Time dependence of radiation-induced hypothalamic-pituitary axis dysfunction in adults treated for non-pituitary, intracranial neoplasms

Running title: Time dependence of HPA dysfunction

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17 **ABSTRACT**

18 **Background and purpose:** Hypothalamic pituitary axis dysfunction (HPA) is a sequela of cranial
19 radiotherapy (RT). The purpose of the study was to use endocrine data from existing publications to
20 characterize the baseline endocrine status, the effects of RT to the HPA during the first follow-up year,
21 and the time dependence of radiation-induced HPA dysfunction in patients treated with RT for non-
22 pituitary intracranial neoplasms.

23 **Materials and methods:** A systematic search of databases was performed for articles that reported the
24 results of prospective endocrine testing for patients aged 16 and older who were treated with
25 neurosurgery (NS) for non-pituitary intracranial or RT for nasopharyngeal neoplasms. To predict the
26 RT-related change in hormone levels over time, long-term prospective endocrine data from
27 nasopharyngeal studies was normalized to baseline hormone data and fitted to an exponential decay
28 model. This process was repeated with normalization to year 1 hormone data.

29 **Results:** Eight unique articles met eligibility criteria. HPA dysfunction occurred in 21.6% to 64.7% of
30 patients who were assessed for endocrinopathies following NS. Studies on the early effects of RT on
31 nasopharyngeal patients showed statistically significant changes in GH, LH, and FSH levels during the
32 1st year of follow-up. Time dependence modeling demonstrated that normalization to year 1 hormone
33 levels yield exponential equations with stronger measures of goodness of fit.

34 **Conclusion:** HPA dysfunction in patients treated for non-pituitary intracranial neoplasms is likely a
35 result of both NS and RT treatment. While significant endocrine changes can occur during this first
36 year of follow-up, those documented at year one may be more predictive of subsequent HPA
37 dysfunction.

38 **Keywords:** hypopituitarism, radiotherapy, non-pituitary intracranial neoplasms, pituitary insufficiency

Introduction

Radiotherapy (RT) is a treatment modality integral to the management of adults diagnosed with non-pituitary intracranial neoplasms. The hypothalamic-pituitary axis (HPA) is often located within the irradiated volume, and HPA dysfunction can occur as a result of collateral radiation to either intracranial structure. A meta-analysis of endocrinopathy studies in patients evaluated 2 to 25 years following radiotherapy treatment showed a 54% prevalence of hypopituitarism, and abnormalities of growth hormone (GH) secretion occurred with the greatest frequency [1]. Hypopituitarism can present with a variety of symptoms, many of which are non-specific (e.g. lethargy, fatigue, weight loss or gain, impaired concentration), and is frequently associated with menstrual disturbance and erectile dysfunction. It is an important independent risk factor for death secondary to cerebrovascular and cardiovascular diseases. As such, careful consideration of the radiation dose delivered to the HPA is important to the minimization of radiation-induced morbidity and mortality [2].

Endocrine status can be evaluated through the measurement of (a) basal serum/plasma hormone levels or (b) peak hormone levels following tests that stimulate or suppress the HPA. Basal levels interpreted within the context of measures of end organ function are, in the majority of cases, sufficient to diagnose unambiguous abnormalities of thyroid stimulating hormone (TSH), luteinizing hormone (LH), and follicle stimulating hormone (FSH) secretion. However, when the results of these tests are equivocal, dynamic evaluation (e.g. using stimulation tests) may help to confirm or exclude more subtle endocrine dysfunction. Likewise, although basal levels of insulin-like growth factor I (IGF-I) should represent an integrated index of pulsatile GH secretion, upwards of 25% of individuals with a normal IGF-I level but suspected GH deficiency will be shown to have a suboptimal GH response on dynamic testing [3]. In some instances, serial measurements of basal or peak hormone levels over time may be required to demonstrate progressive decline/attenuation. Therefore, appropriate evaluation of

the anterior pituitary demands an integrated approach with the routine utilization of both basal and dynamic endocrine testing when HPA dysfunction is suspected.

