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Neuroendocrine Function

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Cancer therapies have become increasingly complex and frequently include many antineoplastic modalities together or in sequence, often separated by the passage of many years. Neuroendocrine dysfunction is generally caused by particular systemic treatments, interventions that are directed at the central nervous system (CNS), or products of the tumors themselves. Hormonal and metabolic abnormalities can profoundly affect the well being of patients or directly prove to be life threatening. If uncorrected, they may alter the toxicity profile of other cancer treatments and complicate the overall care of patients.

Often the neuroendocrine abnormalities last only for the duration of a particular treatment (e.g., exogenous hypercortisolism in patients with hematologic malignancies). In other cases their impact may be prolonged either because an indolent tumor may continue to contribute to certain abnormalities (e.g., hypercalcemia in some patients with islet cell tumors) or because the impact of treatment may evolve over several years and linger thereafter (e.g., hypothalamic or pituitary dysfunction after cranial irradiation; Table 24–1) (Blackman et al., 1978; Odell, 1997).

EFFECTS OF SYSTEMIC THERAPY ON NEUROENDOCRINE FUNCTION

Neuroendocrine dysfunction may compromise patient welfare even when the malignancy is outside the CNS. Some tumors are associated with paraneoplastic syndromes; ectopic hormone secretion in this case may, for example, cause activation of osteoclasts in the skeleton (resulting in hypercalcemia) or stimulation of cortisol secretion from the adrenal glands (resulting in Cushing's syndrome). In other patients, antineoplastic therapy (including medical, radiation, or surgical treatments) may directly affect the normal function of endocrine glands and cause a cascade of hormone deficiencies (outlined in the discussion of hypothalamic/pituitary dysfunction, below). These metabolic abnormalities may increase the morbidity of the patients' disease as well as interfere with their ability to tolerate appropriate cancer treatment. Surveillance for the early detection and correction of such side effects is needed to optimize the oncologic outcome.

Hypercalcemia

The most common endocrine complication of malignancy, hypercalcemia (Mundy and Guise, 1997; Coleman, 1997; Harvey, 1995), not infrequently compromises the health of patients with cancer (especially breast, non–small cell lung cancer, myeloma). Depending on its severity, hypercalcemia can cause neuromuscular morbidity (e.g., weakness, fatigue, obtundation, and even coma); cardiac complications (e.g., bradycardia or arrhythmias); in addition to constipation, anorexia, nausea, vomiting, and dehydration, which may lead to renal insufficiency.

Among several implicated mechanisms, the most prominent etiologies include

1. Paraneoplastic secretion of parathyroid hormone (PTH)-related protein (a peptide that shares similarity with the bioactive N-terminus region of PTH), especially in patients with solid tumors

Table 24–1. Annual Surveillance of Hypothalamic/Pituitary Integrity After Cranial Irradiation Is Suggested for First Decade and Biannual Surveillance Is Suggested for Second Decade After Irradiation

1. Growth hormone
   a. Monitor growth curve (children)
   b. Serum IGF-1 level
2. Gonadotropins
   a. Pubertal maturation (adolescents)
   b. Menstrual regularity (premenopausal women)
   c. Serum FSH level (postmenopausal women)
   d. Serum testosterone level (adult men)
3. Prolactin
   a. Serum level

If any abnormalities in 1 through 3, then add thyroid and adrenal evaluation

2. Destruction of the bone or release of cytokines with osteoclastic activity such as transforming growth factor (TGF) or tumor necrosis factor (TNF) by the tumor, especially in patients with skeletal metastases
3. Increased enzymatic conversion of vitamin D to its biologically active form in some hematologic malignancies (as observed in patients with granulomatous diseases)

The treatment of hypercalcemia depends, in part, on how high the calcium level is and how curable the underlying disease is.

Acutely, therapy usually includes hydration and inhibitors of bone resorption (such as bisphosphonates, calcitonin, plicamycin, or gallium). Many patients with hematologic malignancies may promptly respond to glucocorticoids, in part because of their antitumor efficacy. Numerous patients require chronic management for hypercalcemia, which may include periodic administration of fluids and bisphosphonates. Whereas the progression of the underlying disease generally determines the patient's prognosis, hypercalcemia may itself become lethal in some patients with oncologically indolent neuroendocrine cancers. Clearly, control of the malignancy corrects the problem.

