



HAL
open science

Position statement on the diagnosis and management of congenital pituitary deficiency in adults: the French National Diagnosis and Treatment Protocol (NDTP)

Sarah Castets, Frédérique Albarel, Anne Bachelot, Gilles Brun, Jérôme Bouligand, Claire Briet, Emmanuelle Bui Quoc, Laure Cazabat, Nathalie Chabbert-Bufferet, Sophie Christin-Maitre, et al.

► To cite this version:

Sarah Castets, Frédérique Albarel, Anne Bachelot, Gilles Brun, Jérôme Bouligand, et al.. Position statement on the diagnosis and management of congenital pituitary deficiency in adults: the French National Diagnosis and Treatment Protocol (NDTP). *Annales d'Endocrinologie = Annals of Endocrinology*, 2024, *Annales d'Endocrinologie = Annals of Endocrinology*, 85 (4), pp.327-339. <10.1016/j.ando.2024.03.001>. <hal-04689015>

HAL Id: hal-04689015

<https://lilloa.hal.science/hal-04689015v1>

Submitted on 5 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License



Disponible en ligne sur

ScienceDirect
www.sciencedirect.com

Elsevier Masson France

EM|consulte
www.em-consulte.com



Original article

Position statement on the diagnosis and management of congenital pituitary deficiency in adults: The French National Diagnosis and Treatment Protocol (NDTP)



Sarah Castets^{a,*}, Frédérique Albarel^b, Anne Bachelot^{c,d}, Gilles Brun^{e,l}, Jérôme Bouligand^f, Claire Briet^{s,t}, Emmanuelle Bui Quoc^g, Laure Cazabat^m, Nathalie Chabbert-Buffetⁿ, Sophie Christin-Maitreⁱ, Carine Courtillot^c, Thomas Cunyⁱ, Gianpaolo De Filippo^h, Bruno Donadilleⁱ, Frédéric Illouz^{s,t}, Isabelle Pellegrini^b, Yves Reznik^o, Alexandru Saveanu^e, Natacha Teissier^p, Touraine^j, Marie-Christine Vantyghem^q, Julia Vergier^a, Julianne Léger^{h,r}, Thierry Brue^{a,e,k}, Rachel Reynaud^{a,e,k}

^a Service de pédiatrie multidisciplinaire, centre de référence des maladies rares de l'hypophyse HYPO, hôpital de la Timone Enfants, Assistance publique–Hôpitaux de Marseille (AP–HM), 13005 Marseille, France

^b Service d'endocrinologie, centre de référence des maladies rares de l'hypophyse HYPO, hôpital de la Conception, Assistance publique–Hôpitaux de Marseille (AP–HM), 13005 Marseille, France

^c IE3M, ICAN, Department of Endocrinology and Reproductive Medicine, Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Centre de Référence des Pathologies Gynécologiques Rares, hôpital Pitié-Salpêtrière, AP–HP, Paris, France

^d Sorbonne université, Paris, France

^e Aix-Marseille University, Institut National de la Santé et de la Recherche Médicale (INSERM), U1251, Marseille Medical Genetics (MMG), Assistance Publique Hôpitaux de Marseille, Reference Center for Rare Pituitary Diseases HYPO, Assistance-Publique des Hôpitaux de Marseille, Laboratory of Molecular Biology, Conception Hospital, Marseille, France

^f Molecular Genetic, Pharmacogenetic and Hormonology, Kremlin-Bicêtre Hospital, Paris-Saclay University, AP–HP, Le Kremlin-Bicêtre, France

^g Ophthalmology Department, Robert-Debré University Hospital, Assistance publique–Hôpitaux de Paris, Paris, France

^h Service d'endocrinologie et diabétologie pédiatrique, centre de référence des maladies endocriniennes de la croissance et du développement, hôpital universitaire Robert-Debré, université Paris Cité, Assistance publique–Hôpitaux de Paris, Paris, France

ⁱ Department of Endocrinology, Diabetology and Reproductive Medicine, Centre de Référence des Maladies Endocriniennes Rares de la Croissance et du Développement (CMERC), Centre de Compétence HYPO, Hôpital Saint-Antoine, Sorbonne University, Assistance publique–Hôpitaux de Paris, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France

^j Service d'endocrinologie et médecine de la reproduction, centre de maladies endocriniennes rares de la croissance et du développement, médecine-hôpital Pitié-Salpêtrière, Sorbonne université, Paris, France

^k Inserm, MMG, Laboratory of Molecular Biology, Hospital La Conception, Aix-Marseille University, AP–HM, Marseille, France

^l Hôpital Européen, Pôle imagerie médicale, 13003, Marseille, France

^m Department of Endocrinology, Diabetology and Nutrition, Ambroise Paré Hospital, AP–HP, UVSQ, Boulogne-Billancourt, France

ⁿ Department of Gynecology and Obstetrics, Hôpital Tenon, Assistance Publique–Hôpitaux de Paris, 75020 Paris, France

^o Endocrinology and Diabetes Department, CHU Côte de Nacre and Unicaen, Caen Cedex, France

^p Department of Pediatric Otolaryngology, Robert Debré Hospital, AP–HP Nord, Paris, France

^q Service d'endocrinologie, diabétologie et maladies métaboliques, CHRU de Lille, rue Polonowski, Lille cedex, France

^r Université Paris Cité, NeuroDiderot, Institut National de la Santé et de la Recherche Médicale (INSERM) UMR 1141, Paris, France

^s Département d'endocrinologie-diabétologie nutrition, Centre de référence des maladies rares de la Thyroïde et des Récepteurs Hormonaux, Endo-ERN centre for rare endocrine diseases, CHU d'Angers, 4, rue larrey, 49100 Angers, France

^t Laboratoire MITOVASC, UMR CNRS 6015, Inserm 1083, Université d'Angers, rue Roger Amsler, 49100 Angers, France

INFO ARTICLE

Keywords :

Growth hormone deficiency
Pituitary deficiency
Hypopituitarism
Arginine vasopressin deficiency
Pregnancy
Elderly

ABSTRACT

Pituitary deficiency, or hypopituitarism, is a rare chronic disease. It is defined by insufficient synthesis of one or more pituitary hormones (growth hormone, TSH, ACTH, LH-FSH, prolactin), whether or not associated with arginine vasopressin deficiency (formerly known as diabetes insipidus). In adult patients, it is usually acquired (notably during childhood), but can also be congenital, due to abnormal pituitary development. The present study focuses on congenital pituitary deficiency in adults, from diagnosis to follow-up, including special situations such as pregnancy or the elderly. The clinical presentation is highly variable, ranging from isolated deficit to multiple deficits, which may be part of a syndromic form or not.

* Corresponding author. Service de pédiatrie multidisciplinaire, hôpital d'Enfants de la Timone, Assistance publique–Hôpitaux de Marseille (AP–HM), 264, rue Saint-Pierre, 13005 Marseille, France.

Adresse e-mail : sarah.castets@ap-hm.fr (S. Castets).

Diagnosis is based on a combination of clinical, biological (assessment of all hormonal axes), radiological (brain and hypothalamic-pituitary MRI) and genetic factors. Treatment consists in hormonal replacement therapy, adapted according to the period of life and the deficits, which may be progressive. Comorbidities, risk of complications and acute decompensation, and the impact on fertility and quality of life all require adaptative multidisciplinary care and long-term monitoring.

© 2024 L'Auteur(s). Publié par Elsevier Masson SAS. Cet article est publié en Open Access sous licence CC BY (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Pituitary deficiency, or hypopituitarism, is a rare disease defined by insufficient production or secretion of one or more anterior pituitary hormones (growth hormone [GH], thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], luteinizing hormone [LH], follicle-stimulating hormone [FSH], prolactin), or more rarely post-studio pituitary hormones (vasopressin). Genetic causes are rarer than acquired causes, principally direct tumoral causes (hypothalamo-pituitary tumor) or indirect causes (radiotherapy, surgery, checkpoint inhibitors). The prevalence of congenital hypopituitarism is difficult to establish, but is estimated at between 1/16,000 and 1/26,000 [1]. It may be part of a syndrome or not. Diagnosis is usually made in childhood or at puberty, but in adulthood in up to 7% of cases [2]. These cases of delayed diagnosis are linked to a lack of previous pediatric medical consultation, often in a context of socio-economic difficulties, and/or a poor knowledge of the pathology in adulthood [3]. Comorbidities, acute complications and decompensation, and impact on fertility and quality of life mean that this chronic pathology requires specialized, often multidisciplinary, care, and long-term follow-up.

2. Method

The present study followed the French Health Authority (HAS) 2012 instructions for preparing national diagnosis and treatment protocols (NDTPs) for rare diseases (“Méthode d’élaboration d’un protocole national de diagnostic et de soins pour les maladies rares”, available on the HAS website: www.has-sante.fr). The recommendations were established by a group of authors on the basis of a literature review, then reviewed, edited and discussed by a group of reviewers. The present article is a summary of the NDTP recommendations for the adult population (Fig. 1).

3. Diagnosis and initial assessment

3.1. Clinical signs of pituitary deficiency

3.1.1. Somatotropic deficiency

Isolated growth hormone deficiency can be diagnosed in adulthood in case of short stature. Deficiency is rarely isolated in adulthood, and is most often associated with multiple anterior pituitary insufficiency and impuberism [4]. Other symptoms include asthenia, neuromuscular pain, variably reduced resistance to effort, muscle-wasting in favor of adipose tissue, and impaired quality of life. The voice is often high-pitched [5]. Delayed puberty, early menopause, and impaired sexuality have also been reported [6,7].

3.1.2. Gonadotropic deficiency

Forms of gonadotropic insufficiency can be diagnosed in adulthood.

In women, gonadotropic insufficiency presents as primary amenorrhea in 90% of cases, primo-secondary (after a few cycles) or secondary much more rarely [8]. Breast development may be

normal or absent [9]. Sometimes, diagnosis of moderate forms is suggested by oligomenorrhea, infertility (linked to anovulation when estradiol secretion is normal) or osteoporosis [10].

In men, decreased libido, erectile dysfunction or infertility may suggest diagnosis. Pubertal development varies according to the severity and duration of hypogonadism [11]. Severe forms of isolated hypogonadism are rarely diagnosed in adulthood, with complete impuberism (micropenis, testicular volume < 4 mL, absence of muscle development, unmuted voice, beardlessness), tall stature, gynoid obesity, adipomastia, bone fragility and mood disorder [12]. Partial forms with a more moderate phenotype are more frequent: they present as spontaneous puberty, sometimes incomplete (testicular volume < 10 mL), partial virilization and gynecomastia [8,13].

