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Review

Stress Axis in the Cancer Patient: Clinical Aspects and Management

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Abstract: Hypothalamus–pituitary–adrenal (HPA) axis alterations are common in cancer patients, mainly due to the different antitumoral therapies, which lead to several acute and late endocrine side effects. This review summarizes the most recent evidence regarding HPA derangement, both in patients with active neoplasms and in cancer survivors, with particular attention to the impact of the different antitumoral treatments, focusing on the major clinical aspects. While acute hormone failure usually results from injury caused directly by tumor burden or surgical interventions, short- and long-term effects are generally due to chemotherapy, radiotherapy and, as more recently shown, to different types of targeted- and immuno-therapy. Adrenal insufficiency (AI) is mostly caused by pituitary or hypothalamic injury rather than a direct damage of the adrenal gland. Moreover, other treatments commonly employed as supportive therapy or in the context of palliative care (i.e., glucocorticoids, opioids) can lead to HPA dysfunction. Epidemiology and pathophysiology of stress axis alterations in cancer patients still require clarification. Since AI may represent a life-threatening condition, monitoring adrenal function in cancer patients is mandatory, especially in subjects who experience fatigue or during stress conditions, in order to promptly start replacement treatment when needed.

Keywords: hypothalamus-pituitary-adrenal axis; adrenal insufficiency; adverse event; cancer survivors; chemotherapy; radiotherapy; targeted therapy; immunotherapy

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1. Introduction

The association between chronic stress, hypothalamus–pituitary–adrenal (HPA) axis (the major stress hormone axis in most living species) and cancer occurrence is well known. Indeed, chronic stress affects specific hormones that regulate downstream targets through the HPA axis and sympathetic nervous system (SNS), inducing a variety of events critical for the initiation and progression of cancers [1].

On the other hand, endocrine dysfunctions (including HPA alterations) are common in cancer patients, mainly due to the impact of the different cancer therapies, which lead to several acute and late endocrine side effects. While acute hormone failure usually results from injury caused directly by tumor burden or surgical intervention, short- and long-term effects are generally due to chemotherapy (CT), radiotherapy (RT) and, as more recently shown, to different types of targeted- and immuno-therapy. In particular, late endocrine side effects of cancer treatments are a peculiar feature of cancer survivors, as they show a cumulative incidence of about 50% after a 15-year follow-up from cancer recovery [2]. In cancer survivors previously treated with systemic CT or RT, as well as in patients treated with targeted- and immune-therapy, adrenal insufficiency (AI) occurs more often due to pituitary or hypothalamic injury rather than to direct damage involving the adrenal gland.

In this review, we will focus on the clinical aspects of stress axis function and its management in cancer patients, both with active neoplasms and in cancer survivors, with particular attention to the impact of the different oncological therapy methods.

Data summarized and discussed in this qualitative review are based on an extensive search of the English language medical literature within the PubMed database, using appropriate and relevant keywords for the topic. Manual cross-referencing from reference list of selected articles was used to find additional relevant articles.

2. Stress Axis Response to Surgery, Chemotherapy, and Radiotherapy

2.1. Hypothalamic–Pituitary–Adrenal Axis Dysfunction

2.1.1. The Impact of Tumor Mass and Neurosurgery

The direct involvement of the hypothalamic–pituitary region by a neoplasia can compromise endocrine function by different mechanisms: direct infiltration, mechanical disruption of secreting tissue, or compression from hydrocephalus possibly associated with the tumor. Surgical manipulation may directly contribute to the development of endocrine deficiencies by stretching or shearing of the pituitary stalk, by resection of hypothalamic or pituitary tissue or, indirectly, by ischemia-reperfusion damage, or hemorrhage [3]. These mechanisms can lead to an impairment of pituitary function with a wide range of manifestations, depending on the different hormonal axis affected. In a study performed on 68 children with central nervous system (CNS) tumors, 45 of them (66%) were reported to have some evidence of pituitary deficiencies before irradiation. Particularly, AI was diagnosed by 1 µg adrenocorticotropic hormone (ACTH) test in 15 (22%) patients [4]. More recently, the evaluation by provocative testing of a cohort of 192 pediatric patients affected by primary brain tumors revealed the presence of growth hormone deficiency (GHD), already before irradiation, in 22.9% of them [5].

