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Endocrine manifestations of craniopharyngioma

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Abstract *Rationale:* Due to the proximity of craniopharyngiomas to the hypothalamus and pituitary gland, most children and adolescents presenting with these tumors will exhibit significant endocrine dysfunction. After treatment, these impairments can become a major cause of morbidity and mortality. *Methods:* The postoperative course of children undergoing surgery for craniopharyngioma is reviewed. *Conclusion:* Even if hormone levels seem to be adequate in the short term after treatment, deficiencies may develop over years and need to be monitored closely.

Keywords Craniopharyngioma/surgery · Pituitary neoplasms/surgery · Child · Postoperative complications/drug therapy · Hypopituitarism/drug therapy · Growth hormone/deficiency · Desmopressin/administration and dosage · Pituitary function tests

Introduction

Craniopharyngioma is a parasellar and sellar tumor, which constitutes up to 6–10% of childhood brain tumors. Craniopharyngioma is the third most common intracranial tumor of childhood and the most common pediatric tumor in the hypothalamic and pituitary region. These tumors arise from embryonic squamous remnants of Rathke's pouch and extend towards the hypothalamus. They may be found in the sella turcica and rarely in the nasopharynx [1].

Craniopharyngiomas are slow-growing, benign tumors. There is a bimodal age distribution in childhood with peaks at age 5 and 15 years. In adults, the peak incidence of craniopharyngioma is in the sixth decade or later. These tumors are usually 3–4 cm in diameter, commonly cystic, and, at times, multilobulated. On occasion, they are encapsulated and solid. The two major pathologic variants are adamantinomatous and papillary. The adamantinomatous type is so named because of its hardness, which results from calcifications, which are usually evident on appropriate radiologic studies. This type is most common in children. The papillary type rarely has calcifications.

Radiologically, calcifications are most readily detected by computed tomography. When imaged by magnetic resonance scanning, craniopharyngioma has a solid component as well as a cystic or a multicystic component with intermediate fluid density.

The clinical presentation of craniopharyngioma is not much different from that of other suprasellar tumors. Craniopharyngioma mostly presents in the first decades of life, with rare presentation prior to age 2 years. Approximately 25% of craniopharyngiomas present in the third decade or later. Symptoms tend to arise slowly over months to years.

Common symptoms at presentation include signs of increased intracranial pressure, including headache, vom-

iting, and visual dysfunction. Symptoms of endocrine dysfunction are present in 80–90%. However, these symptoms only rarely comprise the chief complaint prompting families to seek medical attention [2]. Other symptoms include behavioral and cognitive dysfunction.

Visual field defects result from compression of the optic chiasm or of other components of the optic apparatus such as the optic nerves. Such compression may produce optic nerve atrophy. Papilledema, resulting from increased intracranial pressure, may also contribute to vision disturbance. Visual and olfactory hallucinations have been reported, as have seizures and dementia [3]. Monoplegia and hemiplegia have been reported in 6% of patients presenting with craniopharyngioma, whereas gait unsteadiness has been seen in 10% of these children [4].

Other than these common presentations, there is a mention in the literature of a 3-month-old craniopharyngioma patient diagnosed during evaluation for prolonged jaundice and hyperbilirubinemia [5]. It is likely that this presentation resulted from congenital hypopituitarism, which commonly presents in this manner. This presentation may result from deficiencies of adrenocorticotropic hormone (ACTH), growth hormone, and thyroid-stimulating hormone (TSH).

Due to the proximity of the tumor to the hormone-producing cells of the hypothalamus and the pituitary gland, there is significant endocrine dysfunction in most children and adolescents presenting with craniopharyngioma. In the 1970s, two large series demonstrated that, at presentation, only 15% of the children had endocrine complaints [4, 6]. Despite the fact that studies show short stature as a presenting complaint in only 7% of children with craniopharyngioma, 50–86% are found to be short on examination. The majority of these patients have had subnormal growth rates; a quarter are obese; and the majority of the adolescents have pubertal delay at the time of clinical assessment [2].

Growth

Among the hormone deficiencies, growth hormone deficiency is the most common and is seen in approximately 75% of children with craniopharyngioma. Growth failure or deceleration is a rare cause for referral prior to diagnosis of craniopharyngioma. Although up to 86% of the patients have growth deceleration, it is mostly overlooked, leading to a delay in diagnosis of craniopharyngioma. In 1988, among 22 children with craniopharyngioma (age at diagnosis 1.6–18 years), Sorva [7] reported that 19 patients had growth failure preceding the diagnosis by a mean of 4 years (0–9 years).