Kallmann syndrome is the most common diagnosis, defined by the association of gonadotropic deficiency and anosmia/hyposmia in the patient or a relative. There is considerable intra- and inter-familial phenotypic variability. Other associated clinical features may be suggestive: imitation synkinesis for contralateral limbs (5–15% of cases), dental agenesis, cleft lip or palate, unilateral renal agenesis, central deafness, ataxia, and ichthyosis (rare but pathognomonic for contiguous gene syndrome) [14]. Gonadotropic insufficiency in Kallmann syndrome is spontaneously reversible in 15% of patients, especially in case of a particular type of genetic abnormality: mutation of the TAC3/TACR3 neurokinin signaling pathway [15].

3.1.3. Thyroid deficiency

Clinical signs of thyroid deficiency in hypopituitarism are generally milder than in primary thyroid insufficiency, and may depend on the genetic etiology. Severe hypothyroidism is rare, notably because thyroid function is often only partially impaired [16], but does exist, particularly in case of TSHB mutations, which are responsible for profound thyrotropic deficiency (mental retardation in the absence of treatment, growth retardation, myxedema, etc.) [17–20]. In more moderate deficiency, clinical signs may include overweight or obesity [21], growth retardation in childhood, asthenia and/or constipation, without mental retardation [16,21–23].

Isolated congenital thyroid deficiency in adulthood is rare, associating moderate symptoms with other affections depending on the gene involved: macro-orchidism in men with *IGSF1* mutations, central deafness with *TBL1X* mutations, etc.

3.1.4. Corticotropic deficiency

Clinical signs are non-specific: asthenia, both physical and psychological, particularly in the morning, with reduced muscle strength (sometimes atrophy or contracture) and reduced vitality (which may even lead to depression), hypoglycemia, digestive symptoms (weight loss, frequent abdominal pain, less frequent diarrhea) [24]. Nausea and vomiting are frequent and secondary to hyponatremia [25].

The phenotype may associate obesity, pallor, or even abnormal hair pigmentation (red or brown) in the case of POMC mutation [26].

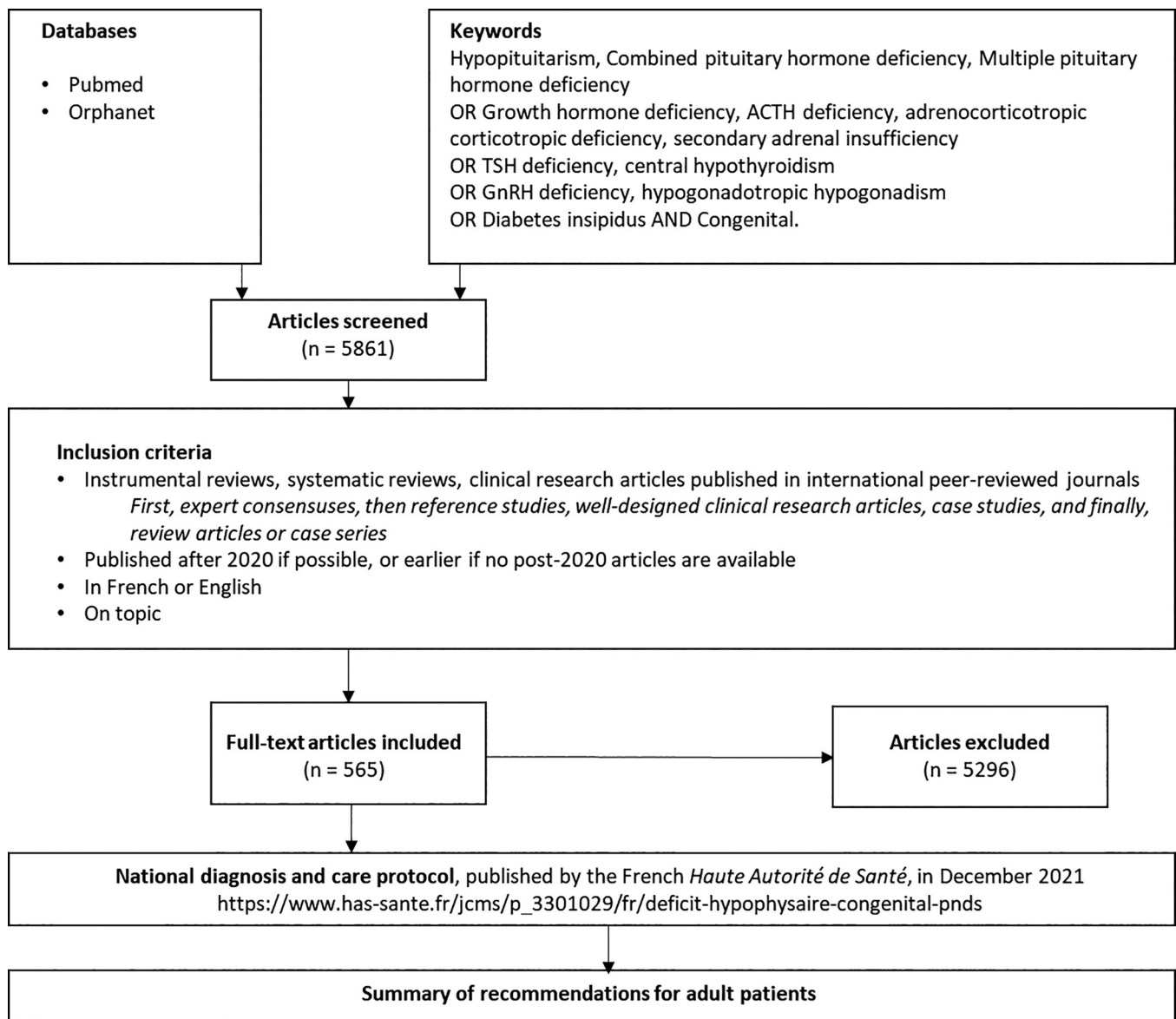


Fig. 1. Flowchart of protocol development and recommendations synthesis: literature search and article selection.

3.1.5. Arginine vasopressin deficiency (AVP-D) (central diabetes insipidus)

In adults, AVP-D is characterized by hypotonic polyuria (>30 mL/kg/h or >3L/day). It is very rarely present in congenital pituitary deficiency, usually associated with a major midline malformation or septo-optic dysplasia. Another etiology (tumor syndrome, granulomatosis, cancer, etc.) must therefore be systematically ruled out when it appears in adulthood.

3.2. Extra-pituitary clinical signs

Extra-pituitary disorders may concern cerebral development (holoprosencephaly, septo-optic or corpus callosum dysplasia) [27], craniofacial development (cleft lip and palate, single median incisor or lateral incisor agenesis, piriform sinus stenosis, choanal atresia), or ocular development (microphthalmia, anophthalmia, retinitis, iris or retinal coloboma) [2], depending on the mechanism responsible and the time of onset during ontogenesis. Other malformations are possible, such as skeletal anomalies (polydactyly, finger agenesis), vertebral anomalies (short neck with limited

rotation of neck and head), and, much more rarely, cardiac, renal or gastrointestinal malformations, neurosensory visual or hearing disorder [2] and/or neurodevelopmental disorders of variable intensity [28]. Finally, hypopituitarism can be part of the symptomatology of various syndromes: CHARGE, Fanconi, Rieger and Pallister-Hall syndromes.

3.3. Confirmation of diagnosis

3.3.1. Biological diagnosis

Diagnosis of hypopituitarism is based on a range of clinical, biological, radiological and even genetic factors.

3.3.1.1. Somatotrophic deficiency. In case of well-demonstrated constitutional GH deficiency in childhood, GH deficiency is considered persistent in adulthood if IGF-I values are low (< -2 SDS) after discontinuation of treatment for 1 month, or in the presence of 3 other anterior pituitary deficiencies (high probability of persistent GHD, with no need to re-evaluate the axis).

In other situations, GH and IGF-I plasma assay is not sufficient to confirm or exclude diagnosis of isolated GH deficiency. Insulin hypoglycemia test is the gold standard, with a GH threshold of 5 ng/mL for BMI < 25 kg/m² and 3 ng/mL for BMI ≥ 25 kg/m². If insulin hypoglycemia test is contraindicated, a glucagon stimulation test or a test combining GHRH plus arginine is recommended. It should be noted that glucagon testing is not informative in patients with glucose intolerance, and that GHRH plus arginine test shows diminished response in case of abdominal obesity [29].

3.3.1.2. Thyroid deficiency. Biological diagnosis is based on a low free T4 level associated with a normal or low TSHus value, or, more rarely, slightly elevated TSHus in case of hypothalamic syndrome [30]. Interferences between fT4 and TSHus assays (drug-related, or linked to the assay technique or a particular clinical situation) must be taken into account [31]. In cases of suspected congenital thyrotropic deficiency without combined pituitary involvement, and with no obvious phenotypic or genetic context, two determinations are required to confirm diagnosis. No stimulation test is required.

3.3.1.3. Corticotropic deficiency. Hormonal diagnosis is based on cortisol and adrenocorticotropin-releasing hormone (ACTH) levels at 8 AM. Apart from emergency situations, cortisol level < 138 nmol/L (5 µg/dL) associated with low or normal ACTH (< 15 pg/mL) suggests corticotropic insufficiency, whereas a cortisol level > 500 nmol/L (18 µg/dL) formally eliminates the diagnosis [32]. However, these thresholds should be adapted according to the assay kits and methods used, in consultation with the hormone biochemistry team carrying out the analysis.

Between these two threshold values, a stimulation test may be necessary. The 250 µg synacthen test can be used: cortisol level < 500 nmol/L at 30 min or 60 min confirms diagnosis of corticotropic insufficiency. In case of diagnostic doubt, another corticotropic stimulation test can be performed: insulin hypoglycemia (with simultaneous evaluation of the somatotrophic axis) or the metopirone test [32].

3.3.1.4. Gonadotropic deficiency. In men, the hormonal diagnosis is based on a low testosterone value, generally < 3 ng/mL, with low or normal FSH and LH [11]. Inhibin B assay, a marker of Sertoli cell damage, is not essential for positive diagnosis of gonadotropic insufficiency, but can be suggestive, being typically very low in case of profound deficiency.

In non-menopausal women, diagnosis is based on low or undeterminable plasma estradiol levels and low or non-elevated gonadotropin [11]. Estradiol must be measured with a sensitive kit with a threshold of 10 pg/mL [33]. AMH levels may be low or normal in gonadotropic insufficiency, so this assay is of little diagnostic value [34].

The GnRH stimulation test has little diagnostic value in either men or women, and is therefore not recommended.

If diagnosis was made in childhood, reassessment of the gonadotropic axis should be carried out in adulthood, after discontinuation of sex steroids for 1 to 3 months, in case of isolated insufficiency, as isolated gonadotropic insufficiency may in some cases be reversible [35].

3.3.1.5. Arginine vasopressin deficiency (AVP-D) (central diabetes insipidus). AVP-D, previously known as diabetes insipidus, is generally diagnosed at pediatric age.

