Dealing with transition in young patients with pituitary disorders

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Abstract

Introduction: The transition age is the period between childhood to adulthood; it refers to a broad set of physical, cognitive and sociocultural modifications, arbitrarily defined as starting in late puberty and ending with full adult maturation. Pituitary disorders in adolescence represent a challenge that requires careful management during the transition to adult care.

Methods: Given the complexity of care of pituitary disorders in the transition age, we have reviewed the relevant medical literature focusing on aetiology, clinical manifestations, treatment strategies of GH deficiency (GHD), hypogonadotrophic hypogonadism (HH) in male and female adolescents, central hypothyroidism (CH), central adrenal insufficiency (CAI) and cranial diabetes insipidus (CDI) at this time. The objective of the present review is to provide an up-to-date evaluation of the transition period to evaluate the specific needs of adolescents with chronic pituitary disease in order to optimise their management.

Results: We provide an overview of current clinical management of GHD, HH, CH, CAI and CDI in the transition age.

Conclusions: Specific changes occur in pituitary function during the transition period. A holistic approach including discussion of patients’ concerns and emotional support should constitute a key component of managing pituitary disorders in adolescence. Special transition clinics where paediatric and adult endocrinologists work together, should be increasingly created and strengthened to bridge care, to promote continuity and adherence to treatment and to limit potential negative development, metabolic, skeletal and cardiovascular sequelae of discontinuity of care among adolescents with pituitary disorders.

Context

The transition age is defined as the transitional phase between the end of puberty until peak bone mass, involving a wide range of physical, psychological and sociocultural changes. It therefore covers the time from early adolescence until young adulthood. The beginning of transition may be seen as the period when patients reach Tanner stage 5, usually occurring at a mean age of 14.7 ± 2.2 years in boys or 14.0 ± 2.4 years in girls (1). The end of transition usually corresponds to the achievement of peak bone mass, corresponding to a mean of 23.1 years in males and 19.9 years in females.

The transition period represents a very complex time, because as adolescents may complete their secondary education, they usually change their routine habits and leave close parental supervision of their medical care. They may start an occupation away from home, may spend more time staying with friends or indeed may move to college or university in a distant city. As they may
now need to regulate their own medication, compliance may be variable or even non-existent in some cases. This particular moment in the life cycle will need careful assessment and sympathetic handling by the clinician.

Pituitary disorders present specific challenges in the transition age which need careful attention in order to provide adolescents with a satisfactory and developmentally appropriate transition to adulthood.

The aim of the present review is to provide an up-to-date evaluation of the transition period and to evaluate the specific needs of young subjects with chronic pituitary diseases including GHD, hypogonadotrophic hypogonadism (HH) in both sexes, CH, CAI and CDI, focusing on disease care in order to personalise the approach and the management to the specific needs of patients in this delicate period of life.

**Growth hormone deficiency in the transition age**

**Introduction**

Growth hormone deficiency (GHD) is a rare disorder with a prevalence of approximately 1 in 4000 during childhood (2). The diagnosis is complex and is currently based on an assessment of auxology, biochemical tests and neuroradiological studies. While relatively uncommon, GHD is an important diagnosis to make correctly considering that therapy with recombinant human growth hormone (GH) is extremely efficacious such that growth alterations can be associated with malnutrition, chronic diseases, endocrine disturbances or psychosocial deprivation (4). Early recognition, prompt diagnosis and initiation of GH treatment of children with growth failure or short stature should enable optimal height outcomes and an improved quality of life (QoL) (4). However, the use of GH replacement during transition is a more complex and variable matter.

**Physiologic actions of GH**

GH treatment is primarily to promote growth, but it also has important metabolic effects. Adequate GH replacement therapy induces a rapid loss of fat due to stimulation of lipolysis and antagonism of the lipogenic actions of insulin, contributing to a lower incidence of cardiovascular disease in later life; it also leads to skeletal IGF-1 synthesis, hypertrophy of osteoblasts and proliferation of pre-chondrocytes, showing positive effects on bone remodelling and mineralisation (5, 6) (Fig. 1).

**GHD in the transition age**

During the transition period from childhood to adulthood, statural growth can be complete but somatic development still progresses and peak bone mass continues to change (7). Discontinuation of GH treatment in the transition age has been associated with abnormal body composition, predominantly an increase in fat mass (8) and in different markers of cardiovascular risk, including total and LDL cholesterol levels. Moreover in adolescent patients with severe GHD, discontinuation of GH at completion of linear growth may limit the attainment of peak bone mass, predisposing to clinically significant alterations of bone density in later adult life and increasing morbidity. Indeed, the development of osteoporosis and the consequent risk of fragility fracture is in part associated with the peak bone mass achieved in adolescence (9). Furthermore, a negative effect of GH discontinuation during the transition period on QoL, psychological complaints and depression has been reported (10).

Instead, numerous studies have shown that continuing GH treatment in patients after completion of linear growth led to greater increases in bone mineral density, lean body mass a better QoL and improvements in anxiety compared to patients who had equally severe GHD but who received no GH replacement (11). Consequently, and following current guidelines, patients with GHD should continue GH replacement therapy during the
transition years with the goal of achieving full skeletal maturation and a better metabolic profile (12). However, there is nevertheless the problem of establishing whether the state of GHD, diagnosed in childhood, still persists. Furthermore, while there is undoubted evidence in favour of GH continuation from a purely metabolic point of view, the adolescent may see the cessation of growth as a means to escape the necessity of daily injections and its impact on their self-esteem and social status; in other words, from the patient’s consideration, they may prefer the ‘de-medicalisation’ of their position. In the future, the introduction of once-weekly injections of long-acting GH may help in this respect.

