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Less known aspects of central hypothyroidism: Part 1 – Acquired etiologies

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ABSTRACT

Central hypothyroidism (CH) is a rare cause of hypothyroidism. CH is frequently overlooked, as its clinical picture is subtle and includes non-specific symptoms; furthermore, if measurement of TSH alone is used to screen for thyroid function, TSH concentrations can be normal or even above the upper normal reference limit. Indeed, certain patients are at risk of developing CH, such as those with a pituitary adenoma or hypophysitis, those who have been treated for a childhood malignancy, have suffered a head trauma, sub-arachnoid hemorrhage or meningitis, and those who are on drugs capable to reduce TSH secretion.

Introduction

Central hypothyroidism (CH) is a rare cause of hypothyroidism, since it is reported to occur in 1:16,000 to 1:120,000 individuals [1]. The aim of our review is to show that acquired CH is not an exceedingly rare entity and that, within anterior hypopituitarism, TSH deficiency is not so rare either. The corresponding aim for congenital CH is addressed in an accompanying review [114].

Diagnosis

CH includes hypothyroidism caused by altered secretion of thyrotropin (TSH) (secondary hypothyroidism) or TSH-releasing hormone (TRH) (tertiary hypothyroidism). CH may occur after birth (acquired CH) or prenatally (congenital CH). In the majority of patients, CH is combined with other pituitary deficiencies (multiple pituitary hormone deficiencies to panhypopituitarism). Acquired CH may result from different conditions that ultimately lead to disruption of the hypothalamus-pituitary-thyroid axis, such as trauma, tumors, inflammation, infections and drugs [1,2]. Even if TSH isoforms are qualitatively defective and display impaired biological activity, they can be quantitatively normal or even elevated, and maintain their immunoreactivity [3]. Therefore, serum TSH concentrations in patients with CH may be

low, normal or even above normal, in the face of low free thyroxine (FT4) concentrations [4]. Measurement of FT4 in turn is also a big challenge with the current use of the manufacturers' different platforms most of which are not mutually calibrated and with very different confounders giving rise to an inherent imperfection of all these measurements [4]. Symptoms and signs of CH, such as fatigue, depression, and drowsiness are nonspecific and usually milder than seen in primary hypothyroidism, and they can be confused with those ascribed to deficiency of other pituitary tropins or even other hormonal and non-hormonal diseases. Thus, because the clinical picture is non-specific and subtle, the diagnosis of CH is frequently delayed [1,2].

Though limited in size, a study from the Waikato region of New Zealand of an initial cohort of 20 patients with CH is quite informative about the delayed diagnosis of CH and the limited recognition by general practitioners that a normal TSH concentration does not exclude the diagnosis of CH [5]. The study was based on a questionnaire completed by 16/20 patients with CH (median age at diagnosis 58 years, range 35–80). Both TSH and T4 were measured in 81% (13/16) of the participants prior to their first endocrine assessment, and 75% (12/16) had results suggesting pituitary disease [5]. Seven participants (44%) had symptoms (e.g. headaches, lethargy, visual disturbances, and weight- and mood changes) for more than one year and another 6 (38%) for more than 2 years. Time to diagnosis ranged from 3

Abbreviations: ADH, antidiuretic hormone; AT/RT, atypical teratoid/rhabdoid tumor; CH, central hypothyroidism; CNS, central nervous system; CPI, conformal primary-site irradiation; CRI, cranial irradiation; DDMS, Dyke-Davidoff-Masson syndrome; FT3, free triiodothyronine; FT4, free thyroxine; FSH, follicle-stimulating hormone; GCT, germ cell tumor; GH, growth hormone; IGF-1, insulin growth factor-1; LH, luteinizing hormone; MB, medulloblastoma; PD-1, programmed cell death-1 receptor; PNET, primitive neuroectodermal tumor; PRL, prolactin; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TRH, TSH-releasing hormone; TSH, thyrotropin

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Table 1

Systematic reviews and meta-analysis including studies on anterior hypopituitarism-induced by traumatic brain injury and subarachnoid hemorrhage. Frequency of pituitary deficit is reported as range of percent values.

	Author [ref]	Any	TSH	ACTH	GH	FSH and/or LH
SAH (n = 102)	Schneider et al. [17]	37.5–55	2.5–9.4	6.3–40	20–6.7	0–13.3
SAH (n = 691)	Khajeh et al. [30]	0–55	0–20	0–40	0–37	0–28
SAH (n = 924)	Can et al. [32] (3–6 months)	4.5–37.5	0–9.3	0–28.1	0–25	0–23.6
	Can et al. [32] (> 6 months)	0–55	0–13.3	0–40	0–36.7	0–36.7
SAH (n = 110)	Valdes-Socin [33]	N/A	2.5–7.5	2.5–32	12.5–37	0–13
TBI (n = 809)	Schneider et al. [17]	15.4–50	1–13.2	0–19.2	5.9–32.7	1.9–20
TBI, children & adolescents (n = 20)	Acerini et al. [19]	N/A	50–100	0–100	50–100	66.7–100

Abbreviations: ACTH = adrenocorticotropic hormone; GH = growth hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TBI = traumatic brain injury; TSH = thyroid-stimulating hormone; SAH = subarachnoid hemorrhage.

All studies reviewed by Acerini et al. [19] are case reports of post-head trauma hypopituitarism, as opposed to screening studies. Accordingly, it is inappropriate to calculate rate of deficiency for at least one anterior pituitary hormone. The percentages of hormone deficits in the Acerini et al. paper are distribution among the 20 cases of post-head trauma hypopituitarism.

to more than 12 months, and 7 participants had 3–6 visits, and 5 had 6–12 visits to their general practitioner prior to diagnosis [5].