No prospective studies that report the development of HPA dysfunction as evidenced by long-term, serial endocrine testing currently exist for adult patients diagnosed with non-pituitary intracranial tumors [4]. Therefore, much of what is understood regarding radiation-induced HPA dysfunction in this population is derived from retrospective and cross-sectional endocrine investigations. Based on temporal presentation and frequency of occurrence, it is believed that the GH axis is most prone to radiation-induced insufficiency, followed by the LH/FSH, adrenocorticotrophic hormone (ACTH) and TSH axes [5]. After a median follow-up of 8 years, Kyriakakis found that 86.9%, 34.6%, 23.4% and 11.2% of patients exhibited GH, LH/FSH, ACTH, and TSH deficiencies, respectively [6]. A similar pattern of hormone loss has been observed in patients diagnosed with primary pituitary tumors, both at baseline and at 5 years post-RT, suggesting that this sequence may indeed reflect the sensitivities of the various axes to insult and/or injury [7]. Other investigators, however, have suggested that hypothalamic-pituitary-thyroid axis dysfunction may be more common following RT, reflecting abnormal thyrotropin releasing hormone (TRH) secretion [8]. Available evidence also indicates that the likelihood of manifesting hypopituitarism increases with dose to the HPA and length of post-RT follow-up [9].

Studies comparing adult patients diagnosed with non-pituitary intracranial tumors and treated with RT versus those treated with both RT and chemotherapy (CT) have failed to demonstrate an increased risk of HPA dysfunction in the latter group and, therefore, HPA dysfunction in these adults is considered to be RT-attributable [4, 6]. In the assessment of baseline endocrine status in children, Merchant et al. identified pre-irradiation endocrinopathies in 15 of 32 (47%) patients diagnosed with posterior fossa tumors [10]. As such, retrospective studies of HPA dysfunction in adults may

overestimate the degree of radiation-induced HPA dysfunction. In a separate study, Merchant et al. described the decline in GH levels in children following cranial RT by an exponential equation dependent on the radiation dose to the hypothalamus and the follow-up time interval [11]. No exponential modeling of the change in hormone levels following cranial irradiation with respect to time has been performed in adults.

The majority of adults treated for non-pituitary intracranial neoplasms will undergo neurosurgery (NS) prior to initiation of RT. Therefore, studies that report post-NS endocrine status in patients operated for extra-sellar tumors may reflect the pre-RT (baseline) endocrine status of patients treated with RT for non-pituitary intracranial tumors. Likewise, as patients who receive RT for nasopharyngeal cancers do not receive NS treatment, endocrine changes in these subjects may inform the RT-specific changes that occur in our population of interest. The purpose of the study was to use endocrine data from existing publications on cohorts of adults treated with NS for intracranial tumors distant to the HPA or RT for nasopharyngeal tumors to characterize the baseline endocrine status, the early effects of RT to the HPA, and the time dependence of radiation-induced HPA dysfunction in patients treated with RT for non-pituitary intracranial neoplasms. This investigation was performed as a prelude to VoxTox, a prospective clinical study that aims to correlate endocrine toxicities in patients treated with RT for non-pituitary intracranial tumors with the radiation dose to the HPA [12].

Materials and methods

A search for prospective studies in English on neurosurgery, cranial irradiation, and endocrinopathies was performed on March 25, 2016. The search strategy focused on the key terms of neurosurgery, radiotherapy, intracranial tumors, nasopharyngeal tumors, hypopituitarism and included the following databases: PubMed, ScienceDirect, EMBASE, CINAHL, Web of Science, Ovid Medline

and Cochrane Library. Variations of key terms (i.e. hypopituitarism and pituitary insufficiency) were used to broaden the scope of the search. The references of returned articles were also reviewed for relevant publications. Studies were eligible for inclusion if they reported the results of prospective endocrine testing for patients aged 16 and older who were treated with NS for non-pituitary intracranial tumors or RT for nasopharyngeal neoplasms.