In the presence of clear suggestive clinical manifestations, the association of hypotonic urine (< 300 mOsm/kg), hypernatremia (> 147 mmol/L), plasma hyperosmolality (> 280 mOsm/kg) and collapsed copeptin (≤ 4.9 pmol/L) indicates diagnosis of complete AVP-D [36].

The basal copeptin assay has emerged as a relevant biological marker in the exploration of polyuropolydipsic syndrome, but is insufficient to distinguish AVP-D from primary polydipsia. When urinary osmolality remains < 300 mOsm/kg and increases by more than 50% after injection of desmopressin, the water deprivation test can diagnose complete AVP-D. However, patients with partial AVP-D are difficult to distinguish from those with primary polydipsia (PP), as urine osmolality can oscillate between 300 and 800 mOsm/kg during the test in both situations: over the long-term, PP alters urine concentration capacity and the corticomedullary concentration gradient of the nephron. The copeptin assay in the water deprivation test has not proved to be effective in this situation. Based on copeptin determination, three tests can further distinguish PP from AVP-D, especially when partial: arginine injection (known to stimulate AVP release), with a copeptin threshold of 3.8 pmol/L, distinguishes AVP-D from PP with good diagnostic performance [37], as does glucagon injection, with a copeptin threshold of 4.6 pmol/L [38]. However, these two tests do not fully distinguish between partial AVP-D and PP. In these contentious cases, infusion of hypertonic saline solution is debatable, as it necessarily requires hospitalization and close monitoring of natremia. It is the test that best distinguishes partial AVP-D from PP (with a copeptin threshold of 4.9 pmol/L) [39], but clinical tolerance is poor.

3.3.2. Imaging

Congenital pituitary deficiencies can be associated with a malformative anomaly of the hypothalamic-pituitary region, in 50–100% of cases of CPHD, and more rarely in cases of isolated congenital GHD [40]. This anomaly may consist in:

- a hypoplastic pituitary (< 3 mm);
- an ectopic posterior pituitary gland associated or not with pituitary stalk interruption syndrome (PSIS: characterized by an interrupted or thin pituitary stalk [< 1 mm] ± anterior pituitary hypoplasia or aplasia);
- an enlarged homogeneous pituitary gland;
- an empty sella turcica;
- septo-optic dysplasia, defined by the association of at least 2 of the following disorders: optic nerve hypoplasia, midbrain anomaly in the form of absence of the septum pellucidum and/or corpus callosum.

PSIS can result in an anterior pituitary deficit and moderate hyperprolactinemia, secondary to the disappearance of inhibitory dopaminergic tonus. Growth hormone deficiency may be complete, partial, isolated or associated with other deficits [41–45].

Empty sella syndrome is a separate entity, often revealed as incidentaloma. In adults, it is defined as herniation of the subarachnoid spaces into the sella turcica and is associated with pituitary deficit in 20–30% of cases [46,47].

On MRI, absence of physiological posterior pituitary T1 hyperintensity does not contribute to AVP-D diagnosis, being absent in 10% of healthy individuals.

In cases of gonadotropic deficiency, MRI can be used to assess olfactory bulb abnormalities. Patients with Kallmann syndrome (KS) usually present with unilateral or bilateral olfactory bulb agenesis, olfactory tract agenesis and/or gyrus malformation associated with anosmia/hyposmia. However, a few KS patients have normal olfactory structures despite clinically confirmed anosmia [48,49].

Other intracranial anomalies may be associated: agenesis of the olfactory bulbs and/or olfactory tract, holoprosencephaly, schizencephaly, heterotopia, Arnold-Chiari malformation, cerebellar malformation, persistent craniopharyngeal canal, microphthalmia, hypothalamic hamartoma.

Identification of a structural abnormality of the hypothalamic-pituitary region and/or of the brain, optic or olfactory structures provides strong diagnostic and etiological evidence. However, normal MRI findings do not rule out diagnosis of hypopituitarism.

3.3.3. Genetic diagnosis

In the absence of a specific syndromic form or previously documented familial form, it is advisable for the index case to undergo genetic analysis of a panel of the most prevalent genes, using next-generation sequencing (NGS). These analyses may be completed or preceded by CGH array study, particularly in syndromic forms. When all these analyses are negative, it is possible to continue investigations with whole-genome sequencing and trio analysis (index case + parents).

There are more than 30 genes involved in the causes of pituitary deficiency, whether isolated or combined, syndromic or not [2,50].

The performance of genetic analysis is strongly affected by whether the deficiency is familial or sporadic, isolated or multiple, and by the presence or absence of extra-pituitary malformations (syndromic or non-syndromic forms). In two large international cohorts of CPHD and IGHD, a genetic cause was identified in between 7% and 10% of cases [2,51]. This percentage varies from 2.6% in sporadic cases to 29.5% in familial cases, and from 3.8% in syndromic forms of CPHD to 12.5–17% in non-syndromic forms.

Genetic analysis is useful for guiding monitoring.

3.3.3.1. Non-syndromic forms.

3.3.3.1.1. Multiple deficiencies. Multiple congenital hypopituitarism with normal MRI is linked to mutations in genes affecting transcription factors involved in pituitary terminal ontogeny. Genetic causes are rarely identified, except in familial cases.

Mutation in *PROPI* is the most frequently identified genetic etiology of non-syndromic CPHD, the frequency of which varies, up to 17% of cases, according to geographical origin [2,51]. Pituitary deficits may initially be isolated or dual, and later become complete (GHD, TSHD, LH/FSHD, and PRLD). Onset of ACTHD is inconstant (40%) and unpredictable (sometimes only in adulthood), requiring prolonged and regular follow-up. *PROPI* mutations can induce pituitary hypertrophy, which must be differentiated from adenoma. Other currently known genetic causes of CPHD are rarer: *POU1F1*, *LHX3*, *LHX4*, *TBX19*, *GH1* gene mutations (non-exhaustive list) (Table 1).

3.3.3.1.2. Isolated deficit. Isolated non-syndromic congenital hypopituitarism is most often linked to an abnormality of the gene concerned, or of the elements regulating expression of the gene.

3.3.3.1.2.1. Isolated growth hormone deficiency (IGHD). IGHD is classified according to mode of inheritance into 3 types: type I (autosomal recessive), type II (autosomal dominant) and type III (X-linked). Mutations in the growth hormone gene (*GH1*) are the most frequent (three-quarters of cases with genetic diagnosis: i.e., up to 5.5% of cases) [51]. In fewer than 10% of cases, *GH1* mutations are associated with other deficits [51]. Mutations in the GH-releasing hormone receptor gene (*GHRHR*) are the second most common cause of IGHD, with autosomal recessive inheritance (IGHD type I). Other identified genetic causes are rare (*GHSR*) or exceptional (*RNPC3*).

Sometimes GHD sets in before other deficits through mutations in genes causing CPHD: usually *PROPI*, exceptionally *POU1F1* [52,53]. X-linked IGHD through *SOX3* mutation results in intellectual disability of variable degree, ectopic posterior pituitary syndrome or, rarely, other deficits (CPHD) [50,54].

3.3.3.1.2.2. Isolated thyroid deficiency. The primary genetic cause appears to be mutations in *IGSF1* [55], causing a constant thyrotropic deficit of variable intensity. Sometimes other deficits (GH, PRL, ACTH) are associated, which are often reversible. Associated signs are constant macro-orchidism in men and ovarian cysts in

women. Isolated thyroid deficiency in adults is mainly caused by mutations in the *TRHR* gene. In men, the association of central hypothyroidism and deafness should suggest diagnosis of an X-linked *TBL1X* mutation [21]. *TSHB* mutations are very rare [16].

3.3.3.1.2.3. Isolated adrenocorticotrophic hormone deficiency (IAC-THD). *TBX19* mutations cause 20–40% of isolated corticotrophic deficits [2]. Diagnosis is usually neonatal, but sometimes later. The families often have a history of neonatal death.

NFKB2 mutations can induce IACTHD, often associated with a variable common immune deficiency [56].

3.3.3.1.2.4. Isolated congenital hypogonadotropic hypogonadism (ICHH). The genetics of ICHH, with anosmia (KS) or without anosmia (normosmic, CHHn) is characterized:

- by great genetic heterogeneity, with more than 35 genes identified as involved in neuronal development and migration or gonadotropic signaling;
- by a great diversity of monogenic or oligogenic modes of transmission [57].

There are a dozen more prevalent genes for which association with CHH has been validated with a high-level of evidence [11], including *KALI/ANOS1*, specific to X-linked recessive KS, *FGFR1*, *PROKR2*, *PROK2*, responsible for both KS and CHHn, and the CHHn-specific genes *GNRHR*, *GNRH1*, *KISS1R*, *KISS1*, *TACR3*, *TAC3*.

3.3.3.2. Syndromic forms. The presence of extra-pituitary signs warrants a clinical genetic consultation for an appropriate etiological approach (specific analysis, CGH array or NGS panel, depending on clinical orientation).

In hypopituitarism associated with PSIS, genetic causes are diverse and rarely identified (<10%) [58,59]. The most frequent genetic cause is currently linked to *GLI2* mutations [51] or exceptionally *LHX4*, *HESX1*, *SOX3*, *PROKR2* mutations.

GLI2 mutations are implicated in IGHD or CPHD with PSIS, alone or associated with polydactyly, cleft lip and palate or other manifestations, or hypomorphic forms of holoprosencephaly. Expression is extremely variable for the same genotype (IGHD or CPHD with or without polydactyly) and penetrance is incomplete, at 30–80% [60]. Rare cases of mutations in the FGF pathway (*FGF8* and *FGFR1*) may also be associated with CPHD or IGHD with PSIS [61,62].

In case of ocular malformation, *OTX2* mutations are major causes of IGHD or CPHD with PSIS and ocular signs of varying severity, microphthalmia/anophthalmia [2]. More rarely, *SOX3* mutations are found. *HESX1* mutations were reported to be associated with SOD with IGHD or CPHD [2].

The involvement of *PROKR2* mutations in PSIS with CPHD is currently debated [63]. The lack of genotype-phenotype correlation suggests oligogenic inheritance [64].

Hypopituitarism may be secondary to hypothalamic dysfunction, and notably alterations in the Sonic Hedgehog pathway, with neurodevelopmental disorders (*GLI2*, *SHH*, *FGF8*), or severe genetic obesity (Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, *POMC*, *LEP*, *LEPR* mutations). In the latter case, the genetic approach relies on specific gene panels [65].