**GH treatment in GHD: who and when to retest**

Treatment with GH should be reserved for patients who show permanent GHD. Previous studies have shown that between 25 and 100% of children with ‘idiopathic GHD’ demonstrated normalisation of GH secretion when retested at the end of puberty or after adult height achievement (13). Appropriate reassessment of childhood-onset GHD is therefore mandatory for such selected patients who may need long-term GH treatment. It is therefore recommended that patients with childhood-onset GHD be retested to confirm the diagnosis of GHD when statural growth is completed (growth velocity <1.5–2 cm/year). Current guidelines suggest that retesting is not required for patients with more than two pituitary hormonal deficiencies, a demonstrated transcription factor mutation, or isolated GHD associated with an identified mutation and or specific pituitary/hypothalamic structural defect except for an ectopic posterior pituitary (7, 14). This translates to an indication for re-evaluation of the somatotrophic axis in patients with GHD and deficiency of only one additional pituitary hormone, idiopathic isolated GHD with or without a small pituitary/ectopic posterior pituitary and in patients...
after irradiation. The re-evaluation should be performed after a trial of at least 1 month off GH treatment. It should also be noted that the thresholds for insufficiency differ between the various dynamic tests and such cut-offs need to be critically appraised.

An optimal GH stimulation test has not yet been identified for the transition age. Nevertheless, the insulin tolerance test (ITT), glucagon and arginine used alone or with GHRH have been used to confirm/reconfirm GHD in the adolescence (12).

A cut-off of GH peak <5 µg/L has been used by many authors for the gold standard ITT test (12), while according to others the best GH cut-off value is 6.1 µg/L (15); other studies showed a GH cut-off value of 5.6 µg/L as the most accurate (16). If the ITT is contraindicated (for example, individuals with seizure disorder), the glucagon test is the most appropriate alternative test with the cut-off peak GH of <3 µg/L (12). However, the normative values for glucagon stimulation are poorly defined for this age group, and in our opinion, the ITT should be used whenever possible. The arginine alone test is not widely used, its cut-point being <0.4 ng/mL (17). The GHRH/arginine test is not recommended with idiopathic GHD because it may result in a false-normal response. However, if used the cut-off values for this test are a peak GH <11 µg/L in patients with BMI <25 kg/m²; <8 µg/L if the BMI 25–30 kg/m², <4 with a BMI >30 kg/m². It should be noted that GHRH is not currently available in the United States (12).

**GH dose in GHD in the transition age**

The optimal GH dose during the transition period is not well defined. In some studies, GH doses varying from 12.5 to 25 µg/kg/day (weight-based dose) to 200 µg/day (fixed dose) have been used (18). The Endocrine Society Guidelines suggest that patients <30 years of age may benefit from initial doses of 400–500 µg daily (higher compared to the initial doses of 200–300 µg daily for patients aged 30–60 years) and those transitioning from paediatric to adult replacement therapy may be prescribed even higher doses. However, during the transition period, patients should have their GH dose modified compared to the childhood dose or, if already stopped, it should be restarted between 200–500 µg/day making adjustments on the basis of age- and gender-adjusted serum IGF-I levels, oestrogen status, clinical response and lack of side effects (19).

Girls who are taking oral oestrogen replacement usually need substantially higher doses of GH, as such oestrogens attenuate the effect of GH on the GH receptor, but those on transdermal oestrogen preparations may not (14) (Table 1). Doses subsequently should be titrated to normalise the serum IGF-I concentration for age and gender and individualising treatment according to the specific patient (14) We would tend to raise the IGF-1 to the upper end of the normal range. The Endocrine Society Guidelines recommend that, after documentation of persistent GHD, GH therapy be continued after completion of adult height to obtain full skeletal and muscle maturation during the transition period (4). This would generally translate to the age of 25 years. Thereafter, such patients should be assessed for GH replacement as in other adults.

**Special considerations for GHD treatment and sex hormone replacement**

In GHD adolescents, the timing of the initiation of sex hormone replacement represents a crucial point for the achievement of the best overall final height. Therefore, it is essential to try and mimic the sex steroid hormone levels seen in peers who do not have GHD, to increase the replacement dose according to age, other comorbidities and drugs used and growth potential. Too early initiation of replacement could slightly compromise final height, so a gradual increase in gonadal steroids should adjust the timing of the onset of menarche in girls or virilisation in boys with their peers – treatment needs to be personalised for each patient (20, 21).

**Potential adverse events of GH treatment in GHD**

Treatment with GH has generally been safe. The most common adverse effect is headache, which is usually benign, but there is also a slightly higher risk of developing glucose disorders and insulin resistance, idiopathic intracranial hypertension and increased intraocular pressure (22). Regarding the occurrence of a second neoplasm during GH replacement in childhood cancer survivors, a recent meta-analysis showed that GH therapy does not appear to increase the risk of second tumours (23). Recently, an increased risk of possibly meningiomas in adult life in GH-treated children was shown to relate to radiotherapy rather than GH treatment (24).

**Conclusions**

GH replacement therapy for the treatment of patients with GHD has been used for more than 30 years, demonstrating significant efficacy and a satisfactory safety profile. GH treatment in the adolescent shows significant effects on bone mineral density and metabolism. Retesting
adolescents for GHD at the transition age is required, except for patients with organic or genetic causes of GHD.

In adolescents with GHD, treatment with GH leads to lower body fat, increased lean mass, better bone mineral density and QoL. However, a one-to-one discussion needs to take place with each patient to determine the impact of such treatment on their personal and social lives, and it may be decided to withhold therapy, at least temporarily, if he or she feels the potential benefits are outweighed by other considerations.