Despite a general lack of data on adult population, the incidence of post-surgery pituitary dysfunction was reported to vary between 21.6 and 64.7% in patients with non-pituitary CNS neoplasm, regardless of tumor volume, site, or surgical approach [6]. Schneider et al. reported evidence of pituitary dysfunction in seven out of 17 adult patients evaluated at 0.8–9 years after the intervention; four of them developed secondary adrenal failure as a part of panhypopituitarism [7]. A study performed in 37 adult patients who have been submitted to neurosurgery for benign CNS tumors without direct involvement of the hypothalamic-pituitary region demonstrated some degree of hypopituitarism in 43.2% of them 3 months after surgery; four patients (10.8%) developed hypoadrenalism, which was no longer detectable at the re-evaluation performed 12 months after surgery [8]. More recently, Fleck et al. found in a population of 51 adult patients with a mean post-neurosurgery assessment interval of 47.2 months, an overall rate of hypopituitarism of 64.7%, with 51% of patients showing ACTH deficiency [9].

2.1.2. The Impact of Chemotherapy

Currently, the cases of pituitary dysfunction after CT described in the literature are anecdotal, in the absence of any clear association between secondary AI and specific chemotherapeutic agents [10]. Controversial data on the hypothalamic–pituitary axis dysfunction have been reported in survivors of childhood-onset non-CNS tumors treated with CT alone [11]. In CNS tumors, treatment protocols are usually based on CT in association with RT and/or neurosurgery; for this reason, it is difficult to distinguish the role played by CT in the development of hypothalamic–pituitary impairment. Nevertheless, the idea of a potentiating effect of CT on RT-induced hypothalamus–pituitary axis damage has been postulated. Indeed, it has been reported in some studies based on patients treated for medulloblastoma that CT could enhance the sensitivity of pituitary gland to the radiation-induced damage [12].

2.1.3. The Impact of Radiotherapy

Due to the advances in cancer treatment protocols and to the better survival of patients affected by CNS tumors, in recent years the radiation-induced pituitary dysfunction has been widely investigated [13]. Nevertheless, due to their higher rates of recovery and to the greater impact of hormonal deficiencies in younger patients, the most of available data on the impact of RT on pituitary function refer to survivors of childhood-onset cancer [14].

The radiation induced damage is always limited to the anterior pituitary function, whereas there is no evidence to support a role for RT in the development of diabetes insipidus. RT-induced pituitary dysfunction seems to be directly related to the total radiation dose [15] and time from the completion of RT [14]. Less evidence is available about a potential role of age at irradiation, fraction size, sex, and concomitant CT [16].

The HPA axis is quite resistant to radiation and, consequently, secondary AI is rarely observed in CNS tumor survivors. Indeed, the susceptibility of each pituitary axis to RT is quite different, depending on the type of secreting cells affected by radiation. Based on the frequency and temporal presentation of hormonal deficits, GH-secreting cells are considered the most sensitive, followed by the follicle stimulating hormone (FSH) and luteinizing hormone (LH) secreting cells, while those secreting ACTH and thyroid stimulating hormone (TSH) are the most resistant [13]. Particularly, ACTH production seems to be resistant to doses lower than 20 Gy, whereas hypoadrenalism has been reported only in about 3% of patients receiving doses between 20 and 50 Gy [14]. By contrast, patients receiving more than 50 Gy reported a significantly higher rate of ACTH deficiency (27–35% after a follow-up of 15-year) [13]. In childhood-onset CNS tumor survivors, older age at RT seems to be a risk factor for ACTH deficiency [17]. A review of 18 studies, including 813 adult patients treated with RT for intracerebral tumors and nasopharyngeal cancer, has shown some degree of hypopituitarism in about two-thirds of them, with ACTH deficiency developing in 22% of cases [18]. An increased risk of AI has also been reported in long-term survivors of childhood-onset leukemia previously treated with cranial RT (18–30 Gy) [19].

Proton beam radiation (PB) is a newer treatment option, which provides targeted delivery to the tumor site while reducing radiation exposure to normal tissues, such as the hypothalamus–pituitary region. In fact, the rapid decline of radiation exit dose in target tissue could theoretically avoid adjacent tissue exposure, thus potentially reducing the rate of hypopituitarism compared with traditional regimens [20]. In a study on pediatric patients with brain tumors, Viswanathan et al. showed a lower rate of ACTH deficiency in children treated with PB (15.8%) compared to those treated with PB combined with conventional RT (25%), despite a similar rate of overall pituitary dysfunctions. Interestingly, in the conventional plus PB group, endocrine dysfunctions were detected sooner in the follow-up than in the PB only group (0.33 ± 0.11 year versus 1.17 ± 0.4 years, respectively) [21]. Conversely, Eaton et al. reported a comparable incidence of AI among patients affected by medulloblastoma and submitted to PB, when compared to those treated with photon irradiation [22].