Hyponatremia

Severe hyponatremia may develop as a result of renal, cardiac, or liver disease or overhydration or hypovolemia in patients who are already compromised from their illness. Another possible cause is paraneoplastic secretion of antidiuretic hormone or atrial natriuretic peptide, especially in patients with small cell lung cancer. Patients with brain or lung involvement may also be affected. Hyponatremia can result in altered mental status, including confusion, seizures, and coma; the severity of symptoms is tempered by the rate of fall of the sodium level and the underlying CNS integrity of the patient (Shapiro and Richardson, 1995; McDonald and Dubose, 1993; Berghmans, 1996).

Acutely, treatment should include fluid restriction and judicious use of lasix or hypertonic saline; this regimen may be problematic for patients who otherwise need chemotherapy with hydration and may necessitate delay of cancer treatment. Chronically, demeclocycline may be helpful for patients with relatively stable disease and mild to modest hyponatremia. Co-existing thyroid or adrenal insufficiency will also impair free water clearance and should be excluded as clinically appropriate.

Hypoglycemia

Hypoglycemia is an expected presenting symptom in patients with insulinoma; surgical resection is generally curative as these are usually benign tumors. In patients with malignant insulinomas, repeated and prolonged episodes of severe hypoglycemia may become a major, if not lethal, morbidity. Infrequently reported are cases of paraneoplastic secretion of insulin-like products (Phillips and Robertson, 1993; Marks and Teale, 1991). These occur most frequently in patients who have mesenchymal tumors; insulin-like growth factor 2 (IGF-2) has been identified in several such cases, presumably causing hypoglycemia by cross-reacting with insulin receptors. Acutely, treatment involves administration of intravenous glucose. Because the underlying disease may pursue a relatively indolent course, chronic management may be needed; glucocorticoids, growth hormone, glucagon, and even glucose infusion have been used successfully.

In other patients, hypoglycemia may be caused by excessive glucose utilization by the tumor coupled with relative liver insufficiency or by glycogen depletion due to destruction of liver parenchyma by the tumor. Infusion of glucagon acutely (1 mg IV) may help distinguish paraneoplastic hypoglycemia (the glucose

rises promptly) from liver failure hypoglycemia (no glucose response). In the latter cases glucose infusion is the mainstay of therapy.

Hypercortisolism

Prolonged hypercortisolism, regardless of etiology, exerts significant morbidity in most clinical settings. Increased weight with a characteristic centripetal distribution, moon facies, and buffalo hump are accompanied by muscle weakness and thinning and easy bruising of the skin. Personality changes, diabetes mellitus, or hypertension may develop or become exacerbated. In addition, suppression of the patients' immune function places them at increased risk for serious and difficult to overcome infections. In patients with malignant diseases, hypercortisolism is rarely the result of functioning adrenocortical cancer; more commonly, however, it results from paraneoplastic secretion of adrenocorticotropic hormone (ACTH) or corticotropin-releasing factor (CRF) and from therapeutic administration of glucocorticoids in high doses.

Paraneoplastic Hypercortisolism

Ectopic ACTH secretion may occur in patients with small cell lung cancer, medullary thyroid cancer, carcinoid tumors, or pheochromocytoma. These tumors may secrete ACTH (Dimopoulos et al., 1992) and, occasionally, ACTH-releasing factor. Because the underlying diseases may have an indolent course, the evolution of Cushing's syndrome is chronic and the clinical features more typical. At the same time, such patients frequently live for many years with stable or slowly progressive disease. The morbidity from hypercortisolism may become the leading medical priority; occasionally, bilateral adrenalectomy is performed, followed by physiologic adrenal replacement therapy (Becker and Aron, 1994).

Therapeutic Administration of High-dose Glucocorticoids:

Glucocorticoids (Walsh and Avashia, 1992; Coleman, 1992) are powerful antineoplastic agents for a number of malignancies that are primarily hematologic. They are also used in various oncology settings: to prevent nausea after chemotherapy, for cerebral edema when brain metastases are a problem, or for chronic graft-versus-host disease after bone marrow transplantation. Prolonged administration of exogenous glucocorticoids exposes patients to complications similar to those seen with endogenous hypercortisolism. In addition, pharmacologic glucocorticoid administration may suppress the hypothalamic-pituitary (HP)-adrenal axis and cause severe secondary adrenal insufficiency if abruptly interrupted. Such patients must, therefore, be closely monitored when taking glucocorticoids and carefully tapered off when the therapeutic indication has ended. Diabetic patients may experience deterioration of blood glucose control during the period of glucocorticoid treatment; this becomes particularly problematic if high-dose glucocorticoids are used intermittently, as they are in several multiple myeloma regimens.