Prevalence

Both textbooks and papers provide information that CH is (very) rare, ranging from 1:16,000 to 1:120,000 [1,6–10]. CH has also been described to occur in fewer than 1% of hypothyroid patients or being about 1000-fold rarer than primary hypothyroidism [2,6–10]. However, an important English paper challenged this widely held opinion about the rarity of CH [11]. Using a combination of TSH and FT4 assays in lieu of the standard TSH alone assay, the authors searched for CH in 56,000 Liverpool inhabitants over 12 months. They found that 17 patients had possible CH with normal TSH [11]. Further investigations found that two of the 17 patients had non-thyroidal illness and the remaining 15 patients had hypopituitarism, which had not been suspected clinically. During the same 12-month period, 11 patients were referred to the same hospital on clinical grounds, and hypopituitarism was confirmed [11]. Extrapolation to the Liverpool population of 471,000 suggested an incidence of CH of 55 cases/million/year, of which 32/million/year might be undiagnosed, in the face of previously reported incidence of CH of 8–9 adult cases/million/year [12].

Over the same 12-month period, the ratio of primary to secondary hypothyroidism detected by the above test strategy was 20:1 [11]. Such 20:1 ratio of primary to secondary hypothyroidism [11] might appear grossly overestimated in view of the aforementioned widely held opinion on the rarity of CH [9]. However, the 20:1 ratio is consistent with what can easily be calculated based on a recent meta-analysis [13]: the incidence of hypothyroidism in Europe is 226 per 100,000 per year, which divided by 5.5/100,000 (incidence of CH according to Wardle et al. [11]) equals 41: 1.

In a Spanish study, the frequency of diagnosed hypopituitarism was significantly higher in the year 1999 (45.5/100,000/year) compared to year 1992 (29/100,000/year), but with similar distribution of etiologies: pituitary tumors accounting for around 60%, extrapituitary tumors for 10%, and non-tumoral causes for approximately 30% [14]. Thus, in 1999 the incidence of CH from non-tumoral causes was 10/100,000/year, which is again an order of magnitude similar to the incidence of CH according to Wardle et al. [11].

Methods

A systematic literature search using PubMed and MEDLINE databases was performed using the strings “acquired central hypothyroidism”, “central hypothyroidism AND traumatic brain injury”, “central hypothyroidism AND subarachnoid hemorrhage”, “central hypothyroidism AND primary hypophysitis”, “central hypothyroidism AND pituitary adenoma”, “central hypothyroidism AND childhood

malignancy”, “central hypothyroidism AND childhood brain tumor”, “central hypothyroidism AND meningitis”, “central hypothyroidism AND infiltrative disorders”, “central hypothyroidism AND drugs”.

Results

Traumatic brain injury (TBI)

The incidence of 5.5/100,000/year for CH [11] may be an underestimate as hypopituitarism secondary to high-incidence conditions might not have been taken into consideration. In the last decade there has been increased attention to hypopituitarism as a complication of traumatic brain injury (TBI) [15]. TBI leading to hospitalization has an incidence of 100–350 per 100,000 in the general population [15–19]. Relatively few cases are fatal; most individuals survive long-term, some of whom continue to suffer from non-specific symptoms such as depression, fatigue, sexual disturbances, cognitive deficits and sleep disorders [20,21]. More recent studies have reported a high prevalence of chronic anterior pituitary hormone deficiency following TBI with an estimated frequency of more than 25% (approximately 5% for CH) (Table 1) [17].

Since single axis failure was most often reported, some authors have questioned the quality of the diagnostic work-up in patients with TBI and, therefore, the related prevalence [18]. Pituitary assessment is generally restricted to patients at risk of hypopituitarism, such as those with hypothalamus-pituitary disease or those who underwent pituitary surgery or brain irradiation, who are referred to tertiary care endocrinology centers. However, making diagnosis of hypopituitarism in patients with non-classical causes of hypopituitarism is challenging. Moreover, the diagnosis is even more challenging in light of false positive tests and gray-zone results for each pituitary hormone [18,22]. Laboratory results should be interpreted in light of clinical features and pretest probability [23], as post-TBI single axis failure can occur [18]. Gonadotropin and GH deficiencies may be misinterpreted because of confounders. One confounder is obesity, since it decreases sex hormone-binding globulin levels and GH response during stimulation tests [18,22].

With a TBI incidence of 100–350 per 100,000 persons/year [15–19] and assuming a 5% frequency of post-TBI CH (Table 1), the resulting incidence of post-TBI CH would approximate 40 per 100,000 persons/year. As the incidence of primary hypothyroidism in Europe is 226 per 100,000 in the general population [13], the primary hypothyroidism to CH ratio would be 226:40, or 5.6:1. The ratio would be even lower in the pediatric setting, given that deficiency of TSH is as frequent as deficiency of other anterior pituitary hormones among children and adolescents with post-TBI hypopituitarism [19]. In this review of 10 studies, addressing post-traumatic hypopituitarism in 20 pediatric case reports, CH occurred in 75% of subjects, whereas GH deficiency, central

hypogonadism and central hypoadrenalism were seen in 85%, 80% and 55%, respectively (Table 1) [19]. In another small series of 15 patients with post-TBI CH (7 men, age at CH diagnosis 50 years, range 19–68, and age at trauma 30 years, range 7–59) [24], 3/15 (20%) had isolated CH whereas coexisting deficiencies occurred at the following rates: 60% (gonadotropins), 47% (GH), 27% (ACTH), 13% (PRL). One patient had panhypopituitarism [24].