### Hypogonadotrophic hypogonadism in the transition age

#### Introduction

Puberty is a unique and extraordinary developmental process that marks the transitional period between childhood and adult life, characterised by the activation of the hypothalamo–pituitary–gonadal (HPG) axis and culminating in sexual maturity and full reproductive capacity. Puberty is a process influenced by genetic and environmental factors, the timing of its onset showing wide variation (25). Gonadal puberty starts in boys as in girls with the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) that stimulates release of the gonadotrophins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) from the pituitary. This hormonal activation causes gonadal maturation and the production of sex steroids, non-steroidal factors and gametes.

Pubertal onset is clinically diagnosed by Tanner stage II breast development in girls and enlargement of the testes (volume >3 mL) in boys (26). The timing of puberty is physiologic if the appearance of these characteristics occurs within two S.D.s from the mean, which means between 8 and 13 years in females and 9 and 14 years in males for European subjects (27).

#### Forms of HH in the transition age

The absence of puberty or partial puberty associated with low serum sex steroids in combination with low or inappropriately normal serum gonadotrophin levels defines the condition of HH in adolescence. A wide range of aetiologies can cause HH, divided into congenital and acquired causes (Table 2).

### Congenital hypogonadotrophic hypogonadism

Congenital hypogonadotrophic hypogonadism (CHH) is characterised by the absence of puberty or partial puberty and infertility. CHH can be associated with anosmia.
or hyposmia, configuring the diagnosis of Kallmann syndrome (28). Other syndromes related to central hypogonadism may also be present.

**HH combined to other pituitary hormone deficiencies**

HH can present as part of a broader pituitary deficiency disorder. Combined pituitary hormone deficiency is defined by the coexistence of two or more pituitary hormonal deficiencies (29).

**Acquired HH**

Intracranial tumours can lead to acquired HH in the transition age. HH can be due to the compression of pituitary tissue or pituitary stalk or secondary to inhibition of GnRH secretion in patients with prolactinomas or Cushing’s disease (30, 31). HH due to prolactinomas are usually treated medically, while surgery is generally first-line treatment for other tumours (32). Moreover, acquired HH can also result from hypothalamo-pituitary infiltrative lesions, an autoimmune process or iatrogenic damage.

**Functional causes**

Functional HH includes different causes that can lead to the inhibition of the HPG axis (Table 2). For example, obesity in adolescence is associated with functional hypogonadotropic hypogonadism affecting the onset, duration and progression of puberty. In this condition, functional hypogonadotropic hypogonadism is considered secondary to excessive aromatisation of testosterone to oestradiol in adipose tissue. The resultant hyperoestrogenaemia suppresses pituitary release of gonadotrophins, leading to further reduction of testosterone levels. Weight loss tends to reverse the disorder and thus restores the timing of puberty (33, 34).

Contrarily, body image becomes very important to many young people at this time; in both girls and boys, food restriction, bulimia and the extreme anorexia nervosa are common problems. This must be borne in mind when considering the responses, or lack of response, to replacement therapy.

**Management of HH in the transition age**

In adolescents, both boys and girls, there are several aims to consider when treating HH: to develop secondary sexual characteristics, normalise growth and induce gonadal maturation for future fertility. In this context psychological aspects should always be carefully considered. Moreover, clinicians dealing with adolescents should consider that a subset of patients diagnosed with idiopathic hypogonadotropic hypogonadism (IHH) may later undergo reversal, resulting in the activation of the HPG axis with normalisation of gametogenesis associated or not with steroidogenesis. Therefore, patients with IHH require lifelong monitoring for such reversal and, if it occurs, monitoring for eventual relapse that may also occur (35).

**Psychological health**

Young adolescents with HH usually show high levels of anxiety and depressive symptoms compared with their peers, and these psychosocial symptoms can significantly alter their QoL (36). Therefore, initiating treatment for the development of secondary sexual characteristics at an appropriate age is essential in order to have maximal beneficial effects on psychosocial problems and social life. Patient acceptability of gonadotrophin therapy in boys for pubertal induction is crucial, and providers who care for adolescents and young adults should be aware of its impact and management (37). As noted earlier, there may be many functional disorders of pubertal maturation associated with weight and stress in the age group, and such features are just as likely, if not more so, to be seen in these patients.

**Treatment of HH in the transition age – Boys**

Induction or progression of puberty is recommended for adolescents who have been diagnosed with hypogonadism. Although sex steroid replacement is used in the majority of cases of hypogonadism for initiation of male puberty, more complex management including gonadotrophin treatment may be required in males with hypogonadism in order to obtain both the development of secondary sexual characteristics and to increase the potential for fertility.

In adolescent boys with a diagnosis of HH, induction of puberty with sex steroids is similar to that in constitutional delay of puberty, but treatment can be considered at a younger age (12 years) if the diagnosis is confirmed. The starting dose of testosterone ester i.m. for HH patients is commonly 50mg each month for 3–6 months, but doses are gradually increased to full adult replacement levels over around 3 years. It is also possible
to consider using oral (testosterone undecanoate) or testosterone gel therapy as an alternative, although the dose regimens for these have not been fully studied.