While a large majority of children with craniopharyngioma have growth retardation, excessive growth has rarely been reported at presentation. A 5-year-old boy who presented with clumsiness and excessive growth experienced near cessation of growth after removal of the craniopharyngioma. The authors speculated that the tumor secreted a growth factor causing excessive growth [8].

After surgical treatment for craniopharyngioma, up to 90% of the childhood patients show growth deceleration [9]. However, in this report from 1986, the replacement dose of hydrocortisone was 15–20 mg/m^2 body surface area, a dose which may have contributed to growth suppression.

Children should be followed at regular intervals after surgery for craniopharyngioma, and growth hormone deficiency should be considered if they exhibit a sustained decrease in growth rate. Initial diagnostic studies for growth hormone deficiency include measurement of serum insulin-like growth factor-1 and insulin-like growth factor binding protein-3 and a bone age X-ray. Delay in bone age is most prominent in children with low IGF-1 levels. IGF-BP-3 levels do not correlate with a delay in bone age [10]. Weinzimer et al. demonstrated that, in children with craniopharyngioma, IGF-1 and IGF-BP-3 levels may not accurately predict growth hormone deficiency. Among 15 children with craniopharyngioma, 7% had normal IGF-1 levels and 31% had normal IGF-BP-3 levels [10]. If both are low and there is a delay in bone age, with history of craniopharyngioma, these children may be considered GH deficient with or without GH provocative tests. If the patient seems to be GH deficient but has a normal IGF-1 level, then provocative tests of growth hormone secretion are the next step.

GH secretion occurs in pulses. In between the pulses, GH levels may be undetectable using most conventional assays. Therefore, random GH levels are of limited value in evaluating GH deficiency. Diagnosis of GH deficiency has relied on provoking growth hormone secretion using physiologic or pharmacologic stimuli. Physiologic stimuli include exercise; pharmacologic stimuli include levodopa, clonidine, arginine, insulin, and glucagon. For a child to be diagnosed with growth hormone deficiency, he/she should fail two provocative tests with two separate stimuli. An adequate growth hormone response to stimuli is considered to be 10 ng/ml, but rigorous studies supporting this cutoff value are not available. In patients with a history of seizures, growth hormone stimulation using insulin-induced hypoglycemia is contraindicated because of the risk of inducing seizures during the test.

Growth hormone treatment is recommended to facilitate catch-up growth in growth-hormone-deficient patients shown to be free of craniopharyngioma after treatment. However, the consequences of growth hormone treatment are unclear in those patients with residual tumors. Although there is no consensus about when to start treatment, most pediatric endocrinologists agree to start growth hormone treatment 1 year after cure of the tumor is documented. Some centers begin such treatment within 6 months after such docu-

mentation. A period of time without GH treatment also helps to determine whether the patient will manifest growth without growth hormone.

Two large studies have shown no increase in the risk of tumor recurrence in children receiving growth hormone following surgical removal of craniopharyngioma [11, 12]. The study of Moshang et al. demonstrated that the tumor recurrence rate in children receiving growth hormone is less than is the recurrence rate in those not receiving GH treatment. This surprising result may be due to a treatment bias of offering growth hormone only to patients with non-active tumors [11]. In 2002, Niu et al. [13] reported a 13-year-old boy with rapid relapse of a craniopharyngioma after growth hormone replacement. The authors suggested that the aggressiveness of the relapsing tumor suggested a role of growth hormone in triggering the recurrence. Although the largest studies show that growth hormone treatment in GH deficient is relatively safe, growth hormone should be used with some caution in patients with prior history of tumors.

Despite the fact that most children demonstrate growth hormone deficiency following treatment of craniopharyngioma, some patients have normal postoperative growth rates. In 1962, Matson described normal height velocity in postsurgical craniopharyngioma patients. Among 27 craniopharyngioma patients, 6 patients showed significant preoperative growth retardation and 11 had marked epiphyseal maturation delay. Despite persistent panhypopituitarism after surgery, most of the children attained normal postoperative height velocity. A majority of these normally growing patients developed marked truncal obesity. At the time of this report, growth hormone measurement was unavailable. To explain this growth pattern, Matson speculated that adequate pituitary tissue was left behind or that the secretion of growth hormone was independent of the hypothalamus [14].