Subarachnoid hemorrhage (SAH)

With an incidence of 10.5 per 10,000 persons/year in Western Europe, SAH is 10–30 times less incident than TBI. SAH results from ruptured aneurysm, perimesencephalic hemorrhage and rare conditions in 85%, 15% and 15% of the cases, respectively. Fatal cases of SAH range from 32 to 67%, and in one-third of nonfatal cases disability is a permanent sequela [25]. Similar to TBI, aneurysmal SAH can pose a risk to pituitary function, because of the vulnerable vascular supply of pituitary and the delicate infundibular-hypothalamic structures [26–28]. However, investigations on SAH-induced hypopituitarism are more limited compared to TBI and have never addressed the effects of SAH *per se* on the pituitary [26]. Compression of the pituitary gland by the aneurysm, changes in tissue pressure post-hemorrhage, hydrocephalus, increased intracranial pressure and vasospasm-induced ischemia have been proposed as mechanisms for the pituitary damage [26]. The majority of these studies [15,16,19,21,24] have taken into account series of patients after either SAH or TBI [20]. The high heterogeneity of results (Table 1) stems from differences in follow-up and in methods and thresholds used to evaluate endocrine function. Nevertheless, CH is one of the rarest deficit as opposed to GH deficiency [29,30].

One review [30] included 16 studies published between 1995 and 2014 and prospective (10 studies) or cross-sectional/retrospective (6 studies) evaluation of pituitary function in the long term. The study populations ranged from 10 to 93 patients, with an interval between SAH and endocrine assessment from 3 months to 10 years. Endocrine function was evaluated basally and, in 12 studies, dynamically. CH occurred in no patient in 6 studies, whereas in the remaining 10 its frequency ranged from 2% to 20% [30]. In particular, in the study that reported the highest frequency (20%) of CH, this deficit was the most prevalent in the ten patients evaluated except for testosterone deficiency (30%) [31] (Table 1). The systematic review by Schneider confirmed that SAH was associated with a higher frequency of hypopituitarism compared with TBI [17]. Recently, Can et al. reviewed and meta-analyzed 17 studies on SAH-induced hypopituitarism at 3–6 months and > 6 months after the hemorrhagic event [32]. The pooled frequency of CH was the same at 3–6 months and > 6 months (0.04 [95%CI 0.02–0.08] and 0.04 [95%CI 0.02–0.07], respectively), whereas, frequencies of central hypogonadism, diabetes insipidus and multiple pituitary deficiencies decreased over time, although this difference was not significant [32]. Finally, in a French-language review of three retrospective studies, post-SAH CH was reported in 6% of cases, with a range of 2.5–7% [33].

Primary hypophysitis

TSH deficiency (and therefore CH) is also frequent in primary hypophysitis [34] (Table 2), which is an autoimmune inflammation of the pituitary gland not caused by drugs or microbes (see 3.6. Meningitis and 3.7. Drugs). Primary hypophysitis is a truly rare pathology of the pituitary with an annual incidence between 0.1 and 0.9/100,000 [34].

Based on the extension of lymphocytic infiltrate, three forms are identified: panhypophysitis, adenohypophysitis and infundibulo-neurohypophysitis [35]. Five histologically different variants are distinguished: lymphocytic, granulomatous, xanthomatous, necrotizing and IgG-related. Lymphocytic hypophysitis is by far the most common variant [35,36]. Finally, IgG4-related hypophysitis with IgG4-positive

Table 2
Frequency of pituitary deficit reported in patients with either hypophysitis.

	Author [ref]	Any	TSH	ACTH	GH	FSH and/or LH
Hypophysitis (n = 66)	Honegger et al. [34]	?	48	47	37	62
Histologically proven (n = 33)		?	64	52	40	70
Lymphocytic (n = 24)		?	57	48	41	57
Granulomatous (n = 9)		?	88	63	38	100
Hypophysitis (n = 21)	Chiloiro et al. [38]					
Adenohypophysitis (n = 9)		29	0	19	0	9
Panhypophysitis (n = 4)		14	5	9	0	5
Infundibulo-neurohypophysitis (n = 8)		33	9	5	24	29

Abbreviations: ACTH = adrenocorticotropic hormone; GH = growth hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

Rate of deficiency for at least one anterior pituitary hormone was not provided by Honegger et al. [34], nor cannot be calculate by the data provided.

plasma cells infiltrating the pituitary has been recently described [37].

In a German nationwide retrospective study [34], 66 patients with primary hypophysitis were identified. Central hypogonadism and GH deficiency were the most and the least frequent endocrine disturbances, with a frequency of 62% and 37%, respectively. CH occurred in around half of patients (48%), with a higher, but insignificant, frequency in histologically confirmed cases of hypophysitis compared to those not confirmed by histology [34]. Recently, in a prospective single-center study, 3/21 (14.3%) patients with primary hypophysitis had CH [38] (Table 2).

Pituitary adenomas

Hypopituitarism, and therefore CH, may result from pituitary adenomas and radiotherapy and surgery thereof. Less frequently, CH may result from pituitary apoplexy [39]. Macroadenomas, i.e. tumors larger than 1 cm, cause hypopituitarism by increasing intrasellar pressure and compressing blood supply, and consequently, interrupting delivery of hypothalamic hormones to the anterior pituitary. Increased intrasellar pressure is considered a major factor determining hypopituitarism, hyperprolactinemia and headache [40]. However, tumor size does not correlate with either mean intrasellar pressure or prolactin levels [40]. The Endocrine Society recommends testing all patients with pituitary adenomas for hypopituitarism, irrespective of tumor size [41]. It is still debated whether CH screening should include FT4 alone or FT4 plus TSH [41]. CH together with central hypoadrenalism, is the least frequent pituitary deficit, as it occurs in up to one-third of patients with pituitary incidentaloma, that is a previously unsuspected pituitary lesion incidentally discovered on imaging study [41].