Assessment of physical virilisation can be considered as the primary outcome measure, but all boys who start testosterone therapy should have an accurate biochemical and haematological evaluation in addition to anthropometric assessment prior to starting therapy and at appropriate intervals. Maintenance therapy can be performed with i.m. testosterone, especially the longer-acting testosterone undecanoate (Nebido) or topical gel therapy. In the management of HH patients, it is essential to note that testosterone therapy does not lead to testicular growth or spermatogenesis in men, and thus, later induction of fertility requires treatment with either pulsatile GnRH (38) or exogenous gonadotropins (39). A huge variety of regimens have been published, differing on the basis of the indication for treatment and the severity of hypogonadism. One regimen involves hCG 500–3000 IU twice weekly, increased to every 2 days, with the dose adjusted based on serum testosterone levels, and rhFSH 75–225 IU 2–3 times weekly; both can be given subcutaneously (39).

**Potential adverse events of testosterone treatment** Treatment with testosterone has generally been safe. The most frequent adverse effects are erythrocytosis, weight gain and prostate hyperplasia. High doses can cause premature epiphyseal closure. All intramuscular preparations can cause local side effects such as pain, erythema and inflammatory reactions.

**Treatment of HH in the transition age – Girls**

The induction of puberty is the first step, and once puberty is complete, ovulation and pregnancy can be achieved by pulsatile GnRH administration or gonadotrophin combination therapy. The appropriate chronological age to start treatment is usually 10–12 years (in accordance with her peers), but the dosing and timing of oestrogen therapy should be tailored. The use of 17β-oestradiol in transdermal, gel or oral form presents a better risk profile in terms of liver toxicity, vascular side effects and growth restriction (40). Therapy with oestrogens should be initiated at a low dose (one-eighth to one-quarter of the adult dose) and increased gradually every 4–6 months (41). One dosage regimen that can be considered is a patch containing 25 μg of 17β-oestradiol/24 h cut into four equal-sized pieces: one piece is applied on the skin before going to bed and removed in the morning. After 4–6 months the dose can be increased to two pieces at night with one piece being removed the following morning and the other remaining on the skin during the day. The dosage is usually increased approximately every 4–6 months to one patch of 25–100 μg positioned continuously and being changed twice a week. Otherwise, oral 17β-oestradiol may be taken 0.5 mg every day or every second day as an initial dosage, increasing gradually (41). The objective is to develop secondary characteristics over a period of 2–3 years. When ‘breakthrough’ bleeding occurs, the treatment should be supplemented with cyclic progesterone, such as 5 mg medroxyprogesterone acetate per day for 10 days every 4–5 weeks in order to avoid endometrial hypertrophy (41). The response to therapy should be monitored evaluating development of secondary sex characteristics, bone maturation and uterine volume, associated with the evaluation of blood pressure and bone density (41).

**Discussing options for fertility and future pregnancy in girls with HH in the transition age**

There is an ongoing need for advice and information during transition, which must be continuously adapted to the girl’s maturity and needs, and there should be space and time to open discussion regarding options for fertility and future pregnancy. In HH induction of gonadotrophin secretion by pulsatile GnRH or continuous gonadotrophin administration may improve folliculogenesis and ovulation, leading to an improvement in pregnancy rates. Pulsatile GnRH treatment can be used to restore periodic gonadotrophin secretion; however, some patients may not tolerate the use of the portable pump for the injection of GnRH for several weeks, and moreover, it is ineffective treatment for diseases of the pituitary gland. In general, to promote follicular growth and maturation, exogenous gonadotrophins, such as human menopausal gonadotropin (hMG) or a combination of recombinant LH and follicle-stimulating (FSH), are administered followed by an injection of human chorionic gonadotropin (hCG) (42, 43). Each treatment option must be customised according to the needs and preferences of the young patient, and her concerns regarding future fertility addressed in a compassionate and measured manner.

**Potential adverse events of oestrogen therapy** The most common adverse effects are represented by liver toxicity, increased levels of some plasma binding proteins, a
potentially greater risk of thromboembolism and arterial hypertension.

Conclusions

Early diagnosis is essential to start therapy in the best moment to develop secondary sexual characteristics and growth, as well as allowing maturation of the gonads for future fertility. Moreover, early treatment may help to attenuate some of the psychosocial problems of hypogonadism in the transition age, ensuring a better QoL. An integrated approach including coordinated transitional clinics into adulthood is essential to guarantee the most personalised management and optimal outcome.

Precocious puberty

Precocious puberty occurs in case of breast development before 8 years of age in girls or testicular growth before 9 years of age in boys (44). Central precocious puberty can occur after disinhibition of hypothalamic GnRH release due to intracranial tumour, cranial surgery or irradiation (44). Female gender and younger age at cancer diagnosis and treatment increase the risk of precocious puberty. Moreover, puberty might begin on time but advance rapidly after cranial irradiation. Early skeletal maturation associated with precocious puberty may result in reduced growth (45). The GnRH stimulation test represents the gold standard for the diagnosis, and treatment with depot GnRH analogues are the standard of care (44).

The physical changes occurring during precocious puberty may cause not only feelings of shame, embarrassment and insecurity, but also fear of comments from peers; these aspects may lead to isolation and social withdrawal, also altering relationships with peer and family (46). After cessation of GnRH analogue administration, the HPG axis restarts and the majority of data report no serious adverse effects on reproductive axis. In girls, menarche usually appears between 2 and 61 months after the discontinuation of GnRH analogues and menstrual cycles progressively became regular in most girls. There are variable data regarding the onset of the polycystic ovary syndrome which occur more frequently in adolescents previously treated with GnRH analogues. In boys, testosterone levels and testis volume progressively increase after the discontinuation of treatment, reaching usually normal values for adults. Moreover, normal bone mineral density has been found after the achievement of adult height, indicating no long-term adverse effects on peak bone mass both in girls and boys (47). However, the precise timing of withdrawal of such analogues requires a careful discussion with the patient in order to provide a smooth transition into puberty concomitant with their peers.