3.4. Screening for comorbidities

Malformations related to developmental abnormalities of the hypothalamic-pituitary region during embryogenesis explain the need for a systematic work-up in search of extra-pituitary anomalies in case of multiple pituitary deficiency or syndromic forms. Neurodevelopmental disorders are most frequently observed when associated cerebral anomalies are seen on MRI [28]. Epilepsy is rare. Ophthalmological disorders, present in 10 to 20% of cases, are highly variable [66]. Coloboma is a closure anomaly that can

Table 1
Main genes involved in congenital pituitary deficiencies (non-exhaustive).

List of genes included in the panel (HGNC international gene nomenclature)	Transcript of interest (NM)	Transmission	Pathology (in order of frequency)	Frequently associated extra-pituitary disorders (not exhaustive)
<i>FGF8</i>	NM.033163	AD, AR	Other, CPHDS, IGHDS	Midline anomalies: holoprosencephaly, DSO, cleft lip and palate, oligodontia
<i>FGFR1</i>	NM.023110	AD	Other, CPHDS, IGHDS	Midline anomalies: holoprosencephaly, DSO, cleft lip and palate, oligodontia
<i>GH1</i>	NM.000515	AD, AR	IGHDNS, CPHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>GHRHR</i>	NM.000823	AR	IGHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>GHSR</i>	NM.198407	AR, AD	IGHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>GLI2</i>	NM.005270	AD	Other, CPHDS, IGHDS	Midline anomalies: holoprosencephaly, PSIS, cleft lip and palate, postaxial polydactyly, dysmorphia
<i>HESX1</i>	NM.003865	AR, AD	Other, CPHDS, IGHDS	Cerebral anomalies (Chiari, hydrocephalus, craniostenosis, microcephaly, cerebellar atrophy, corpus callosum anomaly, interventricular septum, turcic region anomalies[PSIS, SOD, sella turcica hypoplasia]), ophthalmological (optic nerve hypoplasia/chiasma malformation/blindness/amblyopia/coloboma), and extracerebral (heart disease, dental agenesis, syringomyelia. . .)
<i>IGSF1</i>	NM.001555	X	ITSH, CPHDNS	Macro-orchidism
<i>LHX3</i>	NM.178138 NM.014564	AR, AD	CPHDS	Cerebral anomalies (corpus callosum agenesis, deafness) and extra-cerebral anomalies (neck rotation anomaly without vertebral malformation, renal dystrophy)
<i>LHX4</i>	NM.033343	AD	CPHD, CPHDNS, IGHDS	Cerebral anomalies (Chiari, corpus callosum hypoplasia, sella turcica hypoplasia, cerebellar tonsils, epilepsy) and extracerebral anomalies (coloboma, aortic coarctation)
<i>NFKB2</i>	NM.001322934.2	AD	CVID10, and IACTHD	Common variable immune deficiency
<i>OTX2</i>	NM.021728	AD	Other, CPHDS, IGHDS	Ophthalmological abnormalities (anophthalmia or microphthalmia, retinal abnormalities, optic nerve atrophy), neurodevelopmental disorders
<i>POU1F1</i>	NM.001122757 NM.000306	AR, AD	CPHDNS, IGHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant.
<i>PROKR2</i>	NM.144773	AR, AD	Other, CPHDS, IGHDS	Cerebral abnormalities (PSIS, anosmia, arachnoidocele)
<i>PROP1</i>	NM.006261	AR	CPHDNS, IGHDNS, CPHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>RNPC3</i>	NM.017619	AR	IGHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>SOX2</i>	NM.003106	AD	Other, CPHDS	Ophthalmological anomalies (anophthalmia or microphthalmia, short palpebral fissures, optic nerve hypoplasia), cerebral anomalies (microcephaly, corpus callosum anomaly, hypothalamic hamartoma, neurodevelopmental disorder, deafness), and extracerebral anomalies (dysmorphia, dental anomaly, esophageal atresia)
<i>SOX3</i>	NM.005634	X	Other, IGHDNS, IGHDS, CPHDS	Cerebral abnormalities (SOD, neurodevelopmental disorder)
<i>TBX19</i>	NM.005149	AR	IACTHD, CPHDNS	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>TRHR</i>	NM.003301	AR	ITSHD	The presence of extrapituitary anomalies should raise suspicion of another associated variant
<i>TSHB</i>	NM.000549	AR	ITSHD	The presence of extrapituitary anomalies should raise suspicion of another associated variant

affect the iris, lens, choroid, macula, and optic nerve. It may be accompanied by microphthalmia and, in severe forms, be responsible for functional impairment. In cases of optic nerve damage, vision is compromised. Nystagmus may be a symptom of bilateral visual impairment (severe bilateral coloboma, optic hypoplasia) or a symptom of oculomotor anomaly. Midline craniofacial anomalies include bulging forehead, hypertelorism, midface hypoplasia (empty nose syndrome of variable intensity, nasal malformation, choanal stenosis or atresia, piriform orifice stenosis), cleft lip, cleft palate, palatal anomaly, dental agenesis, single median incisor, helix anteversion, deep philtrum and thin upper lip, and short chin. Cleft lip and palate can have an impact on speech quality. Hearing loss may be associated with congenital pituitary deficiency [2]. Lastly, the presence of associated malformations may help to identify syndromic features such as CHARGE syndrome (heart disease,

deafness, hemivertebrae, etc.), KS (anosmia, renal hypoplasia in a male), Webb-Dattani syndrome (hydronephros) or Culler-Jones syndrome (post-axial polydactyly).

Hypothalamic dysfunction may be at the root of pituitary insufficiency, and include more severe neurometabolic impairment: severe obesity due to impaired satiety and basal metabolic rate, hypothalamic adiposia with neurogenic hypernatremia, respiratory or thermal neurovegetative disorder, behavioral disorder.

4. Therapeutic management

The management, treatment, and follow-up of these patients must be explained and carried out within an expert center. The objectives are to correct symptoms and to prevent complications

and acute decompensation, and to optimize social and occupational integration.

4.1. Hormone replacement

4.1.1. Growth hormone deficiency (GHD)

Adult GHD is associated with a number of negative consequences that explain indications for replacement therapy in adulthood, after other deficiencies have been corrected. The main signs associated with GHD are asthenia, reduced muscular performance and muscle mass, impaired quality of life, changes in body composition to the lack of lean relative to fat mass, osteopenia or osteoporosis, increased cardiovascular risk due to lipid abnormalities and insulin resistance, and cardiac alterations [67]. However, the reported efficacy of GH treatment in adults in the context of congenital deficiency is limited [68,69]. It should be noted that, in untreated multiple pituitary deficiencies, there is sometimes still no growth plate fusion in adulthood when GH treatment is initiated, which can result in a gain in height that is sometimes significant [70,71].

In case of well-documented constitutional GHD in childhood, GHD may be considered as persisting into adulthood, without the need for further dynamic investigations (see Diagnosis section). In such cases, treatment is continued with gradual dose reduction according to IGF-I values. In the absence of contraindications, GH treatment may be started at an initial dose of 0.2 to 0.4 mg/day in adult patients under 60 years of age, or 0.1 to 0.2 mg/day after 60 years of age. Dose is adjusted to maintain IGF-I values between the mean and upper limit of normal for age and gender.

4.1.2. Thyroid deficiency

The goal is to have fT4 in the upper range of the reference values, 6 to 8 weeks after starting treatment or changing dose. Replacement may be considered insufficient in case of normal fT4 and TSH > 1 mU/L [72]. Practice shows that patients are liable to be under-dosed [73]. In adults, a weight-adjusted dose of 1.5–1.6 µg/kg/d was shown to improve metabolic parameters and markers of peripheral thyroid hormone impregnation [74–76]. In case of cardiovascular comorbidity, a lower dose, between 1 and 1.2 µg/kg/d, is recommended [17]. In patients over 75 years of age with fT4 at the lower limit, indications for treatment are discussed [77]. Certain situations, such as pregnancy or treatment with growth hormone or estrogen, require higher dosage.

4.1.3. Gonadotropic deficiency

Management and treatment of gonadotropic deficiency must be proposed, implemented and monitored by specialized endocrinologists in an expert center.

In case of late management of an impubertal young woman whose final size is no longer an issue, treatment with 17 β-estradiol by oral or transdermal route should be increased progressively more rapidly than in adolescents, to allow her to acquire secondary sexual characteristics [78]. Transdermal or oral estradiol has the same impact on metabolic parameters (bone mineralization, BMI, and lipid and blood glucose levels) [79]. After the induction period, or immediately in the case of partial deficiency with breast development, progestin therapy is combined with estrogen therapy, usually for 10 days per month, as exposure to estrogen alone induces a long-term risk of endometrial cancer. This combined treatment may be sequential or continuous, depending on the patient's choice [78]. In the absence of contraindications, estrogen-progestin contraception can be used.

Two therapeutic options can be proposed to induce puberty in an impubertal adult male in case of late management:

- treatment with androgens (usually intramuscular testosterone) in increasing doses up to an adult dose (250 mg/15–28d) [80,81];
- treatment with gonadotropins or GnRH pumps, stimulating both testicular Leydig and Sertoli functions.

This treatment leads to testicular growth, progressive androgenization and, ultimately, spermatogenesis [82]. The latest data in the literature suggest that an initial treatment of 2 to 4 months' FSH alone before starting hCG therapy improves subsequent fertility [83,84] with shorter treatment required to obtain spermatozoa [85,86].

Maintenance treatment with androgens is then lifelong, unless there are any contraindications, urological or cardiological in particular. Testosterone is used in various forms, with availability varying according to country:

- intramuscular: enanthate, at variable doses and frequencies; undecanoate, with more widely spaced injections (10–14 weeks);
- oral: undecanoate;
- transdermal: testosterone gel.

4.1.4. Corticotropic deficiency

The aims of glucocorticoid replacement are:

- to correct the symptoms of cortisol secretion insufficiency;
- to ensure optimal quality of life;
- to avoid chronic overdosage, which can generate excess morbidity and mortality;
- to prevent onset of acute adrenal insufficiency, which can result from underdosing, poor compliance or failure to adapt to an acute situation.

Hydrocortisone is used in first-line. Treatment is lifelong in all cases of constitutional corticotropic deficiency. First-generation long-acting glucocorticoids (prednisolone, dexamethasone) should only be used on expert advice if hydrocortisone is not sufficiently effective due to its short-acting pharmacokinetics. Second-generation sustained-release glucocorticoids are not covered by health insurance in France. The hydrocortisone replacement dose should be as low as possible, to avoid the excess cardiovascular and infectious morbidity and mortality, bone damage and impaired quality of life associated with chronic glucocorticoid overdose. Mortality correlates positively with total daily hydrocortisone dose and dose/weight ratio [87]. In adults, a dose of 10–20 mg/d is recommended, divided into 2 or 3 doses, with the highest in the morning. Published studies showed no superiority between 2- or 3-dose daily regimens regarding quality of life [88].