Articles were reviewed for the results of endocrine testing. As many publications presented data in the form of graphs, Plot Digitizer, a freely available Java program, was used to extract hormone values and their respective time points. Unless the results for patients who did not receive cervical lymph node irradiation were specified, endocrine data pertaining to the thyroid axis for nasopharyngeal patients were omitted from our analysis. To study the time dependence of endocrine changes in nasopharyngeal studies that present the results of long-term longitudinal follow-up, hormone levels were normalized by representing all hormone values as a fraction of the baseline hormone level for each axis. MATLAB® Curve Fitting application was used to fit normalized hormone level values to the exponential function $H(t) = a * e^{b*t}$, where H pertains to the hormone axis, a represents the first normalized hormone value and is always equal to 1, b represents the rate of hormone decline with respect to time, and t represents years of follow-up after the normalized hormone measurement. Hormone levels were normalized to the year 1 hormone value and the above process was repeated. As a result, two exponential equations, one representing the decline in hormone levels from baseline and one representing the decline in hormone levels from year 1, were produced for each axis.

Results

Eighty-eight articles were reviewed and lessened to 8 unique articles, based on eligibility criteria. Demographic data for all included studies are presented in Table 1.

Neurosurgery-Related Endocrinopathies

Four studies presented data for patients treated with NS for non-pituitary intracranial tumors [13, 14, 15, 16]. Post-NS endocrinopathies ranged from 21.6% to 64.7%. However, no study demonstrated a statistically significant difference in the incidence of hypopituitarism with tumor location, tumor volume and/or neurosurgical approach. Schneider et al. reported the results of symptom-prompted hormone testing in patients treated with NS, RT, and/or CT for non-pituitary intracranial neoplasms [15]. In a sub-analysis of 17 patients treated solely with NS, 41.2% demonstrated hypopituitarism on endocrine testing. Additionally, 1 patient showed primary hypogonadism as evidenced by elevated LH/FSH in the setting of low testosterone. In a population with a mean post-NS assessment interval of 47.2 months, Fleck et al. found deficiencies of GH, LH/FSH (in men), and ACTH in 31.4%, 9.1%, and 51.0% of patients, respectively [14]. No cases of TSH deficiency were observed, and no significant difference in the rate of endocrinopathies was seen in the 6 of 51 total participants who received RT and/or CT.

In an effort to assess the pattern of hypopituitarism in the year following NS, De Marinis et al. performed endocrine assessments at 3 and 12 months on 37 post-NS patients. GH, LH/FSH, TSH, and ACTH deficiencies were present in 7, 4, 2, and 4 patients at 3 months and in 5, 2, 1, and 0 patients at 12 months. One patient with normal pituitary function at the 3-month evaluation exhibited severe GH deficiency at 12 months, and 2 patients with GH deficiency at 3 months were lost to follow-up [13]. To investigate whether endocrinopathies may exist prior to NS, Wachter et al. performed endocrine testing in 54 patients pre-operatively, as well as at 1 and 7 days, post-operatively. The prevalence of HPA dysfunction pre-operatively (44.4%) was no different from that of the post-operative evaluations [16]. However, several patients were treated preoperatively with medication known to effect the HPA,

including dexamethasone, thyroxine, and L-dopamine. Several other patients demonstrated elevated levels of LH/FSH, ACTH, and IGF-I. None of the 9 patients who received RT and/or CT prior to NS showed evidence of endocrine abnormalities.