Central hypothyroidism in the transition age

Introduction

Hypothyroidism is defined as a pathological condition in which there is an insufficient production of thyroid hormones. Secondary or central hypothyroidism (CH), rarer compared to primary hypothyroidism, is due to insufficient stimulation of a normal thyroid gland due to a deficiency in TSH as a result of hypothalamic or pituitary disease.

Forms of CH

CH is characterised by low thyroid hormone levels and inappropriately low-normal serum TSH. CH can be due to any major inflammatory or neoplastic disease of the pituitary or hypothalamus (48).

Clinical manifestations of hypothyroidism

Thyroid hormones are crucial to a great number of physiologic processes including normal growth and neurodevelopment, but they are also responsible for regulating basal metabolic rate and body temperature, heart rate, cardiac output, the promotion of gastrointestinal motility and renal clearance of salt and water. The signs and symptoms of hypothyroidism are highly variable among individuals; the most frequent in the transition age range are often subtle and non-specific, but may include fatigue, cold intolerance, dry skin, weight gain or constipation, impaired linear growth, delayed puberty and/or abnormal menstrual cycles. Diagnosis is generally based on serum TSH and FT4.

Management of CH in the transition age

Levothyroxine is considered the treatment of choice, administered once-daily, ideally 15–30 min prior to food consumption in the morning (48). Levothyroxine dosing is based on body surface area (100 μg/m²/day) or on age and weight following the general pattern: 3–5 μg/kg/day for patients 3–10 years of age, 2–4 μg/kg/day for patients...
10–16 years of age and 1.6 μg/kg/day for patients 17 years of age or older (49). Obviously, the dose of levothyroxine necessary to restore euthyroidism depends on both the age of manifestation of symptoms and severity of the hypothyroidism. In very selected cases of adolescents struggling with poor compliance with oral thyroxine once-daily, supervised once-weekly oral thyroxine may be a safe, successful and well-tolerated treatment option. However, to obtain a complete biochemical euthyroidism, a slightly higher dose than seven times the standard dose once-daily may be required (50).

The goals of treatment are to maintain clinical and biochemical euthyroidism and to ensure normal linear growth and development throughout childhood and adolescence (49). Adolescent female patients should be informed about the potential need for an increment of levothyroxine dosing when using oestrogen-containing contraceptives and during future pregnancy.

Different studies have underlined the difficulty in achieving optimal substitutional levothyroxine therapy in patients with CH. The main difference with the management of CH is that serum TSH levels cannot guide replacement therapy; therefore, the aim of replacement treatment of CH is to obtain euthyroidism having appropriate serum concentrations of thyroid hormones: serum FT₄ concentration generally represents the most useful marker for this purpose. Most authorities advise that the free T4 level should be adjusted to be towards the upper end of the normal range, while measurement of T3 or free T3 rarely adds useful information.

In recent years, in addition to the tablets, new formulations of levothyroxine have become available in some countries: liquid solution and softgel capsule (51). In selected categories of hypothyroid patients treated with levothyroxine (paediatric, unwilling to delay breakfast, with hypo-achlorhydria, undergone bariatric surgery, polypharmacy, enterally fed), these new formulations have shown promising characteristics in helping attainment of euthyroidism, improving patient compliance. Some studies had also considered combination treatment with T₃ and T₄ in CH, but there is no clear demonstration of superiority compared to levothyroxine alone (52).

Adjustment of levothyroxine

Adjustment of levothyroxine dosage is often required due to the age and weight of the patient, the presence of other pituitary hormone deficiencies, and the potential for adverse events during levothyroxine therapy.

**Management of CH in girls looking for pregnancy**

Adolescent girls of reproductive age should be counselled regarding the likelihood of increased demand for levothyroxine during pregnancy (53). In hypothyroid girls who are planning pregnancy, FT4 should be evaluated pre-conception, and the levothyroxine dose should be adjusted if needed. Hypothyroid adolescents treated with levothyroxine who find out they are pregnant should increase their dose of LT₄ by 20–30% and urgently notify their clinicians for prompt testing and further evaluation. This should ideally be discussed with every patient in the pre-pregnancy setting (53).

**Interference with absorption of levothyroxine**

Food, milk, coffee, juices, soy products and higher fibre intake may influence the absorption of L-T₄, as may some gastrointestinal disorders (Table 3). Some medications (iron supplements, proton pump inhibitors and H2 receptor antagonists, calcium supplements and so forth) may interfere with L-T₄ absorption by altering gastric pH (48).

**Interactions between thyroid hormone replacement with other pituitary hormone deficiencies**

Concomitant use of other replacement hormones in CH may require adjustments of levothyroxine dosage. Girls on oestrogen treatment and adolescents on GH treatment will often need a higher levothyroxine dose to ensure serum FT₄ levels remain in the euthyroid range (54). Oestrogen treatment increases the capacity of T₄-binding plasma proteins, requiring an increment of levothyroxine (55). In terms of GH replacement, GH therapy leads to a slight fall of serum T₄ levels, an increase in serum T₃ levels, associated with a possible fall in serum TSH concentrations (55). Therefore, patients on GH replacement therapy often need higher doses of levothyroxine or initiation of thyroxine replacement when levels were previously borderline-low (Table 1). Moreover, when starting thyroid hormone therapy, in the presence of concomitant ACTH deficiency, there is a high risk of developing adrenal crisis due to adrenal insufficiency (AI); therefore, evaluation of the hypothalamo–pituitary–adrenal axis is essential before starting levothyroxine (55). In case of AI, glucocorticoid replacement therapy should be started several days before levothyroxine to guarantee a euadrenal state before treatment of hypothyroidism.