Finally, some evidence suggests that in cancer survivors without organic pituitary insufficiency, a functional disruption of hypothalamic–pituitary regulation may also occur leading to HPA hyperactivity. Indeed, an increased activity of HPA axis in cancer survivors has been reported [23]. The authors measured the stimulated and spontaneous release pattern of cortisol in 34 subjects who had underwent cranial RT for CNS tumors or leukemia (all with normal peak cortisol responses to the insulin tolerance test), and in 33 age, gender, and body mass index-matched controls; patients showed a significant increase in 24 h circulating cortisol levels, with a 20% increase in cortisol production rates, compared with controls. They hypothesized that chronic stress due to long-term and poor quality of life in cancer survivors may account for this increase in cortisol levels.

From a clinical perspective, AI can be a life-threatening condition. Nevertheless, cancer survivors treated with cranial RT usually show a partial impairment of ACTH production and only a few patients require daily hydrocortisone replacement. Indeed, Kyriakakis et al. reported a 23.4% incidence of secondary hypoadrenalism in adult non-pituitary CNS

tumors survivors, but less than half of affected patients (11 out of 25) required chronic replacement therapy [24]. Clinical presentation is often subtle, due to the fact that peculiar symptoms of AI (asthenia, weight loss, abdominal pain, etc.) can be frequently found in cancer patients with normal cortisol production. In all patients at risk (cranial RT at doses > 30 Gy, surgery involving the sellar or suprasellar region), an annual evaluation of basal or, if needed, stimulated cortisol blood concentration should be performed. When needed, adrenal replacement therapy in cancer survivors can be carried out, as well as for the general population, with oral hydrocortisone, with the warning to increase doses, or with the use of parenteral administration during stress [25].

2.2. Primary Adrenal Insufficiency

In cancer survivors, primary AI is a rare condition that mainly occurs as a consequence of removal or destruction of both adrenal glands (e.g., bilateral adrenalectomy, hemorrhage, metastasis completely involving adrenal glands), or after treatment with adrenolitic agents for primary adrenal cancer [26]. Primary adrenal lymphoma, bilateral in up to 75% patients, may also be a rare cause of AI [27]. Conversely, unilateral adrenalectomy (for neuroblastoma, nephroblastoma or metastasis of other tumors) does not usually cause adrenal failure but may rise the central set-point of the HPA axis to a higher functioning level, thus affecting the cardiovascular risk profile of these patients [28]. Radiation-induced adrenal injury has not been described in the literature and the adrenal glands are reported to be relatively radio-resistant [29]. Management requires prompt glucocorticoid and mineralocorticoid replacement as usually advised for Addison disease.

3. Stress Axis Response to Tyrosine Kinase Inhibitors

In the last decades, the increasing understanding of the mechanisms underlining cancer progression and invasiveness has led to the development of new molecular-targeted agents. Tyrosine kinases (TKs) play a key role in the signaling pathway regulation and their aberrant activation has been implicated in human tumorigenesis [30]. Thus, multitarget TK inhibitors (TKIs), including vascular endothelial growth factor receptor (VEGFR) inhibitors, have been investigated for the treatment of solid and hematological malignancies. In view of their efficacy, these agents currently represent a valid therapeutic option for different neoplasms. However, a large proportion of TKI-treated patients experience adverse events that can affect quality of life; in some cases, drug interruptions or dose reductions are necessary in order to manage these complications. The most common adverse events include fatigue, hand-foot skin reaction, hypertension, gastrointestinal symptoms, endocrinopathies, and metabolic disorders [31].

To date, the effects on the stress axis of these antitumoral drugs have not been widely investigated. The current available evidence is mainly based on studies with a small sample size; moreover, the drug effect on the HPA axis has been analyzed only for a limited number of TKIs.

Histological changes of the adrenal gland have been observed in rats and monkeys receiving sunitinib, including adrenal haemorrhage and necrosis. Although the mechanism of the adrenal damage is not fully understood, a dose- and time-related early impairment of the capillary network in the adrenal cortex was observed, likely mediated by the anti-VEGF action of sunitinib, which preceded the damage observed in the parenchyma [32]. In animals, other histological changes, such as inflammation and hypertrophy of the adrenals were also described [33].