In a Brazilian retrospective study on 104 patients with non-functioning pituitary adenoma, almost completely sized > 1 cm (macroadenoma, 93%), CH was observed in 20.4% of cases [42]. This rate matched well with that found in an Italian study (24.5%), which analyzed 295 patients with non-functioning pituitary adenoma (96.5% of which macroadenoma) [43]. Nevertheless, in another retrospective study, the frequency of inappropriately normal TSH with thyroid hormone levels below the normal reference range (i.e. CH) was 16% in 61 patients with pituitary incidentaloma (one-fifth being ≤ 1 cm) [44].

Within microadenomas, ACTH-secreting tumors have higher prevalence of hypothyroidism compared with either nonfunctioning or other hormone-secreting microadenomas [45]. ACTH-secreting adenomas are rare with an incidence of approximately 0.3/100,000/year [46], and a retrospective study [45] demonstrated that CH was present in 6/34 (17.6%), micro-prolactinomas and nonfunctioning

microadenomas had 1/72 (1.4%) and 0/43 cases of CH, respectively. This difference corresponded to an odds ratio of 11.3 of CH (95% CI 2.169–58.87) in ACTH-microadenomas compared to non-ACTH adenomas of comparable size. In addition, normalized FT4 was significantly lower in the ACTH group than in the non-ACTH group [45]. The TSH-suppressive effect of cortisol may at least in part explain these results, although neither TSH nor FT4 concentrations correlated with the degree of hypercortisolism as measured by urinary free cortisol and salivary cortisol [45]. However, numbers were small and did not have sufficient power for calculating such correlations.

While CH is unusual following selective removal of a pituitary microadenoma, it is relatively more frequent (< 10%) after macroadenoma excision [47]. Concerning radiotherapy, Brada et al. estimated at 30% the probability of receiving either thyroxine or corticosteroid replacement at 10 years after conventional external-beam radiotherapy [48]. Recent advances in radiation treatment of pituitary adenomas have reduced long-term endocrine complications. Stereotactic surgery, which consists of a single-session, highly precise delivery of radiation to one lesion, can be performed either by gamma-knife surgery or other stereotactic modalities. For instance, Sicignano et al. followed up 130 patients treated with gamma-knife surgery (at least 15 Gy for non-functioning pituitary adenomas, at least 25 Gy for secreting pituitary adenomas) for more than 6 months (median 60 months) [49]. During the follow-up, 8/113 (7.1%) patients who had normal baseline thyroid function, developed hypothyroidism, whereas 9/93 patients (9.7%) who had normal baseline thyroid and adrenal function, developed hypothyroidism and/or hypoadrenalism [49].

Survivors of childhood brain tumors and other childhood malignancies

As summarized in a recent article [50], central nervous system tumors (CNS) are the second most common malignancies of childhood with over 3500 annual cases diagnosed in the United States. Modern treatment protocols have resulted in > 70% of children with CNS tumors becoming long-term survivors, so that as of 2005, it was estimated that there were > 50,000 survivors of pediatric central nervous system tumors in the US. One multi-institutional study comprehensively described late effects in 21 survivors treated in the Head Start I/II protocols [50]. Among late effects (frequency; median time of onset since diagnosis), GH (48%; 4.7 years) and TSH deficiencies (33%; 4 years) were seen. None of the 10 irradiation-free survivors was diagnosed with CH as opposed with 7/11 irradiated survivors ($P = 0.004$) [50] (Table 3).

In a questionnaire-based study in 1607 adults who survived for 5 or more years from childhood brain tumors and 3418 controls, GH and gonadotropin deficiencies were much more frequent than CH, as the corresponding relative risks were 278, 86 and 14, respectively [51]. Among patients with medulloblastoma/PNET and ependymoma treated with a combination of surgery, chemotherapy and irradiation, the incidence of GH deficiency or CH ranged from 0 to 53% and from 0 to 47%, respectively, depending on treatment(s). This study concluded that childhood brain tumor survivors are at a significantly increased risk for several adverse endocrine consequences [51]. However, a study of 6 patients treated for acute lymphoblastic leukemia with chemotherapy alone found 2 (33%) with CH [52]. Based on a literature review of 22 studies on childhood brain tumor survivors, the most commonly reported endocrine disorder within the first 5 years after diagnosis was GH deficiency (range 13–100%), followed by primary gonadal dysfunction (0–91%), CH (0–67%) and primary/subclinical hypothyroidism (range 0–64%) [53].

A study at Memorial Sloan-Kettering, New York, evaluated endocrine consequences in a cohort of 88 children with embryonal brain tumors treated with risk-adapted craniospinal irradiation, conformal primary site irradiation, and high-dose chemotherapy [54]. The cumulative incidence of GH deficiency, ACTH deficiency, CH and primary hypothyroidism at 4 years from diagnosis was 93%, 38%, 23%, and

65%, respectively. Radiation dosimetry to the hypothalamo-pituitary axis was associated only with the development of CH. Particularly, the median dose to the hypothalamus was higher in patients who developed CH compared with patients who did not (50.1 vs 40.7 Gy, respectively) [54].