**Potential adverse events during levothyroxine therapy**

Patients treated with excessive levothyroxine dosage for prolonged periods may have symptoms and signs of thyroid hormone excess (56), with a hypermetabolic state which may be associated with increased heart rate.
Central adrenal insufficiency

Introduction

CAI is a life-threatening condition caused by impaired synthesis and release of adrenocorticotropic hormone (ACTH) from the pituitary gland due to pituitary disease (secondary AI) or impaired release or action of corticotrophin-releasing hormone (CRH) or vasopressin from the hypothalamus, due to disease or alterations of the hypothalamus or related regions (tertiary AI).

Forms of CAI

ACTH deficiency can be isolated or, more frequently, may present in association with other hormonal deficiencies of the pituitary and midline defects or impairments. CAI occurs in the context of different congenital, genetic, epigenetic or brain malformation syndromes, but is also seen in certain acquired conditions such as pituitary adenomas, craniopharyngiomas, germinomas, hypothalamo–pituitary lesions or iatrogenic damage such as irradiation. There are also congenital genetic disorders that can cause CAI (57).

Table 3  Gastrointestinal diseases associated with malabsorption of levothyroxine.

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Coeliac disease</td>
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<tr>
<td>Atrophic gastritis – autoimmune gastritis</td>
</tr>
<tr>
<td>Helicobacter pylori infection</td>
</tr>
<tr>
<td>Liver diseases: cirrhosis</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
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<tr>
<td>Previous surgery of the GI tract: jejunostomy, jejunoileal bypass</td>
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and enhanced risk of atrial arrhythmias, increased left ventricular mass and diastolic dysfunction (56).

Conclusions

Early identification and treatment of CH in adolescents is essential to optimise development, metabolic processes and growth. Once-daily levothyroxine is a safe and adequate treatment for CH. Considering that CH is caused by defects in hypothalamo–pituitary–thyroid axis, hypothyroidism in these cases is usually associated with other pituitary hormone deficiencies, and therefore, concomitant use of other replacement hormones in CH may require adjustments of levothyroxine dosage. In general, replacement should aim at rendering the serum thyroxine towards the upper part of the normal range.

Clinical manifestations of CAI

In the transition age, glucocorticoid deficiency may present with frequent infections, weakness, fatigue, nausea, headache, myalgia and arthralgia or more rarely severe hypoglycaemia. However, in cases of ‘partial’ ACTH defect, it can be mainly asymptomatic, the patient presenting with an adrenal crisis in cases of stress, trauma, surgery or illness. In contrast to primary AI, hyperpigmentation is not present in patients with CAI, and changes in salt and water balance, while present, are more mild than with primary AI (58).

The diagnosis of CAI may be challenging, in particular regarding partial deficiency, and it therefore is crucial to determine the ACTH levels and cortisol levels both basally and stimulated (59).

Physiological roles of glucocorticoids

Glucocorticoids (GCs) have predominantly catabolic actions in muscle and adipose tissue (60). GCs also play a significant role in glucose homeostasis leading to a reduction in glucose disposal and to an increased production of endogenous glucose (61). In adipocytes, cortisol stimulates free fatty acid release and inhibits glucose transport and leptin action, contributing to central obesity when in excess (60). GCs exert effects on the cardiovascular system, mainly maintaining normal blood pressure and have major effects on the central nervous and immune systems (60).

In order to evaluate the physiologic changes of cortisol metabolism throughout childhood and adolescence, some authors have used the measurement of salivary cortisol to show a positive correlation between cortisol concentrations and pubertal age, irrespective of sampling time; this suggests that there is an increased cortisol production in adolescents compared to prepubertal children. Moreover, salivary cortisol has been found to be positively related to body weight during adolescence. However, it is unclear as to whether the increased salivary cortisol during puberty is associated with a higher activity of the adrenal glands during puberty or simply changes in weight and fat deposition (62).

Management of CAI

The treatment of AI depends on physiological replacement of absent or deficient glucocorticoid secretion with or without mineralocorticoid substitution. While primary forms are associated with both glucocorticoid and
Mineralocorticoid deficiencies, the secondary and the tertiary forms only show cortisol deficiency (63).

**Conventional glucocorticoid therapy**

In adolescents with AI, pharmacological treatment relies on oral replacement therapy, mainly with hydrocortisone (HC), a short-acting glucocorticoid, which currently represents the treatment of choice. Another option is represented by cortisol acetate, but this needs to be activated in the liver and thus its mode of onset is slower. In CAI, the total recommended HC dose is generally slightly lower compared to primary AI and is between 7 and 9 mg/m²/day, divided in three doses as CAI most frequently results from a partial ACTH deficit (57, 60). The highest dose should be given in the morning, on waking, the second one mid-afternoon (in the two-dose regimen), or at noon followed by a third dose in the evening, 4–6 h before bedtime (in the three-dose regimen), but not later than 18:00 h (57).

HC is the preferred option to treat AI during adolescence because of its immediate efficacy and short duration of action, which facilitates dose titration (57); its safety profile is associated with fewer side effects with a lower impact on linear growth compared to longer-acting GCs (57, 64).

Long-acting GCs such as prednisone or prednisolone may represent an alternative to HC in adolescents who have reached final height, or in young adults, as they are long acting and could be used once a day, facilitating compliance. These types of GCs are generally used in patients presenting poor compliance to a multidaily regimen. Dexamethasone should rarely be used (58).