Subsequent to Matson's report, a number of similar cases were described. This situation, known as "growth without growth hormone," is also seen in other conditions such as other sellar, suprasellar, and hypothalamic disorders (including tumors), empty sella syndrome, septo-optic dysplasia, pseudoacromegaly, fetal life, obesity, and, rarely, in otherwise normally growing children.

A number of mechanisms that can explain growth without growth hormone include obesity-induced hyperinsulinemia, hyperprolactinemia, and the presence of GH variants and of structurally similar lactogenic hormones.

One recent theory suggests that morbid obesity occurs in a subset of patients after surgical removal of craniopharyngioma. This obesity may be multifactorial [15, 16]. Some patients appear to have significantly increased appetite, at times associated with decreased satiety. These patients often have markedly decreased physical activity. Obesity contributes to insulin resistance, a state which typically includes increased endogenous insulin (until or unless type 2 diabetes supervenes). Increased circulating levels of insulin appear to contribute to the increased growth. The magnitude of elevation of insulin levels does not appear to allow direct stimulation of receptors for insulin-like growth factor 1 (IGF-1). However, hyperinsulinemia decreases circulating (and tissue) levels of some growth factor binding proteins and may increase the availability of free IGF-1 to stimulate growth. IGF-binding protein-1 levels fluctuate during the day in an inverse relationship with the changes in plasma insulin levels [17]. Decreased IGF-BP-1 levels may lead to increased free IGF-1 levels and activity.

Replacement of growth hormone in children with "growth without growth hormone" after surgery for craniopharyngioma increases muscle mass and decreases adipose tissue mass but does not influence growth velocity [18]. Such patients must be carefully monitored for worsening of glucose tolerance. They have a degree of insulin resistance prior to GH treatment, and GH can increase insulin resistance.

LH/FSH deficiency

The most common presenting symptom of craniopharyngioma in adults is gonadotropin deficiency [19]. Up to 100% of the adolescents may have complaints of delayed puberty at presentation [5]. It is likely that the actual prevalence of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) deficiency is much higher in prepubertal children, but our ability to detect this deficiency is limited by the limitations of sensitivity of sex steroid and gonadotropin measurements in this age group. Gonadotropin deficiency has been estimated to be present in 85.2% of children evaluated by sex steroid levels and LHRH-stimulated gonadotropins [5].

Gonadotropin deficiency is diagnosed by observation of lack of pubertal development after 13 years in girls and 14 years in boys. Levels of gonadotropin and of estradiol (girls) and testosterone (boys) are prepubertal. Those patients with gonadotropin deficiency require hormone replacement at an appropriate age for pubertal development. The timing of initiation of sex steroids should be individualized to optimize both growth and development. The sex steroids (particularly estrogen in both sexes) contribute to the closure of the growth centers of the bones. Thus, administration of sex steroids to very short postoperative patients may produce cessation of growth before adequate growth has been achieved. Despite the adverse effect of sex steroid replacement on height prognosis, some patients prefer to proceed with induction of puberty. The effect of estrogen treatment on closure of the growth centers of the bones can be monitored by periodic determination of the bone age. This is usually estimated using a radiograph of the left hand and wrist.

Various estrogen preparations are available for puberty induction; their administration should be individualized. In patients with hepatic disease, transdermal estrogen, which eliminates the first pass through the liver, should be considered. Other options are conjugated equine estrogens and micronized estradiol. Conjugated estrogens can be started at a dose one sixth to one fourth the adult dose (0.15–0.3 mg orally each day). This low dose is gradually increased to produce normal pubertal development. Most girls will experience Tanner 3 breast development within 1 year on the low dose of replacement. At a dose of 0.625 mg, Tanner 4 breast development will be reached over time. Since this estrogen dose also stimulates growth of the endometrium, progesterone should be added. Progesterone reduces uterine hyperplasia and the risk of estrogen-induced hyperplasia. For convenience, starting cyclic therapy at the beginning of the calendar month is recommended. In cyclic therapy, estrogen is given daily throughout the month and medroxyprogesterone 5 mg daily is added on days 1–12. If micronized estrogens are used, estrogen levels can be followed to maintain adequate levels. Micronized estrogens are started at a daily dose of 0.25 mg daily and gradually increased to 1 mg daily.