4.1.5. Arginine vasopressin deficiency (AVP-D) (central diabetes insipidus)

Arginine vasopressin deficiency (AVP-D) is often quite well tolerated if water intake is sufficient, freely available and the sensation of thirst is preserved. If this is not the case, there is a major and rapid risk of dehydration and even collapse. Treatment is based on desmopressin, which has an 8-hour duration of action. It is available as an injectable solution (IV, IM, SC), nasal spray or oral lyophilisate for sublingual administration. In adults, the usual doses are 1 to 2 µg 1–2 times a day for the injection, 5 to 20 µg 2–3 times a day for the endonasal route (spray), and 60 to 120 µg 2–3 times a day for the lyophilisate. The risk of hyponatremia appears to be lower with sublingual than intranasal forms [89–91]. This treatment is usually started at a low dose then gradually increased according to the input-output balance.

4.1.6. Prolactin deficiency

There is no treatment for prolactin deficiency.

4.2. Emergency management

4.2.1. Acute adrenal insufficiency

The main risk of corticotropic insufficiency is acute decompensation during an episode of somatic stress. The incidence of acute adrenal insufficiency is between 6 and 8.3 episodes per 100 adult patients per year, whether corticotropic or peripheral, with mortality still estimated in 2015 at 0.5 per 100 patients per year [92]. Signs suggestive of acute adrenal insufficiency include intense fatigue, nausea or vomiting, abdominal pain, hypoglycemia, hypotension, dehydration and, at the biological level, hyponatremia and hyperkalemia.

In situations of acute adrenal decompensation, treatment should be initiated as soon as the diagnosis is suspected, without waiting for biological confirmation [8]. A dose of 100 mg hydrocortisone hemisuccinate should be administered by intravenous or intramuscular injection, immediately followed by continuous intravenous infusion of hydrocortisone hemisuccinate (100 mg/24 h) or by intravenous or intramuscular bolus every 6 h [93]. Onset of hyponatremia during corticotropic decompensation is mainly linked to inappropriate secretion of the anti-diuretic hormone ADH, which is corrected by hydrocortisone. The administration of isotonic saline is reserved for situations of significant digestive loss or hemodynamic disorder. Hypoglycemia is rarely observed in adult corticotropic failure and should be treated with intravenous infusion of 10% glucose serum. Treatment should be adapted to the clinical and biological parameters (blood glucose and natremia) should be monitored closely. Hydrocortisone should be administered orally after symptoms have disappeared and the patient has resumed eating, at double or triple usual dose, in 3 doses per day, then gradually reduced to the usual dose over a few days.

Prevention of acute adrenal insufficiency requires patients to increase their daily dose of hydrocortisone in case of acute intercurrent illness, infection, traumatic or psychological stress, intense physical exercise, surgery or anesthesia. A dose of 60 mg hydrocortisone should be divided into 3 to 4 oral intakes during the day in stressful situations. In the absence of clinical improvement, or in the presence of vomiting preventing absorption of oral hydrocortisone, an injection of 100 mg hydrocortisone hemisuccinate should be made intramuscularly or subcutaneously, by the patient or a nurse [94]. Prevention also includes therapeutic education for patients and families, with the following objectives:

- to be aware of situations at risk of decompensation;
- to be familiar with protocols for adapting glucocorticoid replacement in situations of medical and surgical stress;
- to carry an adrenal insufficiency card;
- to know under what circumstances and how to perform an intramuscular or subcutaneous injection of hydrocortisone if necessary (vomiting, malaise, decompensation not manageable by increasing oral treatment, etc.).

4.2.2. Arginine vasopressin deficiency

4.2.2.1. *Risk of hyponatremia.* Signs of water intoxication (headache, nausea, confusion, convulsions) should be explained to the patient and people around him/her. They may occur as a result of the therapeutic overdosage, excessive drinking, drug interference (particularly non-steroidal anti-inflammatory and psychotropic drugs) or inappropriate infusion. If they occur, treatment should be discontinued until polyuria returns.

Natremia should be particularly monitored in cases of uncompensated corticotropic insufficiency or dilated urinary tract masking polyuria.

4.2.2.2. *Risk of hypernatremia.* In the event of dehydration, urgent treatment with intravenous glucose serum or pure water, possibly via gastric tube, may be combined with injectable desmopressin. Diuresis, input/output balance, weight and natremia should be monitored on a multi-daily, then daily, basis.

In these situations, however, it is very important not to correct the natremia too quickly (less than 12 mmol/24 hrs), in order to avoid wide fluctuations and secondary morbidity and mortality.

Hypernatremia is mostly encountered in cases of associated adipsia [95]. In this case, the use of a portable natremia monitoring device (i-STAT analyzer: www.pointofcare.abbott) and a natremia-based water administration scale are useful tools. Weight monitoring is an important element of monitoring [96].

4.3. Therapeutic patient education (TPE)

TPE must be offered to patients and their families to help them understand their condition, comply with treatment, manage emergency situations safely, optimize social integration, and improve the quality of life of patients and their families.

5. Follow-up

5.1. Frequency and content of consultations

Endocrinology consultations should be scheduled regularly, every 6 months to 1 year.

Through questioning, clinical examination and paraclinical tests, the physician assesses correct substitution of all axes. Complications and comorbidities are investigated. The patient's understanding of their disease and treatment, as well as what to do in emergency situations, must be assessed during consultations, with a therapeutic education approach whenever possible. The patient's lifestyle, social relationships and psychological state are also assessed.

5.2. Adapting hormone supplements

5.2.1. Somatotrophic deficiency

After initiation of treatment, monitoring is recommended after 1–2 months and then every 6 months. GH doses are adjusted to maintain IGF-I values between the mean and the upper reference limit, and to avoid any side effects associated with overdosing (headache, edema, arthralgia or carpal tunnel syndrome). Epidemiological data show no increase in the risk of type 1 or type 2 diabetes [97]. Nevertheless, it remains standard practice to measure glycemic control by means of blood glucose and HbA1c levels before and during treatment. Except in high-risk situations such as obesity or acanthosis nigricans, glucose tolerance test is not recommended. It is important to detect the patient's fear of side effects and understanding of treatment benefits, to encourage compliance. GH replacement therapy does not increase the risk of long-term morbidity and mortality in patients treated for constitutional deficit [98].

5.2.2. Corticotrophic deficiency

It is recommended that monitoring of glucocorticoid replacement be based on well-being, looking for clinical signs of over- or under-dosage [99]. The dose of hydrocortisone should be adapted to weight and symptoms, and its distribution over the day should be adapted to symptomatology.

Chronic hydrocortisone overdose induces overweight, skin fragility, high blood pressure, increased risk of metabolic syndrome and cardiovascular (and particularly cerebrovascular) risk, leading to reduced life expectancy.

Conversely, hydrocortisone underdosing induces symptoms of adrenal insufficiency (asthenia, anorexia, weight loss, muscular pain or difficulty in practicing sports, and sleep disorder) and increases the risk of acute adrenal decompensation.

The use of quality of life scales, and in particular the AddiQol questionnaire, which has been validated in several countries, has been advocated to assess the adaptation of glucocorticoid replacement therapy in adults [100].

Biological markers, such as plasma cortisol measured after hydrocortisone intake, should not be used routinely, but could be useful in cases of suspected inappropriate glucocorticoid replacement [99].

5.2.3. Thyroid deficiency

Monitoring 6–8 weeks after starting treatment and after each change in dose is recommended, with the aim of achieving fT4 at the upper end of the normal range and TSH < 1 mIU/L. Initial monitoring may include fT4 and TSH measurements, then annual fT4 monitoring is sufficient. If growth hormone or estrogen therapy is introduced or discontinued, monitoring should be carried out.

5.2.4. Gonadotropic deficiency

During androgen maintenance therapy in adult males, regular clinical and biological monitoring is recommended (including testosterone, CBC and PSA in men over 55) as well as monitoring of bone densitometry [101].

In women, regular gynecological check-up is recommended.

5.2.5. Arginine vasopressin deficiency

The aim is to achieve normal diuresis in terms of volume and frequency, with at least one sufficient urination between 2 doses. In the absence of diuresis between 2 doses, the patient should postpone or cancel desmopressin intake. The main monitoring factors are diuresis and thirst, a rapid reflection of hydration status. A blood ionogram should be carried out at least every 6 months, if necessary combined with a urine osmolality assay before taking desmopressin.

5.3. Monitoring other routes

Pituitary hormone deficiencies may be present from the outset, or appear secondarily. Clinical and biological evaluation of other axes, and notably the corticotrophic axis, must therefore be regular during follow-up, including in adulthood. Screening for other deficits may be guided by the genetic cause, if identified.

5.4. Management of complications and/or comorbidities

5.4.1. Neurocognitive disorders

The occurrence of these complications depends on severity and possible delay in diagnosis, occurrence of deep and/or repeated hypoglycemia in early childhood, and any associated malformation [102]. In young adults, neuropsychological assessment should be carried out if necessary, with the aim of helping them to achieve maximum autonomy.

5.4.2. Visual impairment

An ophthalmological examination must be carried out systematically at the time of diagnosis, and appropriate care must be offered according to the situation (optical correction, surgical treat-

ment, referral to low-vision referral centers and associations for the visually impaired).

5.4.3. Ear, nose and throat (ENT) disorders

Treatment is carried out by an ENT specialist with appropriate hearing aids in case of hypoacusis and referral for odontologic treatment in case of associated dental malformation.

5.4.4. Metabolic and cardiovascular complications

Rates of metabolic syndrome and cerebrovascular events are higher in case of multiple pituitary involvement, and especially of inadequate replacement [103].

5.4.5. Bone complications

A decrease in bone mineral density, depending on the duration, age at onset and severity of the deficit, is very common in adults with hypopituitarism [104]. Hydrocortisone overdose is also a risk factor. Assessment of bone health is therefore essential, with particular attention paid to the risk of vertebral fracture.

Recommendations comprise:

- checking for adequate calcium and vitamin D intake;
- encouraging regular physical activity;
- detecting osteopenia by bone densitometry at the first adult consultation, then every 5 years if there are no abnormalities. More frequent check-ups should be scheduled in the event of decreased BMD, and contributing factors should be screened for: poor compliance with hormone replacement therapy, alcohol abuse and/or smoking;
- explaining the importance of continuing hormone replacement therapy in women under oral contraception, at least until the physiological age of menopause (50), to prevent risk of osteoporosis.

6. Patient support

6.1. Psychological care

Psychological support is often necessary, and is appropriate for individual patients at different stages. Particular attention must be paid to the psychological experiences of those around the patient.

6.2. Social and occupational integration

Cognitive repercussions of the pathology are possible, and can sometimes lead to difficulties in social integration. The intervention of a social worker or even an occupational physician may be necessary.