Radiotherapy-Related Endocrinopathies

Four unique studies on RT treatment for nasopharyngeal cancers reported the results of basal and/or stimulated endocrine testing performed during the first year of post-RT follow-up [17, 18, 19, 20, 21]. Statistically significant changes were noted in the GH, LH, and FSH axes. Peak GH levels decreased in two of the three studies that reported the results of stimulated GH testing, including from 16.1 ng/ml at baseline to 9.4 ng/ml at one-month evaluation, as reported by Chen et al [18, 20]. However, no significant change in basal GH was noted [18]. Huang et al. and Lam et al. found stimulated LH levels (men only) to decrease as early as 6 months post-RT. In contrast, basal and stimulated FSH values (men only) increased in both studies during this same time interval [17, 19]. No significant changes were observed in stimulated cortisol levels or in basal measurements of serum/plasma cortisol, testosterone, estradiol, or prolactin.

Time Dependence Modeling

One study presented longitudinal, dynamic endocrine data pertaining to 31 patients treated for nasopharyngeal tumors with 39 Gy to the hypothalamus and 62 Gy to the pituitary gland, evaluated at baseline for evidence of endocrinopathies, and assessed annually for 5 years following RT [20]. In comparison to normalization to baseline, normalization to year 1 for GH, LH, FSH, and TSH axes yielded curves with stronger measures of goodness of fit (Figure 1), as evidenced by larger R-squared values and smaller values for sum of squares (Table 2). Based on the exponential equations GH, FSH

(men only), LH (men only), TSH, and cortisol levels at 5 years post-RT represent 27%, 52%, 56%, 57%, and 88% of their 1 year values, respectively.

Discussion

In the application of cranial RT for the treatment of neoplasms, tumor control is often obtained at the expense of increased risk of toxicity to the nervous system. Radiation-induced HPA dysfunction has been more extensively studied in children treated for intracranial neoplasms and adults treated for either pituitary tumors or nasopharyngeal cancers [7, 11, 17, 18, 17, 19, 20]. However, much less is understood regarding the development of HPA dysfunction in patients who receive NS and RT for the management of non-pituitary intracranial neoplasms. As many of these individuals may be taking medications known to effect the HPA axis prior to NS (including glucocorticoids, dopamine, thyroxine, antidepressants, benzodiazepines) and/or may present with hormone abnormalities related to acute illness following NS, evaluation of the HPA axis during the perioperative period is often withheld [14, 22]. Likewise, as the tumors are distant to the HPA, routine post-NS endocrine assessment/follow-up is often considered unnecessary. In this study, we found that HPA dysfunction occurred in 21.6% to 64.7% of patients assessed for endocrinopathies following NS for non-pituitary intracranial neoplasms. No significant association was established between proximity of the tumor to the HPA and hypopituitarism. While the hormone hypo- and hyper-secretion reported during the perioperative period in one study may not be solely attributable to neurosurgical intervention, other studies have shown that permanent hypopituitarism can develop within 3 months following NS. As such, many adults treated for non-pituitary intracranial neoplasms may have pre-existing disruption of the HPA prior to the initiation of RT.

The ability to predict treatment-related HPA dysfunction is integral to the management of patients diagnosed with non-pituitary intracranial neoplasms. Merchant et al. demonstrated that the volume of the hypothalamus that receives specified ranges of radiation dose can be used to predict the peak GH response to stimulated testing within one year following RT treatment in pediatric patients [11]. Although no studies exist that report a similar dose-volume relationship in adults, data from published studies can be used to better understand the time dependence of HPA dysfunction following RT. We found that, in patients treated solely with RT for nasopharyngeal cancers, RT can cause statistically significant changes in hormone secretion during the first year of follow-up. While decreases were seen in stimulated GH and LH levels, both basal and stimulated FSH increased during this same time interval. It has been suggested that the discordance between LH and FSH may be related to the differential effect to the two axes of alterations to the pulse frequency of luteinizing hormone releasing hormone [19].