HYPOTHALAMIC / PITUITARY DYSFUNCTION AFTER SUPRASELLAR SURGERY OR CRANIAL IRRADIATION

The most frequent and important neuroendocrine morbidity of treatment for CNS tumors is the development of hypothalamic and/or pituitary (HP) dysfunction. The extent of injury and its health repercussions depend on the location of the tumor, type of therapy, age of the patient, and compounding effect of other antineoplastic therapies that may be added to achieve tumor control.

Surgery for pituitary tumors directly affects the pituitary gland and may produce pituitary insufficiency (see Chapter 8). Surgery for tumors at or about the suprasellar area may also result in HP dysfunction through direct damage of the hypothalamus or pituitary glands or interruption of the neural pathways that regulate HP physiology. Postoperative HP damage generally occurs relatively soon after treatment and may affect any of the HP/peripheral axes with similar frequency depending on the anatomic location of the surgical interruption.

Cranial irradiation, on the other hand, frequently used to treat CNS tumors and CNS metastases or for CNS prophylaxis, may create HP dysfunction gradually and insidiously several years after its application (Samaan et al., 1987; Shalet et al., 1988; Lam et al., 1991; Constine et al., 1993; Sklar and Constine, 1995; Shalet, 1983; Rappaport and Brauner, 1989; Ober-

field et al., 1997a,b; Heikens et al., 1998; Arlt et al., 1997). Radiation-induced HP damage varies depending on the dose to the HP region, the age at time of treatment, and the lag time since therapy. Its overall health impact is often determined by the age and life situation of the patient. Induction of secondary hypogonadism due to gonadotropin deficiency, for example, is a much more serious complication for children who have not yet entered puberty (who face both physical maldevelopment and infertility). It is less serious for young adults who have matured normally but have not yet had their own family (and face infertility); it is least critical for mature adults or elderly individuals past their reproductive years who also have an overall more limited life expectancy. The secretion of growth hormone (GH) and gonadotropins is most frequently affected, whereas HP-thyroid and HP-adrenal axes appear more resistant.

Growth Hormone Deficiency

Growth hormone deficiency develops in most patients who receive cranial irradiation either for leukemia prophylaxis (lower dose) or brain tumor treatment (higher dose). Hypothalamic damage affecting the production of GH-releasing hormone appears more frequent than pituitary hyposecretion of GH, per se. The health implications of GH deficiency are quite different for children, who are still growing physically, than for adults. Because normal GH secretion is required to achieve normal adult height, untreated GH-deficient children are at risk for extreme short stature, which is associated with psychosocial morbidity (McGauley et al., 1996; Burman et al., 1995). Growth hormone deficiency also contributes to decreased skeletal (Vassilopoulou-Sellin et al., 1999) and lean body mass, increased cardiovascular morbidity, and, perhaps, impaired quality of life.

Because of these nonstatural morbidities of GH deficiency, GH replacement is approved and generally considered appropriate regardless of the patient's age. For patients with cancer, the decision to begin GH replacement is often tempered by concerns that it might induce tumor recurrence; this does not appear to be a problem in children (Ilveskoski et al., 1997; Vassilopoulou-Sellin et al., 1995), whereas no data are available for adults. Growth hormone replacement therapy should be considered for patients (especially children) who have been treated successfully and have a good prognosis for disease-free survival.

Hypogonadism

Ovarian and testicular integrity and fertility rely on a precise interplay between hypothalamic and pituitary rhythm periodicity under the influence of the pineal gland and higher CNS centers; cranial irradiation frequently disturbs these circuits and results in gonadal dysfunction. It should be noted that abdominal irradiation and several cytotoxic chemotherapy agents might directly damage the gonads and create premature testicular failure or ovarian dysfunction.