In a Lithuanian study of 51 children treated for low-grade glioma and medulloblastoma with surgery, radiotherapy, chemotherapy or combined treatment, CH was observed in 25.9% of patients, and was significantly more prevalent in patients who were treated with radiotherapy compared with those who were not (41.2% vs. 0%, $P = 0.045$) [55]. The cumulative incidence of CH was 33.7% at 24 months, and remained unchanged 5 years after the end of treatment [55].

A British registry study [49] asked 10,483 childhood cancer survivors if they had been diagnosed with hypothyroidism. Eight percent of patients reported such diagnosis (etiology not specified), with the highest risk among Hodgkin lymphoma survivors and those who had been treated with radiotherapy [56].

In a Danish study of 71 survivors of childhood brain tumors treated with surgery, radiotherapy and chemotherapy, the rate of primary hypothyroidism was four-fold greater compared to CH (24% vs. 6%) [57]. Survivors who underwent cranial irradiation had a similar rate of primary hypothyroidism and CH (12% and 9%, respectively), whereas those who underwent craniospinal irradiation experienced only primary hypothyroidism (41%) [57]. In another Danish study [58], 95 survivors of childhood acute lymphoblastic leukemia who underwent chemotherapy either alone ($n = 57$) or combined with cranial irradiation ($n = 38$) were challenged with three to five μg of TRH per kg intravenously. The authors concluded that a TRH test did not contribute to the diagnosis of CH [58]. Another study published four years later confirmed the limited utility of TSH surge after TRH challenge to detect CH in childhood tumors survivors [59]. However, the results of the TRH test in 37 survivors after cranial irradiation for childhood tumors and 33 matched controls demonstrated abnormalities in TSH dynamics of survivors representing subtle alteration of hypothalamus-pituitary-thyroid axis consisting of a shift in the timing of the peak and/or nadir TSH and not an actual loss of TSH diurnal rhythm [59].

The rate of hypothyroidism (either primary failure or CH) in 205 survivors of childhood cancers from a Dutch study [60], did not depend on the applied treatment. A history of brain tumor was the only predictor for CH in the multivariate analysis [60].

Finally, a recent review showed that cranial irradiation with ≥ 30 Gy, total body irradiation and surgery or tumor in suprasellar region are all risk factors for developing CH and other pituitary deficits [61].

Meningitis

The incidence of meningitis is ten-fold higher in developing than in developed countries. The incidence of neonatal bacterial meningitis is 0.25–1 case per 1000 live births and higher in premature births (2.5 cases per 1000) compared to 0.15 cases per 1000 full-term births. Aseptic meningitis, of which viruses are the major cause, has a reported incidence of 10.9 cases per 100,000 persons/year [62].

Two studies investigated pituitary function months to a couple of years after an infectious disease of the central nervous system [63,64]. One of them [63] evaluated a total of 19 patients with previous neuroborreliosis ($n = 4$), encephalitis ($n = 2$), or meningitis ($n = 13$) following an interval between 10 and 56 months (mean 26.1 months) after the acute event. They were 22–65 years old (mean 38.7 ± 11.7 years). Four patients (21%) showed isolated ACTH insufficiency (peak cortisol < 496.6 nmol/L during an insulin tolerance test), two (10%) showed borderline gonadotropin insufficiency, but none had GH or TSH insufficiency nor evidence of diabetes insipidus. The clinical picture of such patients with endocrine abnormalities might be misinterpreted as post-encephalitic syndrome [63]. In the other study [64], 14 children (3.8 years, range 0.03 months to 15.8 years), previously hospitalized

Table 3
Frequency of pituitary deficit reported in survivors of childhood malignancies.