In a clinical setting, AI during treatment with sunitinib was anecdotally described: one out of 400 patients across multiple clinical trials showed consistently abnormal ACTH stimulation test results, without clinical evidence of AI [34].

A high risk of ACTH and cortisol deficiency was reported during treatment with imatinib in Abelson proto-oncogene (BCR-ABL) positive chronic myelogenous leukaemia. Bilgir et al. evaluated the HPA axis in a group of 25 patients treated with imatinib, using glucagon stimulation test and low dose ACTH test: an impairment of cortisol secretion was

detected in 48% of cases. Janus kinase-signal transducers and activators of the transcription (JAK2-STAT) pathway seems to play a role in the ACTH and cortisol release. Therefore, it could be speculated that imatinib might have led to an alteration of the HPA axis by inhibiting the tyrosine phosphorylation of JAK2 by BCR-ABL [35]. However, the small sample size, the lack a control group, and the absence of a baseline evaluation does not permit definite conclusions to be drawn.

Conversely, an increase of plasma cortisol was found in patients with medullary thyroid cancer treated with vandetanib, both in basal conditions and after ACTH stimulation; moreover, ACTH and cortisol binding globulin (CBG) levels increased with therapy. The pathogenesis of this apparent activation of the HPA axis is unknown. However, the diagnosis of hypercortisolism was not supported by the 24-h urine free cortisol levels, which resulted within the normal range in all the 14 subjects on vandetanib [36].

More recently, basal and stimulated adrenal function was evaluated in advanced radioiodine-refractory differentiated and medullary thyroid cancer receiving lenvatinib or vandetanib, respectively. Ten out of 12 patients with fatigue had a gradual ACTH increase and normal plasma cortisol levels; the diagnosis of primary AI was confirmed in six of them after the detection of a blunted plasma cortisol response upon ACTH stimulation. In all but one patient, replacement therapy with cortisone acetate improved the degree of fatigue, suggesting a role of the impaired adrenal function in the genesis of asthenia [37]. Nevertheless, these results need to be confirmed in larger studies, possibly with a control group and a baseline evaluation before the start of TKI.

To summarize, information on adrenal function during TKI treatment is scant and partly controversial. However, since AI may represent a life-threatening condition, it is advisable to monitor adrenal function in TKI-treated patients, especially in subjects who experience fatigue or during stress conditions, in order to start replacement treatment when needed [38].

4. Stress Axis Response to Immunotherapy

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies (Abs) that restore the antitumoral immune response blocked by the cancer itself, acting on immune checkpoints such as the cytotoxic T-lymphocyte antigen-4 (CTLA-4; e.g., ipilimumab), the programmed cell death protein-1 (PD-1; e.g., nivolumab, pembrolizumab), and its ligand (PD-L1; e.g., avelumab, durvalumab, atezolizumab). In recent years, this new class of agents has revolutionized the management of several malignancies, showing a durable disease response and improved survival in treated patients [39]. However, immune checkpoints also play a pivotal role in maintaining immunological self-tolerance. Therefore, ICIs may cause several immune-related adverse events, including endocrinopathies. In the context of ICI-related endocrine toxicity, both hypophysitis and primary AI can occur [40].

Hypophysitis is one of the most common ICI-related endocrinopathies. According to a metanalysis of 38 randomized clinical trials, it is more commonly observed on anti-CTLA-4 therapy (3.2%) than during the sole anti-PD-1 or anti-PD-L1 therapy (<1%); moreover, its incidence is higher under anti-CTLA-4/anti-PD1 combination therapy (6.4%) [41]. During anti-CTLA-4 therapy, several large retrospective studies reported rates that exceeded 10% of treated patients, probably reflecting differences in hormone monitoring or an increased awareness of this adverse event [42].

Hypophysitis occurs mainly in men and older patients, approximately 8–10 weeks following the initiation of therapy, less commonly after the first 3 months, but the onset can be even earlier (after 30 days) during anti-CTLA-4/anti-PD-1 combination treatment [40,43].