In adults, abnormalities may be limited to fertility impairment (irregular menstrual cycles or anovulation in women and decreased sperm count in men); for patients who have completed their family these defects do not pose a significant problem. For patients who have HP-gonadal dysfunction wishing to have children, stimulation of the target gonads with gonadotropin infusions can theoretically restore fertility but remains relatively cumbersome. When HP damage also causes impaired sex steroid production, additional problems ensue (e.g., accelerated bone loss, increased adipose tissue, and decreased muscle mass). Unlike primary gonadal failure, climacteric symptoms are not likely to develop with HP dysfunction. Estrogen and testosterone replacement therapy are appropriate for such patients unless they have been treated for a hormone-responsive tumor (e.g., breast or prostate cancer).

The impact of HP-hypogonadism is far more serious for prepubertal children. In this group, normal growth and development rely on the timely stimulation of the gonads, which allows the development of secondary sex characteristics, pubertal growth spurt, skeletal maturation, and initiation of ovarian cycles in girls and spermatogenesis in boys. Because GH, an important participant in normal pubertal development, is also almost always deficient in this group of children, the problem is compounded. Careful and coordinated sex hormone (and GH, if appropriate) replacement is needed to achieve a smooth progression of puberty without accelerating epiphysial closure of the growth plates that might compromise final adult height. Infertility is almost always permanent in these patients. In a minority of patients cranial irradiation may, instead, induce precocious puberty,

perhaps due to pineal gland dysfunction (Quigley et al., 1989; Brauner et al., 1984).

Because GH and sex steroids participate critically in the development of normal peak bone mass, especially during the second and third decades of life, careful monitoring of skeletal health should include periodic measurements of bone mineral density and counseling about proper nutrition and physical fitness. Adjustment of the hormone replacement schedule for these children may be needed to avoid the development of osteopenia, or even osteoporosis, both becoming recognized as other clinically important sequelae of cancer therapies.

Hyperprolactinemia

Prolactin secretion by the pituitary is under the influence of hypothalamic inhibition and is easily disturbed by various drugs and by cranial irradiation. Mild to moderate hyperprolactinemia is a fairly frequent occurrence. Although no direct morbidity has been attributed to prolactin elevation in people, it may disrupt HP-gonadal function and cause galactorrhea, amenorrhea, or infertility. Medical therapy (e.g., bromocryptine or cabergoline) is quite effective and may be sufficient to restore normal gonadal function, including fertility, in affected individuals.

Hypothalamic-Pituitary Thyroid Dysfunction

Irradiation-induced pituitary or hypothalamic deficiency of thyroid-stimulating hormone (TSH) or TSH-releasing hormone occurs infrequently. Although it is possible to demonstrate some impairment of TSH secretion using dynamic endocrine testing, clinically significant hypothyroidism occurs in fewer than 15% of patients. When the radiation field abuts the neck or after total-body irradiation for bone marrow transplantation, however, primary hypothyroidism may develop from direct damage of the thyroid gland. Thyroid hormone replacement is readily available and should be used to treat affected patients.

Hypothalamic-Pituitary Adrenal Dysfunction

The HP-adrenal axis, like the HP-thyroid axis, is also relatively resistant to damage from irradiation, and clinically significant adrenal insufficiency is uncommon. More often, HP-adrenal suppression in patients with malignant diseases is due to pharmacologic administration of glucocorticoids, which are used frequently and often for prolonged periods of time to prevent edema (e.g., CNS tumors) or chemotherapy-induced nausea and to treat steroid-responsive diseases (e.g., multiple myeloma or hematologic malignancies). This practice may result in prolonged, although reversible, HP-adrenal suppression, which may be difficult to distinguish from direct and irreversible irradiation damage in patients who have received both interventions. Careful tapering of steroids should be followed by dynamic endocrine testing to avoid the life-threatening sequelae of untreated adrenal insufficiency. Parenthetically, high-dose Megace (Mann et al., 1997), a progestational agent frequently used to improve appetite, may also interact with glucocorticoid receptors and contribute to HP-adrenal suppression.

Diabetes Insipidus

Interruption of the pituitary stalk or destruction of the supraoptic and paraventricular nuclei of the hypothalamus may disrupt the HP tract and cause vasopressin deficiency (i.e., central diabetes insipidus). This problem may develop after sellar or suprasellar surgery but does not generally ensue from irradiation alone. Metastatic deposits (e.g., breast cancer) may also disrupt the HP tract and cause diabetes insipidus. Intranasal and oral vasopressin are effective for preventing dehydration. Because some patients with hypothalamic damage may also have abnormalities of thirst perception, they may become severely dehydrated (or accidentally overmedicated and water overloaded) unless a careful therapeutic regimen is developed for them.