**Modified-release compounds**

In order to better mimic the physiological circadian rhythm of cortisol, new drugs have been developed, although currently they are licensed in only a few countries. Plenadren® represents a once-daily (OD) modified-release HC that has immediate-release coating combined with an extended-release core, developed to obtain a more natural cortisol exposure time profile and to improve the outcome of GC replacement therapy. It is taken in the morning on waking. Some studies, all on patients over the age of 18 years, have shown that OD modified-release HC is safe and has positive effects on metabolic, cardiovascular and immune systems (65, 66, 67).

Chronocort® is another modified-release hydrocortisone formulation currently under development. This formulation can reproduce the physiological overnight cortisol growth providing a prewaking rise in cortisol levels. Chronocort® has to be administered with a twice daily ‘toothbrush’ regimen: 15–20 mg at 23:00 h and 10 mg at 7:00 h, with the aim of reproducing physiological cortisol levels throughout a 24-h period (68). At present, it is principally being developed for the treatment of congenital adrenal hyperplasia.

**Paediatric formulations**

Neither Plenadren® nor Chronocort® is licensed for paediatric use. Infacort® is an immediate-release granulated HC formulation developed recently and licensed in Europe for use in paediatric AI. The formulation contains a microcrystalline core coated by an HC layer, further coated by binding layers and an outer ‘taste-making’ one. It can be administered with food, liquids or as dry granules directly onto the child’s tongue. It is available in 0.5, 1, 2 and 5 mg doses (69). Infacort® may represent a valid option for precise dosing in paediatric patients with AI.

**Continuous subcutaneous HC infusion**

Some clinical trials have shown positive results with continuous subcutaneous HC infusion using insulin pumps obtaining more physiological cortisol profiles (70). However, this is an expensive and more invasive option compared to oral HC and should be considered only for selected patients with poor response to conventional therapy.

**Special considerations on GC treatment in specific categories of patients**

AI may be associated with a raised serum TSH and normal or low T4 concentrations; this usually reflects lack of GC inhibition on TSH release rather than hypothyroidism. These abnormalities may be completely reversible with GC treatment alone; therefore, this is important to recognise as commencing thyroid hormone treatment without replacing glucocorticoids can precipitate adrenal crisis.

In case of multiple pituitary hormonal deficiencies, it is essential to note that GH treatment may unmask CAI, especially in adult patients, as GH attenuates 11β-hydroxysteroid dehydrogenase type-1 isoenzyme activity thus reducing cortisol to cortisone conversion, and thus, evaluation of the HPA axis and possible dose adjustment is crucial in these patients (71) (Table 1).
Adrenal crisis management

The most serious complication of AI is adrenal crisis. Adrenal crisis consists in an acute health impairment characterised by a variable association of sign and symptoms such as hypotension, acute abdominal pain, hyponatraemia (as GCs are essential for free water clearance), hypoglycaemia, pyrexia and altered consciousness, all of which should rapidly resolve after parenteral GCs administration. First-line management consists on rapid intravenous fluid infusion and immediate parenteral GC administration, either intramuscularly or intravenously.

Adrenal crisis prevention

Prevention of adrenal crisis should consider predicting precipitating risk factors. The most common precipitating factors are represented by infections, surgical procedures, physical or psychological stress or sudden interruption of GC replacement therapy. Patients with primary AI are more prone to develop adrenal crisis because of the deficit of mineralocorticoid hormones (72). In practice, adrenal crisis is prevented by increasing the GC doses and dividing them into three to four intakes during an acute illness or adequately adapting them before surgical procedures and by avoiding immediate cessation of GC therapy (73, 74).

Patient education plays a crucial role in the management of CAI in ameliorating QoL and minimising morbidity. Physicians must instruct patients to correctly adapt their GC oral dose during stressful events and recognise that situations when parenteral HC administration is requested; in addition, each patient should be equipped with a steroid emergency card (75). However, adolescence presents a particularly problematic time, as patients may be moving from childhood and parental dependence to a new sense of independence; they may be leaving home for further education, and compliance tends to be more variable. This is especially important for GC replacement therapy. In addition, such patients may be introduced to alcohol and other stimulants, may stay out late with varying and often bizarre sleeping habits and possess less awareness of the significance of their medication. Patients who stay up late, for example on weekends, might postpone the afternoon dose of hydrocortisone to cover the hours they will be awake compared to what they do routinely. It is therefore of paramount importance that the clinician develops a good rapport with the young patient, and as far as possible tailors the treatment to the patient’s lifestyle, while emphasising the dangers of missing doses or ignoring sinister signs of an impending adrenal crisis.

The adolescent needs to establish ‘ownership’ of their disorder and medication, such that they understand they can modify the medication to their lifestyle rather than vice versa.

Potential adverse events of GC treatment

GCs over-replacement results in exacerbation of the metabolic syndrome, cardiovascular, bone and neurologic disease. The higher the replacement dose, the greater the risk of arterial hypertension, metabolic disorders such as higher rates of central adiposity, hypertriglyceridaemia, hypercholesterolemia and glucose intolerance, as well as a reduction in bone mineral density; worsening of QoL and impairment of memory and executive cognitive functions have also been observed.

Conclusions

Central AI is an important feature of patients with hypothalamo–pituitary disease, and it is crucial that is carefully diagnosed, treated and managed in their follow-up. GC treatment represents life-saving therapy, albeit subject to numerous limitations. HC is the first choice drug, should optimally be administered thrice-daily, and its dosage must be increased in stressful situations. Education is essential to protect patients from life-threatening events and to improve their QoL, and tailoring requirement to lifestyle is vital in the transition.