The pathogenesis of ICIs-induced hypophysitis remains mostly unknown. CTLA-4 is expressed in both murine and human pituitary tissue; conversely, a significant expression of PD-1 or PD-L1 in normal human pituitary gland has not been demonstrated. The activation of both Ab-dependent cell-mediated cytotoxicity and the complement pathway have been observed in anti-CTLA-4-related hypophysitis in murine models [42]. In the human setting, the presence of anti-pituitary Abs (anti-thyrotrophs, anti-corticotrophs, and

anti-gonadotrophs Abs) was detected in the serum of patients with hypophysitis secondary to anti-CTLA-4 treatment [44].

The diagnosis is based on a combination of clinical, biochemical, and radiographic findings. Clinical manifestations are usually non-specific and the diagnosis is even more challenging in cancer patients due to the overlap of tumor-related symptoms. ICI-related hypophysitis should be suspected after the onset or the worsening of headache or profound fatigue [42]. Brain magnetic resonance Imaging (MRI) allows to rule out the presence of a pituitary metastasis and might show a pituitary enlargement, generally mild to moderate, which can precede the clinical manifestation in some cases, and usually resolves after several weeks [40].

At the time of diagnosis, multiple pituitary hormonal deficiencies are commonly detected. Together with central hypothyroidism and hypogonadotropic hypogonadism, ACTH deficiency is one of the most common clinical manifestations, occurring in nearly 80% of patients with ICI-related hypophysitis [43]. Basal ACTH and plasma cortisol levels peaking in the early morning permit the identification of an alteration of HPA axis; ACTH stimulation can be helpful to disclose a mild cortisol deficiency, even if a normal test cannot exclude a secondary AI of recent onset [42].

Since this condition may be life-threatening, glucocorticoid replacement should be promptly initiated, prior to thyroid replacement to avoid the worsening of an adrenal crisis. The clinician can postpone the anticancer therapy in the acute phase, but withdrawal of ICI is not required [43].

Recovery of the ACTH axis is rare in patients with ICI-induced hypophysitis. Therefore, patients should be adequately informed about the need of increasing the dose in stressful situations or employing hydrocortisone injections in case of inability to use the oral route of administration [40,42].

As other ICI-induced adverse events, the onset of hypophysitis seems to be associated with improved cancer outcomes and to positively predict survival [45]. However, data are limited by the sample size of the studies and by their retrospective nature; further research is necessary to confirm the association between ICI-induced HPA axis dysfunction and tumor response [42].

More rarely, ICI has been associated with primary AI. Its incidence is difficult to estimate because several studies have reported AI without specifying its etiology (primary or central), hence data should be cautiously interpreted. Primary AI was observed in less than 1% of patients with ICI monotherapy (either CTLA-4 or PD-1) and up to 8% during combination therapy [40].

It can occur after a median time of 4 months, even if the time of onset can vary from one week to 18 months after the start of ICI treatment [43]. Its occurrence was described also after ICI withdrawal [46].

The pathogenetic mechanisms underlying the development of adrenal damage during ICIs are mostly unknown. An auto-immune destruction of the adrenal glands is the most plausible; anti-adrenal Abs have been detected in few patients. Computed tomography performed in patients with ICI-induced primary AI showed morphological signs of adrenal inflammation or atrophy; moreover, a uniform increase in 18F-fluorodeoxyglucose (18F-FDG) uptake in the adrenal glands consistent with adrenalitis has been reported [40,41].

According to a recent review, 90% of patients with ICI-induced primary AI presented with adrenal crisis (fatigue, hypotension, nausea, vomiting, abdominal pain) and mortality was reported in 7% of cases [47].

When adrenal crisis is suspected, blood sample for plasma cortisol and ACTH should be immediately collected if possible, and empiric treatment must be started without waiting for test results [40]. In non-urgent situations, diagnosis can be made from a low morning plasma cortisol (<140 nmol/L) with a high morning ACTH; when basal morning plasma cortisol values are in grey zone (140–500 nmol/L), primary AI can be confirmed by a poor response to ACTH stimulation test. Electrolyte monitoring commonly permits the identification of hyponatremia or hyperkalemia. Measurement of plasma renin (or plasma renin

activity) and aldosterone can be helpful to evaluate the presence of a mineralocorticoid deficiency [42]. Testing for anti-21 hydroxylase is not commonly performed in clinical practice [43].