Authors [ref]	N. of survivors (tumor)	Age at diagnosis	Time from diagnosis through follow-up	Therapy [n (%)]	Deficit
Saha et al. [50]	21 (MB = 13, supratentorial PNET = 4, AT/RT = 1, ependymoma = 3)	1.7 years (median; range 0.2–7)	12.6 years (median; range, 9.6–20.8)	surgery (gross total, n = 14; partial, n = 7), radiotherapy (n = 10), chemotherapy (Head Start I protocol, n = 4; Head Start II protocol, n = 17)	GH deficiency (48%, median time of onset since diagnosis of 4.7 years) CH (33%, 4 years) GH deficiency (n = 337, 21%) S, n = 10 SR, n = 144 SRC, n = 168 O, n = 15
Gurney et al. [51]	1607 (astrocytoma/glioma = 1066, MB/PNET = 343, ependymoma = 118, other tumors = 80)	≤ 4 years (n = 547, 34%) 5–9 years (n = 480, 29.9%) ≥ 10 years (n = 580, 36.1%)	≥ 5 years	only surgery (S) (n = 414) surgery + radiotherapy (SR) (n = 682) surgery + radiotherapy + chemotherapy (SRC) (n = 446) other therapy (O) (n = 65)	S, n = 10 SR, n = 144 SRC, n = 168 O, n = 15 CH (n = 255, 16%) S, n = 12 SR, n = 111 SRC, n = 125 O, n = 7 CH, n = 2 (33%)
Baronio et al. [52]	6 (acute lymphoblastic leukemia)	3.8 years (mean; range 0.3–6.0)	6 years (mean; range, 6–13)	chemotherapy (N = 6)**	GH deficiency (cumulative incidence at 4 years, 93 ± 4%; diagnosis at 1.8 years [median; range 0.9–4.3]) CH (23 ± 8%; diagnosis at 1.8 years [1.1–3.7])
Laughton et al. [54]	88 (supratentorial, n = 10 [AT/RT, n = 5; pinealoblastoma, n = 4; PNET, n = 1]; infratentorial, n = 78 [AT/RT, n = 2; MB, n = 75; PNET, n = 1])	7.3 years (median; range, 3.0–20.1)	5.1 years (median; range, 2.1–9.6)	surgery + radiotherapy (risk-adapted CSI and CPI) + chemotherapy (n = 88)***	ACTH deficiency (38 ± 6%) IGF-1 deficiency (58.3%, mean time after treatment, 30.7 months) CH (25.9%, 61.1 months) Cortisol deficiency (4.2%, 83.4 months) TSH (6%; all underwent GRI)
Ramanauskienė et al. [55]	51 (glioma, n = 19; MB/PNET, n = 13; ependymoma, n = 9; intracranial germ tumor n = 1, unidentified, n = 9)	< 10 years (n = 34, 66.7%) ≥ 10 years (n = 17, 33.3%)	21 months (median; range, 0.25–10.6)	surgery (n = 42), radiotherapy (n = 29), chemotherapy**** (n = 26)	GH deficiency (cumulative incidence at 4 years, 93 ± 4%; diagnosis at 1.8 years [median; range 0.9–4.3]) CH (23 ± 8%; diagnosis at 1.8 years [1.1–3.7])
Schmiegelow et al. [57]	71 (astrocytoma, n = 31, MB, n = 22; ependymoma, n = 5; GCT, n = 3; glioma, n = 3; pinealoma, n = 1; hemangio-pericytoma, n = 1; PNET = 1; nonhistological verified diagnosis, n = 4)	8.4 years (median; range, 0.8–14.9)	12 years (median; range, 2–28)	surgery (n = 66), radiotherapy (CSI, n = 29; CRI, n = 42), chemotherapy#	ACTH deficiency (38 ± 6%) IGF-1 deficiency (58.3%, mean time after treatment, 30.7 months) CH (25.9%, 61.1 months) Cortisol deficiency (4.2%, 83.4 months) TSH (6%; all underwent GRI)
Van Santen et al. [60]	205 (acute lymphoblastic leukemia, n = 38.2%, Hodgkin/non-Hodgkin lymphoma, n = 26%; brain tumors, n = 25%; other malignancy, n = 10.8%)	8.1 years (mean; range 0.1–19.7)	19.1 ± 9.3 years (mean ± SD)	radiotherapy (CRI, CSI, cervical, mediastinal, thoracic) alone (172) or in combination with chemotherapy§ (n = 33)	GH (9%; radiotherapy alone, 24.2%; radiotherapy ± chemotherapy, 6%)

Abbreviations: AT/RT = atypical teratoid/rhabdoid tumor; CRI = cranial irradiation; CPI = conformal primary-site irradiation; CSI = craniospinal irradiation; GCT = germ cell tumor; MB = medulloblastoma; PNET = primitive neuroectodermal tumor.

*Including vincristine, cisplatin, cyclophosphamide, etoposide, methotrexate.

**AIEOPPLS 2000, AIEOPPLA 9502, ILLA 9102, including prednisone, dexamethasone, vincristine, cisplatin, cyclophosphamide, etoposide, methotrexate, daunoblastin, adriamycin, L-asparaginase.

***Including cisplatin, vincristine, cyclophosphamide and peripheral-blood stem cell infusion.

****Including carboplatin, vincristine, etoposide, lomustine, cisplatin, methotrexate.

#Including lomustine, vincristine, methotrexate, cisplatin, bleomycin, etoposide, carboplatin, endoxan.

§Alkylating agents, antineoplastic antibiotics, antimetabolites, vinca-alkaloids, carbo/cisplatin, topo-isomerase inhibitors, asparaginase, steroids (see ref. [60]).

due to meningitis, were evaluated 2.7 ± 1.2 years after the acute event with measurement of basal TSH, FT4, cortisol and insulin growth factor-1 (IGF-1). All the axes evaluated were normal. Only one child had low height but showed a normal response to a GH stimulation test [64].

One prospective study assessed pituitary function, anti-pituitary antibodies and anti-hypothalamus antibodies in 16 adults aged 40.9 ± 15.9 years with acute bacterial or viral meningitis, during the acute phase and at 6 and 12 months after the acute phase [65]. The rates of GH, ACTH, gonadotrophin and TSH deficiencies were 19%, 12%, 12% and 0% in the acute phase, respectively. At 12 months the corresponding rates were 43%, 7%, 7%, 0%. The rate of isolated deficiencies was two-fold greater compared with combined deficiency (29% vs. 14%) [65]. Importantly, 44% of hormone deficiencies at 6 months recovered at 12 months, whereas 37% appeared *de novo* at 12 months. Finally, up to half of the patients were positive for anti-pituitary antibodies and anti-hypothalamus antibodies throughout the follow-up [65]. However, this has not been confirmed by other research groups.

Another study enrolled 19 children with a history of infectious meningitis at an average age of 4.3 years [66]. Eighteen \pm 10 months from the infectious meningitis, none of the subjects had CH, nor other axis deficits. Thus, the authors concluded that hypopituitarism is an infrequent complication in children after infectious meningitis [66]. However, the literature reports cases of CH in neonates (almost always accompanied by other deficiencies) [67,68] and even panhypopituitarism [69–73] as a complication of bacterial meningitis.