The time-dependence modeling predicted hormone levels as a fraction of those values measured at year 1. Such normalization reduces the likelihood of skewing of exponential equations by outlying values. Our analysis demonstrated that modeling based on normalization to baseline hormone levels yielded an exponential equation with a greater rate of decline (more negative decay constant) when compared to that which resulted from normalization to year 1 hormone levels. However, normalization to year 1 hormone levels resulted in exponential equations with stronger measures of goodness of fit. In fact, normalization to baseline for FSH produced an equation with an implausible, positive decay constant as the result of an increase in stimulated FSH from baseline to year 1 and then a decline in FSH during subsequent years to levels that were still above the baseline value. These results suggest that, while more marked changes in hormone levels may occur during the interval between baseline and

the first year of follow-up, hormone levels documented at 1 year of post-RT follow-up may be more predictive of the long-term course of endocrine hormone decline.

It is well documented that neuroendocrine dysfunction observed in the context of acute illness does not always correlate with subsequent long-term hypopituitarism. Characterized by low serum triiodothyronine (T₃) and TSH, with low normal levels of thyroxine (T₄), “sick euthyroid syndrome” or “non-thyroidal illness” is a relatively common finding in acutely ill patients and may reflect an adaptive response, or result from the administration of drugs that are commonly used in the critical care setting (e.g. high-dose corticosteroids and dopamine) [23, 24]. Thyroxine supplementation has not been shown to be of benefit in this context, and thyroid function tests typically return to normal following recovery. Although endocrine changes of acute illness almost certainly do not account for all of the early endocrine abnormalities observed in patients treated for non-pituitary intracranial neoplasms, they do lend support to the case for using hormone data acquired at one year following radiotherapy (i.e. after the “acute phase” has settled) to establish post-treatment hormone status and endocrine trajectories, with the important caveat that any patient manifesting clinical features of hypopituitarism (especially ACTH or TSH deficiency) merits urgent assessment to avoid missing life-threatening hypoadrenalism or hypothyroidism.

There are a few limitations to our analysis. Our assessment of baseline endocrine status included some publications on non-pituitary intracranial neoplasms in which patients received endocrine testing greater than a year following NS. As such, we cannot confirm whether the reported incidences of hypopituitarism in these studies reflect that which was present prior to RT treatment or that which developed during/subsequent to RT treatment. However, that permanent HPA dysfunction can develop after NS for tumors distant to the HPA is important to note.

We used nasopharyngeal patients as a surrogate to understand RT-induced HPA dysfunction in the absence of NS. However, patients diagnosed with nasopharyngeal cancers are treated with much greater doses of RT than that which would be applied in the treatment of non-pituitary intracranial neoplasms. Therefore, our time dependence modeling may over-estimate the rate at which RT-attributable HPA dysfunction develops, although as neurosurgical operations can increase the likelihood of post-treatment pituitary insufficiency, the time-dependence of HPA dysfunction may be comparable between the two tumor populations. Future prospective studies, such as VoxTox, are necessary to assess adequately both the dose and time dependence of HPA dysfunction in patients treated for non-pituitary intracranial neoplasms.

Conclusions

We have demonstrated that HPA dysfunction can occur in patients treated with NS for non-pituitary intracranial tumors. The available evidence suggests that the degree of HPA dysfunction will likely be exacerbated by RT in those patients who are also managed with this treatment modality. As such, endocrine assessments at baseline (following NS and prior to RT) and at 1 year of post-RT are essential to understanding the development of RT-attributable hypopituitarism in this population. While important and statistically significant endocrine changes can occur during this first year of follow-up, the endocrine assessment performed at year one may be more predictive of the likelihood of endocrinopathies during subsequent years.