6.3. Recourse to patient associations

All healthcare professionals and patients should be aware of the existence of patient associations involved in these diseases. In the field of rare diseases, they help create links between patients, share experiences and information, and promote acceptance of the disease. They can also help improve patient care by providing information on recognized care networks (expert centers).

7. Special situations

7.1. The transition

Patients with somatotrophic insufficiency, including those with ectopic posterior pituitary gland (possibly reversible deficit), should be reassessed hormonally for somatotrophic function after

the end of growth. First, IGF-I is measured, and, if IGF1 is $\leq 2\sigma$, a stimulation test using insulin hypoglycemia is performed (or glucagon stimulation test or a test combining GHRH plus arginine if insulin hypoglycemia is contraindicated). However, this reassessment is not necessary in case of multiple involvement (≥ 3 pituitary lineages affected) or severe congenital pituitary deficiency, or of pituitary deficiency related to an identified genetic cause and/or to a cerebral or craniofacial midline anomaly [105]. In the event of persistent somatotrophic insufficiency, resumption of GH replacement therapy is recommended. In some cases of reversible somatotrophic insufficiency, long-term follow-up with reassessment a few years later may be necessary. This is particularly important if IGF-I remains within the lower limit of normal (between -1 and -2σ) under correct nutritional conditions, or if there is an ectopic posterior pituitary gland or pituitary stalk interruption, as one or more hormonal insufficiencies may occur at a later stage.

In the case of substituted isolated gonadotropic insufficiency, the gonadotropic axis should be reassessed after the end of puberty, after stopping sex steroids for 1 to 3 months, as isolated gonadotropic insufficiency may in some cases be reversible [84].

Reassessment of thyroid function may be necessary after discontinuation of GH therapy, if thyroid insufficiency was diagnosed after the introduction of GH.

7.2. Fertility and pregnancy

Genetic counseling is necessary when the genetic abnormality involved in anterior pituitary insufficiency is known.

7.2.1. In men

Prior spermogram assessment of spontaneous spermatogenesis should be proposed. Treatment to stimulate spermatogenesis is most often based on gonadotropins administered by subcutaneous self-injection [106] or, more rarely, GnRH pumps [107]. The treatment of choice is currently based on FSH and hCG [107]. hCG is the same molecule as LH, but is preferred for therapeutic purposes because of its greater efficacy and longer half-life [108]. Monotherapy with hCG can restore spermatogenesis in men with partial congenital hypogonadotropic hypogonadism (CHH) with testicular volume > 4 mL, but this treatment, even prolonged, is generally ineffective in complete CHH and/or when testicular volume is < 4 mL [109]. These protocols allow spermatozoa to be obtained in the ejaculate in 75% of cases [107] after 3 to 19 months' treatment [109]. In patients with a history of cryptorchidism, prognosis is poorer and treatment time may be longer [110].

Administration of exogenous testosterone before stimulating spermatogenesis has no adverse effect on fertility prognosis, according to a recent meta-analysis [107].

Regular clinical monitoring is required (testicular volume in particular) as well as monitoring of biological parameters (LH, FSH, total and bioavailable testosterone, inhibin B) and sperm parameters. Treatment to stimulate spermatogenesis is generally continued until the 2nd trimester of the partner's pregnancy in the event of spontaneous miscarriage. Once spermatogenesis has been achieved, sperm cryopreservation should be proposed, before resuming androgen replacement therapy.

7.2.2. For women

It is important to bear in mind that AMH levels are underestimated in cases of CHH. As such, it is not a good marker of ovarian reserve in CHH.

If the CHH is partial, the first-line treatment is clomiphene citrate. If the hypogonadism is complete, it is advisable to induce folliculogenesis by administering a gonadotropin treatment combining LH and FSH. When hypogonadism is of hypothalamic origin, nutritional and psychological management is advisable before star-

ting treatment with a GnRH pump. This treatment is implemented if BMI is ≥ 18.5 [111]. The cumulative pregnancy rate following induction of folliculogenesis in CHH ranged from 47% to 100%, depending on the study [112]. The rate of twin pregnancies is no higher than for stimulation in another context (e.g., polycystic ovary syndrome).

There are few published series including patients with HH combined with other anterior pituitary deficiencies, treated in the context of a desire for pregnancy:

- in cases of thyrotrophic deficiency, a 30% increase in thyroid hormone dosage is recommended as soon as pregnancy is diagnosed. Free T4 should be measured every 4 to 6 weeks [113];
- in case of corticotrophic deficiency, the dose of hydrocortisone should be increased by 30% during the 3rd trimester of pregnancy, and an injection of hydrocortisone 100 mg should be made at delivery. It is not recommended to measure cortisol levels during pregnancy, as they are physiologically high [114];
- in case of known GH deficiency in childhood, the probability of pregnancy is somewhat lower than in HH without GH deficiency [115]. It is not necessary to maintain GH treatment during pregnancy [116]. In case of known GH deficiency after childhood, a higher rate of placental dysfunction may be expected, but data concerned small samples;
- in case of lactotropic deficiency, breast-feeding is generally not possible. The patient must be informed of this;
- in AVP-D, desmopressin treatment may need to be increased during the first trimester of pregnancy. Desmopressin is not degraded by placental vasopressinases.

Few studies have evaluated the route of delivery in CHH. The C-section rate was high in the series published to date.

7.3. The elderly (> 60–65 years)

7.3.1. In case of thyrotrophic deficiency

A reduction in levothyroxine dose should be considered in elderly patients, particularly if there are associated cardiovascular pathologies, or if free T4 values are above or close to the upper limit of normal. The dose usually recommended is lower in the elderly: between 1.0 and 1.2 $\mu\text{g}/\text{kg}/\text{d}$ [17].

7.3.2. In case of corticotrophic deficiency

There are no specific recommendations for the elderly. It is advisable to use the minimum dose necessary to correct symptoms such as asthenia and hypotension, and to maintain a normal blood ionogram. There are no indications for additional with dehydroepiandrosterone (DHEA) treatment due to lack of solid safety and efficacy data in the elderly.

7.3.3. In case of somatotrophic deficiency

The necessary dose of GH in elderly subjects is lower than in younger adults and must be adapted to IGF-I levels. Some studies reported benefit in terms of cognition, lipid balance or quality of life in elderly subjects [117]. However, there are few safety data in this population, and no data for subjects over 80.

After more than 20 years' experience with GH therapy in adults, there are no data to suggest that this treatment increases the risk of cancer. However, ongoing long-term surveillance and standard cancer screening should be carried out in patients continuing this treatment.

7.3.4. In case of gonadotropic deficiency

In women, there is no indication for continuing estrogen-progestin hormone therapy beyond the physiological age of menopause, at around 50. If it is continued, it falls within the scope

of menopausal hormone therapy, for which the risk-benefit ratio must be discussed with the patient.

In men, the continuation of age-appropriate testosterone replacement therapy will be discussed in the light of cardiovascular disease and hormone-dependent cancer. This treatment is not associated with an increased risk of prostate cancer or benign prostatic hyperplasia, but there are inconsistencies between studies. It requires regular clinical, PSA and hematocrit monitoring. It is contraindicated in cases of prostate cancer, breast cancer, elevated PSA, elevated hematocrit, uncontrolled congestive heart failure, etc. [118].

7.3.5. AVP-D

Desmopressin treatment may require close monitoring of the input-output balance and blood ionogram, with dose adjustment in situations likely to lead to dysnatremia (drug interference, infusion, intercurrent illness, etc.). Care must be taken to maintain free access to water, particularly for elderly people with reduced autonomy. If thirst is impaired, fixed water intake may be necessary, with desmopressin adapted to weight and diuresis.

8. Conclusion

The presentation of congenital pituitary deficiency is highly variable (from isolated hormone deficiency to pan-hypopituitarism, syndromic or non-syndromic forms). Diagnosis of congenital forms is most often made in childhood, but may be made in adulthood in certain cases. Genetic analysis is an integral part of management (NGS panel with or without CGH array with or without genomic analysis), sometimes helping to guide long-term monitoring. Treatment is based on hormone replacement adapted to sex and period of life (fertility, pregnancy, old age), as well as specialized, often multidisciplinary, follow-up. Therapeutic education of patients and their families is essential, to prevent complications and acute decompensation, but also to ensure optimal quality of life and social integration.

Funding

The preparation of national diagnosis and treatment guidelines for congenital hypopituitarism was funded by the French government (Direction Générale de l'Offre de Soins 2019). This article is based on the guidelines published on the French Health Authority (HAS) website on 1 December 2021.

Disclosure of interest

The authors declare that they have no competing interest.