Few studies focused on the relationship between meningitis and hypopituitarism from the opposite perspective. For instance, in a cohort of 230 evaluable hypopituitary patients, 2 had post-meningitis hypopituitarism, one of whom had CH [74]. Thus, post-meningitis CH accounted for 0.4% of the 211 cases of hypopituitarism.

Of interest, past history of meningitis has been reported in patients with the very rare Dyke-Davidoff-Masson syndrome (DDMS) in whom an endocrine evaluation was [75,76] or was not performed [77] [cross ref – Central Hypothyroidism, Part II, Ref: *JCTE_2018_65*].

Other inflammatory/infiltrative disorders

The pituitary may be also involved in a number of inflammatory/granulomatous diseases, which include idiopathic diseases (such as giant cell hypophysitis), systemic diseases (such as sarcoidosis, Wegener's granulomatosis, Takayasu's disease and Cogan's syndrome), and systemic histiocytosis (such as Langerhans' cell histiocytosis and Erdheim-Chester disease) [78]. Symptoms encompass headache, cranial neuropathy, mental changes, visual disturbance and hydrocephalus. Also, within hypopituitarism, CH may occur with variable prevalence [78].

Sarcoidosis is a chronic disorder with multisystemic deposition of epithelioid granulomas. Its etiology is still unknown. In up to 15% of cases, the central nervous system is involved (i.e. neurosarcoidosis), but hypothalamus-pituitary infiltration by sarcoidosis granulomas is rare [79]. CH is the second most common pituitary deficit (56%), after central hypogonadism (88%). One-third of patients have panhypopituitarism [80]. Langerhans' cell histiocytosis is a rare disorder characterized by unbridled proliferation of Langerhans' cell, a type of dendritic cells. This granulomatous disease varies from self-limited to fatal forms in which vital functions are compromised [78]. Up to 50% of patients develop hypopituitarism, with diabetes insipidus being the most common endocrine manifestation. In about 4% of patients, CH occurs either alone or in combination with other deficits [81]. Wegener's granulomatosis, also known as granulomatosis with polyangiitis, is a rare disorder with unknown etiology, which is characterized by vasculitis involving small vessels. The pituitary is rarely affected, CH being reported in half of cases [82].

Finally, CH caused by other granulomatous diseases is extremely rare, and only anecdotal reports are found in the literature [83–85].

Drugs

Glucocorticoids

Both endogenous and exogenous glucocorticoids are potent inhibitors of TSH secretion [86]. Glucocorticoids have been known for long time to influence TSH secretion, since patients with ACTH-secreting microadenomas (thereby without any mass effect on the normal pituitary) were shown to be associated with CH more often than other types of microadenomas (see 3.4. Pituitary adenomas). Physiologically hydrocortisone plays an important role in the diurnal variation of TSH, with lower concentrations in the morning and higher at night. This also explains why TSH levels are high in patients with untreated adrenal insufficiency [87]. High doses of glucocorticoids suppress TSH in both normal and in hypothyroid subjects. However, a prolonged administration of high dose glucocorticoids usually does not cause CH [86].

Dopaminergic drugs

These drugs cause profound inhibition of TSH secretion even at doses that do not influence blood pressure. Thus, after cessation of dopamine infusion, there is a rapid reversal of TSH suppression within a few hours [86,88]. Dopamine and its agonists, such as bromocriptine, suppress TSH secretion by activating its D_2 receptors [86]. The administration of dopamine or its derivatives dobutamine and dexamphetamine may cause difficulty in the interpretation of serum concentrations of TSH, as is often the case in CH. If ultrasensitive methods detecting TSH levels within the range of 0.01 mU/L are used, TSH concentration during treatment with these drugs are usually between 0.08 and 0.4 mU/L. These values are clearly different from those commonly observed in primary hyperthyroidism (TSH lower than 0.01 mU/L), but not incompatible with CH [4].

Somatostatin analogs

Somatostatin analogs are mostly used in treatment of acromegaly or neuroendocrine tumors [89]. They have also demonstrated therapeutic effectiveness in patients with the syndrome of pituitary resistance to thyroid hormones and with thyrotropinomas [90,91]. Administration of somatostatin to healthy volunteers decreases both TSH pulse frequency and amplitude [86]. Colao et al. stated that prolonged use of somatostatin analogues reduced TSH and its response to stimulus with thyrotropin-releasing hormone without affecting serum concentrations of thyroid hormones [89]. In a review of somatostatin analogues in acromegaly, an incidence of 2% of CH was described [92]. However, although somatostatin analogues suppress TSH through direct action on thyrotropes, these effects seem temporary and generally do not promote the appearance of CH.

Mitotane

Mitotane is a steroidogenesis inhibitor with adrenolytic properties, which is used to treat adrenocortical cancer. However, it has many side effects one of which is to affect thyroid function. Daffara et al. studied 14 patients operated for adrenocortical carcinoma on therapeutic adjuvant mitotane treatment [93]. They found a number of endocrine-related changes related to almost all hormone axes and binding proteins, but notably, the changes seen in the hypothalamic-pituitary-thyroid axis resembled those seen in CH, with reduction of FT4 concentrations in the face of normal free triiodothyronine (FT3) and TSH [93]. This was consistent with an experimental mouse model, where the secretory capacity of thyrotrophic cells was shown to be inhibited by therapeutic concentrations of mitotane [94]. In another clinical study [95] the pattern of CH was confirmed and expanded. Five female patients with adrenocortical carcinoma (median age 47 years; range 31–65) were treated with mitotane (dosage 1.5 g/day; range 1.0–3.0). Basal TSH was normal, FT3 concentrations were also normal but below the median of the reference range, while FT4 concentrations were below the normal range in all patients. The FT3/FT4 ratio was in the

upper range in four patients and higher than normal in one patient, revealing an enhanced T4 to T3 conversion. A blunted TSH response to TRH was also observed [95].