Sleeping patterns in adolescence

Sleep represents a key moment in adolescent development, but it often becomes irregular, shortened and delayed during the period of transition to the adult life, resulting in circadian clock desynchronisation and sleep loss. Indeed, there is evidence that the circadian rhythm shifts during this period to later wakefulness at night and later waking in the morning. In addition, adolescents in the West now almost invariably spend excessive amounts of time using electronic media, consuming alcohol and using drugs of abuse. Such behaviour may induce harmful effects on circadian physiology and impacts strongly on adolescent mental, social and physical health (76). While these are generic problems associated with their period of life, one should again stress that it is a better tactic to try and modify medication strategy to changes in sleep patterns and lifestyle rather than to insist on strict adherence on socially difficult regimens.
Cranial diabetes insipidus

Introduction

CDI is the most common form of diabetes insipidus (DI). It is caused by inadequate synthesis or secretion of arginine vasopressin AVP or antidiuretic hormone (ADH), resulting in hypotonic polyuria and a compensatory polydipsia (77).

Forms of CDI

CDI may result from traumatic brain injury, surgery, pituitary tumours, craniopharyngioma, germinoma, meningioma, granulomatous diseases, inflammatory or autoimmune and congenital diseases (30, 77).

Clinical manifestations

Symptoms of DI include persistent polyuria and polydipsia, but also fatigue, dizziness, nocturia and signs of dehydration (dry skin and mucus membranes, weight loss, poor skin turgor); hypotension and tachycardia and an altered level of consciousness may occur (77).

Polyuria (>50mL/kg), dilute urine (osmolality <300mosmol/L) and increased thirst (intake of up to 20L fluid/day) are typical of DI. Subsequent investigations mainly involve the water deprivation test, although recent studies on co-peptin may change the diagnostic algorithm.

Management of CDI

The AVP analogue desmopressin is the treatment of choice and should be prescribed according to the patient’s specific need, preferably oral administration. For patients requiring parenteral therapy, intramuscular desmopressin is normally chosen (77).

Desmopressin formulations include an intranasal spray, oral tablet, orally disintegrating tablets (ODTs) and parenteral formulations. Desmopressin intranasal spray is no longer approved in the United States to treat primary nocturnal enuresis due to safety issues, with tablets or melt formulations preferred in a majority of countries.

The first objective of initial management of a patient with CDI is to ensure an euvolaemic state, with a sodium at 135–150mmol/L and a serum osmolality within normal limits. Patients with DI showing an intact thirst mechanism and who are able to tolerate oral fluid should never be fluid restricted. They should be encouraged to only drink enough to satisfy thirst avoiding excess fluid intake. Much lay advice suggest that it is vital to have water available at all times and to drink requisite minimal amounts of fluid for optimal health; it is increasingly common to see young people in this age group, and indeed beyond, carrying water bottles at all times and drinking according to rote rather than to thirst. This nonsensical situation is especially harmful to these patients who have lost the physiological responses to over drinking and appropriate advice should be given to patients who are unable to tolerate oral fluids or who are vomiting. Fluid resuscitation and then volume replacement is required to prevent hypernatraemia. In the monitoring of CDI, it is crucial to evaluate input and urine output in patients, which will normally indicate overtreatment or undertreatment with desmopressin (78).

New formulation of desmopressin: ODT

The ODT formulation has been recently introduced; it is a wafer-like formulation which dissolves instantly in the mouth with no need for water (80). It is advantageous compared to the intranasal formulation which requires cold storage and where absorption may be unstable due to alterations in the nasal mucosa.

Adipsic diabetes insipidus

Adipsic DI represents a rare but challenging complication of some hypothalamic disorders, associated with high morbidity and mortality. It consists of a lack of polydipsia and polyuria that may delay the diagnosis and lead to severe complications such as chronic hyperosmolar status. Clinicians, health workers and families should supervise fluid and desmopressin intake as in adults, with fixed regimens of fluid throughput, weight assessment and fluid output measurement (79).

Special considerations

Managing CDI it is important to evaluate if a patient on desmopressin is also on GC replacement therapy. Cortisol is essential for the free excretion of water; thus, AI can lead to hyponatraemia which may be exacerbated by the administration of desmopressin. Adolescents with hypothalmo-pituitary diseases are often taking GCs and desmopressin simultaneously; therefore, clinicians and patients should be aware of the need to increase GC dosage in case of concomitant disease and to check electrolytes before further administration of desmopressin to prevent dilutional hyponatraemia (81).
drugs such as MDMA (‘ecstasy’) can also lead to over-drinking which may be particularly dangerous in patients on desmopressin (82).

Adolescents should be appropriately educated on how to dose desmopressin keeping them comfortable and instructing them to avoid thirst and frequent urination. They should be informed to allow their thirst to guide adequate fluid intake and to drink only when thirsty and to re-evaluate the desmopressin dose when the patient is using the restroom often (every hour), the patient’s urine is clear, resembling water and/or the patient is very thirsty (83).

**Potential adverse events of desmopressin treatment**

The most serious adverse reaction is hyponatraemia, which may cause headache, nausea, vomiting, weight increase, dizziness, confusion, abdominal pain, memory impairment, vertigo, falls and in severe cases convulsions and coma.

**Conclusions**

CDI is a disorder that can be debilitating. It is important to identify the aetiology of DI and to treat it accordingly. Patients with DI should never be fluid restricted and desmopressin should not be omitted or delayed. Desmopressin has been demonstrated safe and effective in the management of CDI. Newer preparations including oral and ODT formulations show advantages over nasal preparations as they are useful in patients who have mental or physical disabilities or have chronic nasal problems.

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