Références

- [1] argumentaire_pnds_deficit_hypophysaire_congenital.pdf, https://www.has-sante.fr/upload/docs/application/pdf/2021-11/argumentaire_pnds_deficit_hypophysaire_congenital.pdf (accessed November 17, 2023).
- [2] Jullien N, Saveanu A, Vergier J, et al. Clinical lessons learned in constitutional hypopituitarism from two decades of experience in a large international cohort. *Clin Endocrinol (Oxf)* 2021;94:277–89.
- [3] Doknic M, Gasic V, Stojanovic M, et al. Hypopituitarism in five PROP1 mutation siblings: long-lasting natural course and the effects of growth hormone replacement introduction in middle adulthood. *Pituitary* 2020;23:400–8.
- [4] Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. *N Engl J Med* 2019;380:2551–62.
- [5] Barreto VMP, D'Avila JS, Sales NJ, et al. Laryngeal and vocal evaluation in untreated growth hormone deficient adults. *Otolaryngol Head Neck Surg* 2009;140:37–42.
- [6] Menezes M, Salvatori R, Oliveira CRP, et al. Climacteric in untreated isolated growth hormone deficiency. *Menopause N Y N* 2008;15:743–7.
- [7] Monzani ML, Pederzoli S, Volpi L, et al. Sexual dysfunction: a neglected and overlooked issue in adult gh deficiency: the management of AGHD study. *J Endocr Soc* 2021;5:bvab002.
- [8] Young J, Xu C, Papadakis GE, et al. Clinical management of congenital hypogonadotropic hypogonadism. *Endocr Rev* 2019;40:669–710.
- [9] Cangiano B, Swee DS, Quinton R, et al. Genetics of congenital hypogonadotropic hypogonadism: peculiarities and phenotype of an oligogenic disease. *Hum Genet* 2021;140:77–111.
- [10] Bry-Gaillard H, Trabado S, Bouligand J, et al. Congenital hypogonadotropic hypogonadism in females: clinical spectrum, evaluation and genetics. *Ann Endocrinol* 2010;71:158–62.
- [11] Boehm U, Bouloux P-M, Dattani MT, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism – pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol* 2015;11:547–64.
- [12] Bonomi M, Vezzoli V, Krausz C, et al. Characteristics of a nationwide cohort of patients presenting with isolated hypogonadotropic hypogonadism (IHH). *Eur J Endocrinol* 2018;178:23–32.
- [13] Lawaetz JG, Hagen CP, Mieritz MG, et al. Evaluation of 451 Danish boys with delayed puberty: diagnostic use of a new puberty nomogram and effects of oral testosterone therapy. *J Clin Endocrinol Metab* 2015;100:1376–85.
- [14] Salenave S, Chanson P, Bry H, et al. Kallmann's syndrome: a comparison of the reproductive phenotypes in men carrying KAL1 and FGFR1/KAL2 mutations. *J Clin Endocrinol Metab* 2008;93:758–63.
- [15] Ravio T, Falardeau J, Dwyer A, et al. Reversal of idiopathic hypogonadotropic hypogonadism. *N Engl J Med* 2007;357:863–73.
- [16] Persani L, Cangiano B, Bonomi M. The diagnosis and management of central hypothyroidism in 2018. *Endocr Connect* 2019;8:R44–54.
- [17] Persani L, Brabant G, Dattani M, et al. 2018 European Thyroid Association (ETA) guidelines on the diagnosis and management of central hypothyroidism. *Eur Thyroid J* 2018;7:225–37.
- [18] Bonomi M. Hyperplastic pituitary gland, high serum glycoprotein hormone –subunit, and variable circulating thyrotropin (TSH) levels as hallmark of central hypothyroidism due to mutations of the TSH gene. *J Clin Endocrinol Metab* 2001;86:1600–4.
- [19] Borck G, Topaloglu AK, Korsch E, et al. Four new cases of congenital secondary hypothyroidism due to a splice site mutation in the thyrotropin-beta gene: phenotypic variability and founder effect. *J Clin Endocrinol Metab* 2004;89:4136–41.
- [20] Özhan B, Boz Anlaş Ö, Sarıkeçe B, et al. Congenital central hypothyroidism caused by a novel thyroid-stimulating hormone-beta subunit gene mutation in two siblings. *J Clin Res Pediatr Endocrinol* 2017;9:278–82.
- [21] Heinen CA, Losekoot M, Sun Y, et al. Mutations in TBL1X are associated with central hypothyroidism. *J Clin Endocrinol Metab* 2016;101:4564–73.
- [22] Bonomi M, Busnelli M, Beck-Peccoz P, et al. A family with complete resistance to thyrotropin-releasing hormone. *N Engl J Med* 2009;360:731–4.
- [23] Roche EF, McGowan A, Koulouri O, et al. A novel IGSF1 mutation in a large Irish kindred highlights the need for familial screening in the IGSF1 deficiency syndrome. *Clin Endocrinol (Oxf)* 2018;89:813–23.
- [24] Andrioli M, Pecori Giraldi F, Cavagnini F. Isolated corticotrophin deficiency. *Pituitary* 2006;9:289–95.
- [25] Diederich S, Franzen N-F, Bähr V, et al. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. *Eur J Endocrinol* 2003;148:609–17.
- [26] Krude H, Biebermann H, Luck W, et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 1998;19:155–7.
- [27] Cameron FJ, Khadilkar VV, Stanhope R. Pituitary dysfunction, morbidity and mortality with congenital midline malformation of the cerebrum. *Eur J Pediatr* 1999;158:97–102.
- [28] Garcia-Filion P, Epport K, Nelson M, et al. Neuroradiographic, endocrinologic, and ophthalmic correlates of adverse developmental outcomes in children with optic nerve hypoplasia: a prospective study. *Pediatrics* 2008;121:e653–9.
- [29] Yuen KCJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. *Endocr Pract* 2019;25:1191–232.
- [30] Persani L, Ferretti E, Borgato S, et al. Circulating thyrotropin bioactivity in sporadic central hypothyroidism. *J Clin Endocrinol Metab* 2000;85:3631–5.
- [31] Favresse J, Burlacu M-C, Maiter D, et al. Interferences with thyroid function immunoassays: clinical implications and detection algorithm. *Endocr Rev* 2018;39:830–50.
- [32] Chanson P, Guignat L, Goichot B, et al. Group 2: adrenal insufficiency: screening methods and confirmation of diagnosis. *Ann Endocrinol* 2017;78:495–511.
- [33] Rosner W, Hankinson SE, Sluss PM, et al. Challenges to the measurement of estradiol: an endocrine society position statement. *J Clin Endocrinol Metab* 2013;98:1376–87.
- [34] Bry-Gaillard H, Larrat-Ledoux F, Levaillant J-M, et al. Anti-Müllerian hormone and ovarian morphology in women with isolated hypogonadotropic hypogonadism/Kallmann syndrome: effects of recombinant human FSH. *J Clin Endocrinol Metab* 2017;102:1102–11.
- [35] Braslavsky D, Grinspon RP, Ballerini MG, et al. Hypogonadotropic hypogonadism in infants with congenital hypopituitarism: a challenge to diagnose at an early stage. *Horm Res Paediatr* 2015;84:289–97.
- [36] Christ-Crain M, Winzeler B, Refardt J. Diagnosis and management of diabetes insipidus for the internist: an update. *J Intern Med* 2021;290:73–87.