Bexarotene

Bexarotene is a synthetic compound that represents a new subgroup of retinoids agents, namely compounds that activate retinoid X receptors, which can therefore be defined as a retinoid agent [96–98]. It is used in the treatment of patients with cutaneous T-cell lymphoma, in whom it suppresses TSH, as confirmed by *in vitro* experiments. Bexarotene also increases the peripheral metabolism of thyroid hormones by inducing glucuronyl transferases and sulfotransferases [96]. Consequently, hypothyroid patients on bexarotene require a higher replacement dose (up to two times) of levothyroxine and due to the suppression, TSH concentrations cannot be used to monitor the treatment dose [82]. The TSH-suppressing effect was not reported for 13-*cis*-retinoic acid (isotretinoin), which is used for severe acne, whereas it was observed in 2 of 4 patients in a pilot study on oral alitretinoin for congenital ichthyosis [99].

Cytokines

Cytokines directly affect TSH secretion. For example, tumor necrosis factor- α does not affect basal TSH secretion in rat thyrotropes, but is capable to reduce TRH-stimulated TSH secretion [100]. Also, infusion of interferon- α in normal volunteers results in a 60–70% decrease in serum TSH within 8–12 h, prior to any significant change in serum thyroid hormone concentrations [101].

Monoclonal anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) antibodies

These monoclonal antibodies, by blocking a key immune checkpoint pathway, are used in the treatment of several neoplasias, such as metastatic renal carcinoma and melanoma. Both ipilimumab and tremelimumab target the monoclonal anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and binds to the same epitope with similar binding affinity [102]. By blocking CTLA-4, which is a receptor expressed on T-cells that blocks the immune response after T-cell/antigen-presenting cell interaction, these monoclonal antibodies enhance T-cell activation and have antitumor effects. It is still debated whether antitumor actions stem from an immune response against antigens shared by tumor and normal self cells, or from activation of specific antitumor T-cells [103].

Ipilimumab has a higher dissociation rate compared with tremelimumab, and consequently, has different pharmacokinetics [102]. The administration of either ipilimumab or tremelimumab may induce development of acute lymphocytic hypophysitis with panhypopituitarism, CH being the most frequent deficiency (90%) [104]. The incidence of this adverse effect seems to be dose-dependent [103]. Roughly one in ten patients on ipilimumab develop hypophysitis, whereas primary hypothyroidism is much less frequent. Interestingly, the association of ipilimumab with chemotherapy and radiotherapy seems to prevent ipilimumab-induced hypophysitis by depletion of immune cells [103]. The clinical presentation of hypophysitis includes headache, and nuclear magnetic resonance reveals an enlarged pituitary gland with suprasellar convexity, thickening of the stalk and hyperintense heterogeneous signal [105–107]. Ipilimumab-induced hypophysitis typically develops in men in their sixties and affects the anterior lobe [98,106].

Monoclonal anti-programmed cell death-1 receptor (anti-PD-1) antibodies

Rarely, monoclonal anti-programmed cell death-1 receptor (anti-PD-1) antibodies, such as pembrolizumab and nivolumab cause hypophysitis [98,107]. They interfere with the interaction between PD-1 and its PD-1 ligand, which downregulates T-cells and allow cancer cells to elude the immune system [108]. The block of either PD-1 or PD-1 ligand results in antitumor immunity enhancement both *in vitro* and *in vivo* [103]. Unlike anti-CTLA-4 antibodies, anti-PD1-induced hypophysitis is less frequent compared with thyroiditis [109]. The rate of CH

is 1.2% and 0.9% for pembrolizumab and nivolumab, respectively [107]. Conversely, primary hypothyroidism is reported in up to 20% of cases [104].

The difference in the rate of hypophysitis between anti-PD-1 antibodies and anti-CTLA-4 antibodies may be explained by different activation of T-cells and ectopic expression of CTLA-4 in pituitary cells [109]. As expected, combination of these antibodies increases the risk of hypophysitis, which have a milder clinical presentation compared to that caused by monotherapy [109]. In a recent review of combination therapy clinical trials, hypophysitis was reported in 8% of cases [110].

Conclusions

The present review has provided evidence that acquired CH is less rare than previously anticipated. In particular, in patients with certain conditions, such as in those with ipilimumab-induced hypophysitis and in childhood brain tumors survivors, CH occurs most frequently. The causes of CH cover direct insults such as traumatic brain injury and SAH, inflammatory disorders such as primary autoimmune hypophysitis, rare forms of hypersecreting pituitary adenomas, meningitis as well as treatment-induced forms such as irradiation in survivors of childhood cancers, and a variety of drugs.

The reported incidences and prevalences are extremely variable in the different published studies, indicating differences in patient populations but also in methods for diagnosing CH. The latter is particularly challenging due to inherent imperfections of quantitatively accurate measurements of both TSH and FT4. The status of the other pituitary hormones can further affect these measurements as can a variety of other factors [4,9,18, cross ref – Central Hypothyroidism, Part II, Ref: JCTE_2018_65]. Considering the importance of a normal thyroid function for metabolism and cardiovascular risks [111,112], it is of paramount importance to improve the diagnostic procedures for CH, in particular the measurement methods for FT4 concentrations. Tandem mass spectroscopy might be an obtainable method, despite the high price [113]. More studies are clearly needed to improve management of patients with CH.

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