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Characteristics	Studies							
	De Marinis	Fleck	Schneider	Wachter	Chen	Huang	Kuo	Lam
Cancer	non-pituitary intracranial neoplasms	non-pituitary intracranial neoplasms	non-pituitary intracranial neoplasms	non-pituitary intracranial neoplasms	nasopharyngeal neoplasms	nasopharyngeal neoplasms	nasopharyngeal neoplasms	nasopharyngeal neoplasms
No. of patients (male/female)	37 (13/24)	51 (22/29)	68 (40/28)	54 (28/26)	24 (16/8)	14 (8/6)	25 (19/6)	31 (22/9)
Age in years (range)	median 54.6±13.9 (27-78)	mean 54.9 (20-75)	mean 45.0±1.8 (20-79)	median 56.8	mean 41 (16-67)	mean 47.3±15.3	(36-65)	mean 43.7±8.4
No. received radiotherapy	0	6	44	7	24	14	25	31
RT dose (structure)	-	-	-	-	mean 6480 cGy (tumor bed), 7000 cGy (HPA)	mean 7000 cGy (tumor bed), 4600-5600 cGy (HPA)	mean 7000-7500 cGy (tumor bed), 4500-6000 cGy (HPA)	40 Gy (hypothalamus), 62 Gy (pituitary gland)
No. received neurosurgery	37	51	68	54	0	0	0	0
No. received chemotherapy	0	6	27	6	0	0	0	0
Basal serum hormones measured	GH, IGF-1, TSH, fT4, LH, FSH, estradiol, testosterone, prolactin, cortisol	cortisol, fT4, TSH, IGF-1, FSH, LH, testosterone	cortisol, TSH, fT4, fT3, prolactin, FSH, LH, testosterone, estradiol	FSH, LH, estrogen, testosterone, prolactin, TSH, fT4, fT3, IGF-1, cortisol	-	FSH, LH, TSH, prolactin, GH, cortisol, ACTH, estradiol, testosterone	GH, ACTH, LH, FSH, prolactin, TSH, T3, T4	LH, FSH, prolactin, TSH, estradiol, testosterone, T4
Dynamic tests (hormone evaluated)	-	ITT (GH, ACTH, and cortisol), GHRH+ARG (GH), ACTH stimulation test (ACTH)	GHRH+ARG (GH)	GHRH (GH), LHRH (LH/FSH), CRH (ACTH), TRH (TSH)	LHRH (LH/FSH), ITT (GH, cortisol), TRH (prolactin, TSH)	GnRH (LH/FSH), GHRH (GH), TRH (TSH), ITT (GH, cortisol)	-	ITT (GH, cortisol), GnRH (LH, FSH), TRH (TSH)
Post-treatment assessment intervals	3 months, 12 months	5-168 months	-	baseline, 1 day, 7 days	baseline, 1-1.5, 15-18 months	baseline, 6, 12, 24 months	baseline, 1 week	baseline, 1, 2, 3, 4, 5 years

Table 1: Demographic data from 8 studies of HPA dysfunction secondary to NS and/or RT.

Abbreviations: ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; FSH, follicle stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; GH, growth hormone; GnRH, gonadotropin-releasing hormone; IGF-1,

insulin-like growth factor 1; GHRH+ARG, growth hormone releasing hormone-arginine stimulation test; ITT, insulin tolerance test; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone.

	GH		LH		FSH		Cortisol		TSH	
	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1
<i>b</i>	-0.4263	-0.2646	-0.1659	-0.1179	0.04687	-0.1311	-0.02895	-0.02595	-0.1981	-0.1126
R-square	0.9157	0.9587	0.9318	0.9903	0.6737	0.7892	0.8621	0.7554	0.8447	0.9315
SSE	360.5	88.92	119.4	8.214	4902	165.4	23.26	30.52	316.8	56.42

Table 2: Normalized hormone level values were fitted to the exponential function $H(t) = a * e^{b*t}$, where b represents the rate of hormone decline with respect to time.

Figure 1: Normalized GH, LH, FSH, TSH, and cortisol values beginning at the point of normalization (either baseline or year 1), plotted for four successive years, and fitted to exponential curves. The plus sign (+) and circle (°) markers correspond to baseline and year 1 normalization values, respectively. The dashed and solid lines correspond to the exponential modeling to baseline and year 1 normalization values, respectively. As evidenced by FSH, normalization to baseline hormone levels can produce exponential curves that poorly represent physiologic hormone decline.