Management requires prompt glucocorticoid and mineralocorticoid replacement; ICI therapy is not contraindicated [43]. In case of acute adrenal crisis, higher doses of corticosteroids are required (intravenous or intramuscular injection of 100 mg hydrocortisone followed by continuous infusion of 100 mg hydrocortisone over 24 h and rehydration therapy), as for non ICI-related primary AI. After biochemical improvement and clinical recovery, treatment can be continued using oral administration, with subsequent tapering to physiological doses and introduction of fludrocortisone, as recommended in Addison's disease [40].

According to the available data, recovery is unusual and hormonal replacement therapy is often lifelong; therefore, patient education in terms of sick day rules and emergency hydrocortisone is essential [43].

5. Stress Axis Response in the Context of Supportive Therapies and Palliative Care

5.1. The Impact of Glucocorticoid Therapy

Glucocorticosteroids (GC) are often used in cancer patients. Indeed, they are employed either in long-lasting therapy to counteract side effects of CT, to hinder cytokine-mediated inflammatory processes, to control peritumoral edema and neurological symptoms (due to increased intracranial pressure by primary cancer or metastasis), for complications such as graft versus-host disease after stem-cell transplantation, or in pulses in treatment regimens [48].

Tertiary AI is a well-known result of chronic steroid treatment in patients treated with equivalent dose higher than 30 mg/day of hydrocortisone or 7.5 mg/day of prednisolone for over 3 weeks [49,50]. AI should be considered in every patient with a story of abrupt cessation of chronic GC administration who complains of generally feeling-sick. To prevent an adrenal crisis, a rapid hydrocortisone administration should be started at the same time of confirmatory ACTH test.

Normal adrenal function may take months or years to recover after a chronic GC treatment [51]. On the other hand, the risk of AI, in patients receiving high-dose but relatively short-term corticosteroids, remains a debatable issue. These regimens are commonly used for the treatment of various hematologic malignancies, such as acute lymphoblastic leukemia and diffuse large B cell lymphoma [52], the most common lymphoma subtype worldwide. An R-CHOP (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine plus prednisone or prednisolone) regimen remains the standard protocol for diffuse large B cell lymphoma treatment and each cycle includes five consecutive days of high-dose prednisolone (100 mg/day of prednisolone for five continuous days in each cycle) [53].

Owattanapanich et al. have studied adrenal function in 10 patients during treatment for diffuse large B cell lymphoma. They performed an ACTH low-dose test (1 µg) before starting CT and repeated it three weeks after every cycle. Patients with a peak stimulated cortisol lower than 500 nmol/L at the last cycle, repeated the low-dose test after 30 and 60 days, to assess adrenal function recovery. AI was diagnosed in 3 out 10 patients, mostly after the fifth cycle. The adrenal function recovered at 30 days after the last cycle of CT in all but one patient, whose HPA axis suppression lasted till 90 days from the last administration of CT [52].

The incidence of AI, as well as the recovery period, in this study was lower than that reported in other studies, despite the use of a comparably high dosage of GC per day [54,55], possibly due to different therapy schedule.

Acute lymphoblastic leukemia represents 30% of all malignancies in children and adolescents [56]. In these contexts, high doses of GC are usually part of CT treatment [57]. GC are commonly discontinued with no tapering, raising the risk of a transient suboptimal cortisol secretion [58,59].

In the study of Ahmad et al., 21 children were enrolled, younger than 14 years and with a new diagnosis of acute lymphoblastic leukemia. The GC therapy was given during the induction phase and discontinued without tapering in all patients. Fourteen patients received dexamethasone 6 mg/m^2 for 28 days, five patients received dexamethasone 10 mg/m^2 for 14 days and one patient received prednisolone 60 mg/m^2 for 14 days. The first HPA assessment was made before starting the treatment protocol, dosing serum cortisol and plasma ACTH at 8:00 a.m. The second HPA axis evaluation with a low-dose ACTH test (1 µg) has been scheduled one/two weeks after the conclusion of the induction phase. Post-induction evaluation showed that fifteen children (75%) had a peak serum cortisol concentration > 500 nmol/L, whereas five children (25%) had an insufficient response (cortisol peak between 300 and 500 nmol/L). No patients showed a markedly decreased cortisol response to ACTH (cortisol peak < 300 nmol/L) [60].

Rensen et al. recently reviewed seven studies associated with AI after GC therapy for childhood acute lymphoblastic leukemia. The majority of children recovered from AI after a few weeks, but prolonged suppression occurred in a few of them, lasting more than several months [61].

