubertal development, the attainment of bone mass peak and, frequently the reduction in the dimensions of the tumor. To reduce possible side effects (nausea, orthostatic hypotension) the bromocriptine should be started with a dose not more than 1.25 mg

daily and eventually increased; and the cabergoline with initial dose of 0.25 mg once a week, then twice a week, checking prolactin levels. Only in prolonged treatments with high dosages, it is advisable to program an echocardiographic control for the rare possibility of cardiac valve alterations. Only in selected situations or when the response to dopamine agonists is lacking a neurosurgical intervention can be indicated. Concerning psychotropic drug-induced hyperprolactinemia, it is useful to discuss with the psychiatrist taking care of the girl the possible options. The choice is among the use of an alternative drug less active on dopamine receptor (as aripiprazole as substitution or added at low doses) [18], the addition of dopamine agonist to the treatment (not always effective and sometimes with the risk of worsening the psychotic symptoms) or the possibility of starting a hormone therapy to induce puberty and maintain menstrual function.

Gh deficiency requires a specific replacement treatment, able to promote growth and pubertal progression.

The management of constitutional delay of growth and puberty is essentially a follow-up supported by explanation and reassurance about its spontaneous evolution. In selected situations, the use of a short cycle of estrogen therapy has been proposed, using a dosage related to the degree of development of secondary sex characteristics (for instance 12.5–25 μg transdermal estradiol daily). This option, above all justified by the psychological repercussions in the comparison with peers, induces an acceleration in breast and genitals development and in linear growth, combined with the spontaneous pubertal progression. The treatment does not influence final height, which results anyway slightly reduced in these subjects with regard to their genetic target [19].

In functional hypogonadisms the therapeutic goal is usually to improve the general health, suggesting for girls with eating disorders a psychological counselling and an adequate nutritional support, for athletes a nutritional counselling and sometimes the reduction of intensity of training.

In coeliac disease, a gluten free diet is generally sufficient to promote a spontaneous pubertal development. In several chronic diseases, the pathogenesis of pubertal delay is multifactorial: so it is important an in-depth evaluation of energetic and metabolic homeostasis and, sometimes, of the therapeutic regimen. The treatment plan should be evaluated also in adolescents with pubertal delay suffering from endocrine dysfunctions; particularly in subjects with 21-hydroxylase deficiency under treatment with hydroxycortisone, because pubertal endocrine milieu modifies the metabolic clearance of cortisol but from the other side the linear growth is extremely sensitive to a glucocorticoid excess. A reduction of dosages could sometimes be required to allow an adequate growth and sexual development [20].

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