Hypothalamic Obesity

Patients whose hypothalamic region has been disrupted by neoplasms or surgery tend to gain weight relentlessly until they become obese. This has generally been attributed to destruction of the satiety center (in the ventromedial nucleus) and resetting of the weight set point. Whether additional abnormalities of leptin regulation are also involved is not clear at this time. In adults, long-learned eating behavior patterns can be used to control caloric intake. Children, however, cannot easily restrict themselves and are more likely to become morbidly obese. Their obesity is compounded by the reduced lean body mass and in-

creased adipose mass that characterize gonadotropin and GH deficiency (which frequently co-exist in such patients), creating a unique phenotype.

Weight loss is extremely difficult if not unachievable. It is, therefore, important to recognize the potential for obesity early and to intervene with rigorous education and behavior modification before the obesity becomes established. In addition, careful replacement of the other deficient hormones can be used to improve cardiovascular, skeletal, and overall health.

SURVEILLANCE OF NEUROENDOCRINE INTEGRITY AFTER CANCER TREATMENT

Patients who have been treated with cranial irradiation in particular require prolonged surveillance because the deleterious effects of irradiation may not become apparent for many years. Although it is generally true that GH and HP-gonadal axes are most susceptible to radiation-induced HP damage, whereas the HP-adrenal and HP-thyroid axes are most resistant, exceptions do occur especially if additional therapies (with potential independent toxicities) have been applied. A comprehensive review of the patient's oncologic history is needed at completion of therapy to design an appropriate surveillance strategy. Irradiation-induced HP dysfunction usually manifests itself within the first 5 years, and the incidence tends to plateau after the first decade. Accordingly, surveillance tailored to the anticipated potential abnormalities should continue annually for at least 5 years and preferably for 10 years or longer.

For children who have received cranial irradiation, growth velocity should be monitored closely, and an updated growth curve should be maintained; foot size is also a reliable measure of growth that is less subject to posture or measuring error. For children who fail to meet expected growth standards more detailed evaluation should include a GH secretion assessment using standard biochemical dynamic and radiologic testing. If GH deficiency is detected, replacement therapy is effective in correcting growth failure and allowing patients to achieve their genetic height potentials. Around the age of 8 to 10 years, particular attention should focus on the detection of delayed or precocious puberty, combining physical examination and Tanner staging with biochemical screening tests as needed. For children with documented GH or HP-gonadal dysregulation, bone mineral density should also be evaluated to appropriately manage potential osteopenia.

Detection of HP abnormalities is more challenging in adults because growth and development, very sensitive and easily detected features in children, are not useful parameters for adults. Although not foolproof, one reasonable strategy is to routinely screen for the integrity of the GH axis (serum IGF-1 level) and HP-gonadal axis (menstrual and sexual history or hormone levels), the most sensitive of HP axes. Physical examination should focus on signs of pituitary dysfunction, such as loss of axillary or pubic hair, fine wrinkling of the skin, and adipose tissue redistribution. If HP dysfunction is suspected, more thorough evaluation can be performed with standard biochemical basal or dynamic tests to diagnose and accurately treat prolactin, HP-adrenal, or HP-thyroid abnormalities. Advancing age and hypopituitarism both constitute additional risk factors for the development of osteoporosis in adults of either gender; periodic bone mineral density measurement, nutritional counseling, and life-style education are very important for this group of patients.

CONCLUSION

Neuroendocrine dysfunction is frequently seen in patients who are treated for cancer. It may develop due to secreted tumor products, as a result of systemic treatments, or more directly after therapy to the CNS. The severity of these changes is related to patient age, treatment dose intensity or agent combinations, the underlying health of the patient, and the presence of co-morbid conditions. The appropriate interventions and the therapeutic priorities to correct neuroendocrine dysfunction can vary depending on the age and prognoses of the involved patients. Careful surveillance for the early detection of potential problems is particularly important because both accurate diagnosis and effective treatment are generally available for most neuroendocrine abnormalities.

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