5.2. The Impact of Opioid Therapy

The prevalence of cancer-related pain ranges between 30% and 50% in patients who are receiving cancer-directed therapies and in more than 70% of patients with advanced stages of disease [62]. It covers a large group of pain syndromes (postoperative pain, radiation, or CT-induced mucositis, CT-induced neuropathy, unresectable bone metastasis, etc.) that frequently require the use of opioids, because of their fast and powerful effect in treating moderate to severe pain [63]. The treatment lengths are variable and it can last several months.

Several adverse effects of opioids, such as addiction, sedation, constipation, and nausea are generally well recognized. A number of studies have reported their induction of endocrinopathy. In chronic opioid-treated patients, hypogonadism may be present in up to 89% of men and 67% of women, whereas adrenal failure can be found in 8% and 29%, respectively [64–68].

Opioids exert negative effects on HPA axis through the three main opioid receptors (µ, δ, and κ) involved the opioid actions [69]. At the hypothalamic–pituitary level, they can inhibit the secretion of corticotropin releasing hormone (CRH) and antidiuretic hormone (ADH), resulting in decreased ACTH release [70–72]. The inhibitory action of opioids is evident after both short-and long-term use. In healthy volunteers, a single morphine administration suppresses basal and CRH-stimulated ACTH and cortisol levels [71,72], while buprenorphine, hydromorphone, and remifentanil have been reported to attenuate cortisol response to psychosocial or surgical stress [73,74].

In patient with chronic pain, many opioid formulations have been found causing HPA axis suppression that can be recovered after drug withdrawal or dosage lowering [75].

Clinical diagnosis could be challenging in patients with chronic pain where symptoms of AI could be attributed to the underlying syndrome or associated therapies.

A recent metanalysis, including 21 studies and 1095 patients, investigated the effects of opioid use on HPA axis activity. Only nine studies reported an inhibitory effect of opioids on HPA function. The largest studies (including 176 and 170 patients, respectively) reported lower cortisol and ACTH levels in treated patients in comparison to controls. A dose–response relationship between opioid use and cortisol levels was reported by two studies. For every 10 mg morphine analog the fasting cortisol levels decrease of 8.6 nmol/L and an impaired cortisol response after ACTH administration has been demonstrated for treatment with a higher dose of opioids [76].

Recently, Lamprecht et al. [77] evaluated pituitary function in 25 patients with chronic pain, on therapy with oral or transdermal opioids for a duration of >6 months at a dose of ≥25 mg morphine-equivalent daily dose, in comparison with a control group. They performed 250 µg ACTH stimulation and overnight metyrapone test to detect AI. AI

was found in 22.5% of patients taking opioids, compared to none of the control patients. Moreover, the treated group were more likely to have morning serum cortisol levels below 5 μg/dL. Patients with a blunted cortisol response after stimulation were taking higher median morphine-equivalent doses.

It has also been observed that opioid users with lower cortisol levels reported higher levels of bodily pain. This may indicate a stress–induced hypocortisolism due to pain itself [78]. In a pilot randomized placebo-controlled trial, Nenke et al. showed that cortisol replacement at physiological dosage in patients treated with opioids for non-cancer pain resulted in a better pain control [79].

Finally, the clinical significance of AI in cancer patients using opioids (especially in those with mild suboptimal response to dynamic tests) and the need of routine GC replacement in this context requires further investigations. Nevertheless, in the context of palliative care, GC treatment is frequently employed at supra-physiological doses, reducing the clinical significance of HPA axis dysfunctions.

6. Conclusions

The current literature indicates that stress axis derangement can occur in cancer patients, as part of endocrine dysfunction, mainly due to oncological therapies. It can appear as an acute adrenal failure (i.e., after adrenalectomy), a short-term (mainly after targeted- or immune-therapy) or a late side effect (mainly after CT or RT) of treatments, especially in cancer survivors. Moreover, glucocorticoid treatment commonly used as supportive therapy as well as drugs used in the context of palliative care (i.e., opioids) can lead to HPA dysfunction. AI occurs more often due to pituitary or hypothalamic injury rather than to direct damage involving the adrenal gland.

Epidemiology and pathophysiology of stress axis alterations are still to be clarified in cancer patients and clinical prospective trials in large populations are needed to highlight these issues. On the other hand, since AI may represent a life-threatening condition, monitoring adrenal function in cancer patients is mandatory, especially in people who experience fatigue or during stress conditions, in order to promptly start replacement treatment when needed.

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