- [37] Winzeler B, Cesana-Nigro N, Refardt J, et al. Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. *Lancet Lond Engl* 2019;394:587–95.
- [38] Atila C, Gaisl O, Vogt DR, et al. Glucagon-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a double-blind, randomized, placebo-controlled study. *Eur J Endocrinol* 2022;187:65–74.
- [39] Fenske W, Refardt J, Chifu I, et al. A copeptin-based approach in the diagnosis of diabetes insipidus. *N Engl J Med* 2018;379:428–39.
- [40] Pampanini V, Pedicelli S, Gubinelli J, et al. Brain magnetic resonance imaging as first-line investigation for growth hormone deficiency diagnosis in early childhood. *Horm Res Paediatr* 2015;84:323–30.
- [41] Bar C, Zadro C, Diene G, et al. Pituitary stalk interruption syndrome from infancy to adulthood: clinical, hormonal, and radiological assessment according to the initial presentation. *PLoS One* 2015;10:e0142354.
- [42] Miyamoto J, Hasegawa Y, Ohnami N, et al. Development of growth hormone and adrenocorticotrophic hormone deficiencies in patients with prenatal or perinatal-onset hypothalamic hypopituitarism having invisible or thin pituitary stalk on magnetic resonance imaging. *Endocr J* 2001;48:355–62.
- [43] Reynaud R, Albarel F, Saveanu A, et al. Pituitary stalk interruption syndrome in 83 patients: novel HESX1 mutation and severe hormonal prognosis in malformative forms. *Eur J Endocrinol* 2011;164:457–65.
- [44] Simon D, Hadjiathanasiou C, Garel C, et al. Phenotypic variability in children with growth hormone deficiency associated with posterior pituitary ectopia. *Clin Endocrinol (Oxf)* 2006;64:416–22.
- [45] Vergier J, Castinetti F, Saveanu A, et al. Diagnosis of endocrine disease: pituitary stalk interruption syndrome: etiology and clinical manifestations. *Eur J Endocrinol* 2019;181:R199–209.
- [46] De Marinis L, Bonadonna S, Bianchi A, et al. Primary empty sella. *J Clin Endocrinol Metab* 2005;90:5471–7.
- [47] Guitelman M, Garcia Basavilbaso N, Vitale M, et al. Primary empty sella (PES): a review of 175 cases. *Pituitary* 2013;16:270–4.
- [48] Hacquart T, Ltaief-Boutrigou A, Jeannerod C, et al. Reconsidering olfactory bulb magnetic resonance patterns in Kallmann syndrome. *Ann Endocrinol* 2017;78:455–61.
- [49] Quinton R, Beirne P, Bouloux PM, et al. Routine neuroimaging in classical isolated gonadotropin deficiency is of limited clinical value. *Clin Endocrinol (Oxf)* 2001;54:127–9.
- [50] Fang Q, George AS, Brinkmeier ML, et al. Genetics of combined pituitary hormone deficiency: roadmap into the genome era. *Endocr Rev* 2016;37:636–75.
- [51] Blum WF, Klammt J, Amselem S, et al. Screening a large pediatric cohort with GH deficiency for mutations in genes regulating pituitary development and GH secretion: frequencies, phenotypes and growth outcomes. *EBioMedicine* 2018;36:390–400.
- [52] Binder G, Schnabel D, Reinehr T, et al. Evolving pituitary hormone deficits in primarily isolated GHD: a review and experts' consensus. *Mol Cell Pediatr* 2020;7:16.
- [53] Otto AP, França MM, Correa FA, et al. Frequent development of combined pituitary hormone deficiency in patients initially diagnosed as isolated growth hormone deficiency: a long-term follow-up of patients from a single center. *Pituitary* 2015;18:561–7.
- [54] Castinetti F, Reynaud R, Saveanu A, et al. Mechanisms in endocrinology: an update in the genetic aetiologies of combined pituitary hormone deficiency. *Eur J Endocrinol* 2016;174:R239–47.
- [55] Joustira SD, Schoenmakers N, Persani L, et al. The IGSF1 deficiency syndrome: characteristics of male and female patients. *J Clin Endocrinol Metab* 2013;98:4942–52.
- [56] Brue T, Quentien M-H, Khetchooumian K, et al. Mutations in NFKB2 and potential genetic heterogeneity in patients with DAVID syndrome, having variable endocrine and immune deficiencies. *BMC Med Genet* 2014;15:139.
- [57] Maione L, Dwyer AA, Franco B, et al. Genetics in endocrinology: genetic counseling for congenital hypogonadotropic hypogonadism and Kallmann syndrome: new challenges in the era of oligogenom and next-generation sequencing. *Eur J Endocrinol* 2018;178:R55–80.
- [58] Peters C, van Trotsenburg ASP, Schoenmakers N. Diagnosis of endocrine disease: congenital hypothyroidism: update and perspectives. *Eur J Endocrinol* 2018;179:R297–317.
- [59] van Trotsenburg P, Stoupa A, Léger J, et al. Congenital hypothyroidism: a 2020–2021 Consensus Guidelines Update—An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid* 2021;31:387–419.
- [60] Bear KA, Solomon BD, Antonini S, et al. Pathogenic mutations in *GLI2* cause a specific phenotype that is distinct from holoprosencephaly. *J Med Genet* 2014;51:413–8.
- [61] Erbaş İM, Paketçi A, Acar S, et al. A nonsense variant in *FGFR1*: a rare cause of combined pituitary hormone deficiency. *J Pediatr Endocrinol Metab JPEM* 2020;33:1613–5.
- [62] Raivio T, Avbelj M, McCabe MJ, et al. Genetic overlap in Kallmann syndrome. *J Clin Endocrinol Metab* 2012;97:E694–9.
- [63] Reynaud R, Jayakody SA, Monnier C, et al. *PROKR2* variants in multiple hypopituitarism with pituitary stalk interruption. *J Clin Endocrinol Metab* 2012;97:E1068–73.
- [64] McCormack SE, Li D, Kim YJ, et al. Digenic inheritance of *PROKR2* and *WDR11* mutations in pituitary stalk interruption syndrome. *J Clin Endocrinol Metab* 2017;102:2501–7.
- [65] [texte_pnds_oberar19072021.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2021-07/texte_pnds_oberar19072021.pdf), https://www.has-sante.fr/upload/docs/application/pdf/2021-07/texte_pnds_oberar19072021.pdf (accessed 23 November 2023).
- [66] Jullien N, Saveanu A, Vergier J, et al. Clinical lessons learned in constitutional hypopituitarism from two decades of experience in a large international cohort. *Clin Endocrinol (Oxf)* 2021;94:277–89.
- [67] Doga M, Bonadonna S, Gola M, et al. Current guidelines for adult GH replacement. *Rev Endocr Metab Disord* 2005;6:63–70.
- [68] Correa FA, Nakaguma M, Madeira JLO, et al. Combined pituitary hormone deficiency caused by *PROP1* mutations: update 20 years post-discovery. *Arch Endocrinol Metab* 2019;63:167–74.
- [69] Lee JK, Zhu Y-S, Cordero JJ, et al. Long-term growth hormone therapy in adulthood results in significant linear growth in siblings with a *PROP-1* gene mutation. *J Clin Endocrinol Metab* 2004;89:4850–6.
- [70] Crone J, Pfäffle R, Stobbe H, et al. Familial combined pituitary hormone deficiency caused by *PROP-1* gene mutation. Growth patterns and MRI studies in untreated subjects. *Horm Res* 2002;57:120–6.
- [71] Vallette-Kasic S, Barlier A, Teinturier C, et al. *PROP1* gene screening in patients with multiple pituitary hormone deficiency reveals two sites of hypermutability and a high incidence of corticotroph deficiency. *J Clin Endocrinol Metab* 2001;86:4529–35.
- [72] Shimon I, Cohen O, Lubetsky A, et al. Thyrotropin suppression by thyroid hormone replacement is correlated with thyroxine level normalization in central hypothyroidism. *Thyroid* 2002;12:823–7.
- [73] Hirata Y, Fukuoka H, Iguchi G, et al. Median-lower normal levels of serum thyroxine are associated with low triiodothyronine levels and body temperature in patients with central hypothyroidism. *Eur J Endocrinol* 2015;173:247–56.
- [74] Slawik M, Klawitter B, Meiser E, et al. Thyroid hormone replacement for central hypothyroidism: a randomized controlled trial comparing two doses of thyroxine (T4) with a combination of T4 and triiodothyronine. *J Clin Endocrinol Metab* 2007;92:4115–22.
- [75] Ferretti E, Persani L, Jaffrain-Rea ML, et al. Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism. *J Clin Endocrinol Metab* 1999;84:924–9.
- [76] Klose M, Marina D, Hartoft-Nielsen M-L, et al. Central hypothyroidism and its replacement have a significant influence on cardiovascular risk factors in adult hypopituitary patients. *J Clin Endocrinol Metab* 2013;98:3802–10.
- [77] Goichot B, Raverot V, Klein M, et al. Management of thyroid dysfunctions in the elderly. French Endocrine Society consensus 2019 guidelines. Short version. *Ann Endocrinol* 2020;81:511–5.
- [78] Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol* 2017;177:G1–70.
- [79] Reinehr T, Lindberg A, Toschke C, et al. Weight gain in Turner Syndrome: association to puberty induction? Longitudinal analysis of KIGS data. *Clin Endocrinol (Oxf)* 2016;85:85–91.
- [80] Dunkel L, Quinton R. Transition in endocrinology: induction of puberty. *Eur J Endocrinol* 2014;170:R229–39.
- [81] Pazderska A, Mamoojee Y, Artham S, et al. Safety and tolerability of one-year intramuscular testosterone regime to induce puberty in older men with CHH. *Endocr Connect* 2018;7:133–8.
- [82] Rohayem J, Hauffa BP, Zacharin M, et al. Testicular growth and spermatogenesis: new goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? A multicentre prospective study of hCG/rFSH treatment outcomes during adolescence. *Clin Endocrinol (Oxf)* 2017;86:75–87.
- [83] Liu PY, Baker HWG, Jayadev V, et al. Trial of recombinant follicle-stimulating hormone pretreatment for GnRH-induced fertility in patients with congenital hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 2013;98:E1790–5.
- [84] Raivio T, Wikström AM, Dunkel L. Treatment of gonadotropin-deficient boys with recombinant human FSH: long-term observation and outcome. *Eur J Endocrinol* 2007;156:105–11.
- [85] Liu PY, Baker HWG, Jayadev V, et al. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. *J Clin Endocrinol Metab* 2009;94:801–8.
- [86] Zacharin M, Sabin MA, Nair VV, et al. Addition of recombinant follicle-stimulating hormone to human chorionic gonadotropin treatment in adolescents and young adults with hypogonadotropic hypogonadism promotes normal testicular growth and may promote early spermatogenesis. *Fertil Steril* 2012;98:836–42.
- [87] Zueger T, Kirchner P, Herren C, et al. Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma. *J Clin Endocrinol Metab* 2012;97:E1938–42.
- [88] Bleicken B, Hahner S, Loeffler M, et al. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. *Clin Endocrinol (Oxf)* 2010;72:297–304.
- [89] Arima H, Oiso Y, Juul KV, et al. Efficacy and safety of desmopressin orally disintegrating tablet in patients with central diabetes insipidus: results of a multicenter open-label dose-titration study. *Endocr J* 2013;60:1085–94.
- [90] Kataoka Y, Nishida S, Hirakawa A, et al. Comparison of incidence of hyponatremia between intranasal and oral desmopressin in patients with central diabetes insipidus. *Endocr J* 2015;62:195–200.
- [91] Murakami T, Hatoko T, Nambu T, et al. Desmopressin orally disintegrating tablet in Japanese patients with central diabetes insipidus: a retrospective study of switching from intranasal desmopressin. *Endocr J* 2014;61:773–9.

- [92] Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *J Clin Endocrinol Metab* 2015;100:407–16.
- [93] Cortet C, Barat P, Zenaty D, et al. Group 5: acute adrenal insufficiency in adults and pediatric patients. *Ann Endocrinol* 2017;78:535–43.
- [94] Hahner S, Burger-Stritt S, Allolio B. Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. *Eur J Endocrinol* 2013;169:147–54.
- [95] Behan LA, Sherlock M, Moyles P, et al. Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study. *Eur J Endocrinol* 2015;172:243–50.
- [96] Hameed S, Mendoza-Cruz AC, Neville KA, et al. Home blood sodium monitoring, sliding-scale fluid prescription and subcutaneous DDAVP for infantile diabetes insipidus with impaired thirst mechanism. *Int J Pediatr Endocrinol* 2012;2012:18.
- [97] Poidvin A, Weill A, Ecosse E, et al. Risk of diabetes treated in early adulthood after growth hormone treatment of short stature in childhood. *J Clin Endocrinol Metab* 2017;102:1291–8.
- [98] Säwendahl L, Cooke R, Tidblad A, et al. Long-term mortality after childhood growth hormone treatment: the SAGHe cohort study. *Lancet Diabetes Endocrinol* 2020;8:683–92.
- [99] Reznik Y, Barat P, Bertherat J, et al. SFE/SFEDP adrenal insufficiency French consensus: introduction and handbook. *Ann Endocrinol* 2018;79:1–22.
- [100] Arlt W, Rosenthal C, Hahner S, et al. Quality of glucocorticoid replacement in adrenal insufficiency: clinical assessment vs. timed serum cortisol measurements. *Clin Endocrinol (Oxf)* 2006;64:384–9.
- [101] Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab* 2000;85:2670–7.
- [102] Regal M, Páramo C, Sierra SM, et al. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol (Oxf)* 2001;55:735–40.
- [103] Abe SY, Dos Santos KS, Barbosa BFB, et al. Metabolic syndrome and its components in adult hypopituitary patients. *Pituitary* 2020;23:409–16.
- [104] Mazziotti G, Chiavistelli S, Giustina A. Pituitary diseases and bone. *Endocrinol Metab Clin North Am* 2015;44:171–80.
- [105] Juul A, Kastrup KW, Pedersen SA, et al. Growth hormone (GH) provocative retesting of 108 young adults with childhood-onset GH deficiency and the diagnostic value of insulin-like growth factor I (IGF-I) and IGF-binding protein-3. *J Clin Endocrinol Metab* 1997;82:1195–201.
- [106] Pitteloud N, Hayes FJ, Dwyer A, et al. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 2002;87:4128–36.
- [107] Rastrelli G, Corona G, Mannucci E, et al. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. *Andrology* 2014;2:794–808.
- [108] Padrón RS, Wischusen J, Hudson B, et al. Prolonged biphasic response of plasma testosterone to single intramuscular injections of human chorionic gonadotropin. *J Clin Endocrinol Metab* 1980;50:1100–4.
- [109] Dwyer AA, Raivio T, Pitteloud N. Gonadotrophin replacement for induction of fertility in hypogonadal men. *Best Pract Res Clin Endocrinol Metab* 2015;29:91–103.
- [110] Trsinar B, Muravec UR. Fertility potential after unilateral and bilateral orchidopexy for cryptorchidism. *World J Urol* 2009;27:513–9.
- [111] White DM, Hardy K, Lovelock S, et al. Low-dose gonadotropin induction of ovulation in anovulatory women: still needed in the age of IVF. *Reprod Camb Engl* 2018;156:F1–10.
- [112] Vila G, Fleseriu M. Fertility and pregnancy in women with hypopituitarism: a systematic literature review. *J Clin Endocrinol Metab* 2020;105 [dggz112].
- [113] Alexandraki KI, Grossman A. Management of hypopituitarism. *J Clin Med* 2019;8:E2153.
- [114] Lindsay JR, Nieman LK. The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. *Endocr Rev* 2005;26:775–99.
- [115] de Boer JA, Schoemaker J, van der Veen EA. Impaired reproductive function in women treated for growth hormone deficiency during childhood. *Clin Endocrinol (Oxf)* 1997;46:681–9.
- [116] Vila G, Akerblad A-C, Mattsson AF, et al. Pregnancy outcomes in women with growth hormone deficiency. *Fertil Steril* 2015;104:1210–70.
- [117] Kokshoorn NE, Biermasz NR, Roelfsema F, et al. GH replacement therapy in elderly GH-deficient patients: a systematic review. *Eur J Endocrinol* 2011;164:657–65.
- [118] Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2018;103:1715–44.