Intramuscular estrogen given in low doses of 1–1.5 mg each month can be used in patients who want additional growth in height. Intramuscularly administered estrogen bypasses the liver, thereby avoiding the inhibitory effect of the oral estrogen on hepatic production of IGF-1.

In boys with hypogonadotropic hypogonadism, androgen replacement is often started between 12 and 15 years of age. The precise timing is determined by the patient's growth needs and by his desire for pubertal development. On initiation of testosterone treatment, a bone age X-ray should be obtained; it should be repeated periodically to assess effects of testosterone replacement on the maturation of the growth centers of the bones.

Testosterone is available in various preparations. Most commonly, intramuscular testosterone in the form of testosterone enanthate, propionate, or cypionate is administered every 4 weeks starting at 25–50 mg. The dose is increased gradually to 200–300 mg every 2 weeks. Testosterone gels are gaining popularity because of the consistency of the delivered dose once the dose is increased to a level at which daily administration is feasible. The current preparations are not ideal for use in young adolescents since the smallest packet (2.5 g) is intended for androgen replacement in adults. Currently, this amount can be given once or twice weekly to begin testosterone replacement. In the future, a device will become available to more precisely measure smaller daily doses of testosterone gel. Within a year on treatment, most patients develop secondary sex characteristics and have penile enlargement. The oral 17 alpha alkylated testosterone derivatives have hepatotoxic side effects and are not used for androgen replacement. Oxandrolone has been used to enhance sexual maturation in boys wanting to optimize growth in height. This androgen appears to have a less marked effect on maturing the growth centers of the bones than do other androgens in virtue of its resistance to aromatization. Patients who have inadequate pubertal development on testosterone may benefit from HCG treatment [20].

When males with hypogonadotropic hypogonadism desire fertility treatment, hCG is usually started in a dose of 1,500–2,000 IU intramuscularly twice weekly. A prolonged course of hCG (approximately 20 months) is frequently needed, and success with fertility treatment may take many years [21]. In some men, fertility requires treatment with both hCG and FSH.

Although it is relatively uncommon, successful pregnancy has been reported after development of panhypopituitarism [22, 23]. The medication of choice depends in part on whether the craniopharyngioma has damaged the hypothalamus, pituitary gland, or both. If only the hypothalamus is rendered dysfunctional by the tumor, then gonadotropin releasing hormone may be administered in a pulsatile manner. If pituitary function is disturbed, then hCG or recombinant LH and recombinant FSH may be utilized. Of note, the patient reported by Volz et al. did not require oxytocin treatment to initiate labor. Due to the short half-life of oxytocin, no measurements were made in this patient; however, it was proposed that adequate oxytocin production would be unlikely in a patient with panhypopituitarism [22].

While many children with craniopharyngioma have pubertal delay, some manifest precocious puberty. The initiation of secondary sex characteristics before the age of 8 years in females and 9 years in males is considered as precocious puberty. Banna et al. [4] reported three boys at ages 3, 4, and 7 years with sexual precocity at presentation of craniopharyngioma. Precocious puberty has also been reported in a girl after surgery for craniopharyngioma [24]. The problem of precocious sexual development may be treated with analogues of gonadotropin releasing hormone.

TSH dysfunction

Hypothyroidism was reported in 2.7–24% of the children presenting with craniopharyngioma [5, 6]. Signs and symptoms of classic hypothyroidism include cold intolerance, constipation, dry skin, sparse or brittle hair, weight gain, decreased energy, and bradycardia. Hypothalamic and/or pituitary hypothyroidism presents with inappropriately low TSH level in the setting of a low T4 or free T4 levels. A subset of patients has low free thyroxine levels and mildly elevated TSH (the degree of TSH elevation being much less than the degree of free T4 deficit). This has been shown to result from decreased biologic activity of TSH, which is subnormally glycated [25]. Children with hypothalamic–pituitary disorders also have a blunted TSH surge [26].

Postoperative hypothyroidism was reported in 29–85% of the children treated with surgery only or with surgery and radiotherapy [6, 27].

T4 and TSH levels are routinely checked 6 weeks after surgery in those children with normal pretreatment thyroid function (the half-life of T4 is 1 week; waiting 6 weeks allows the equilibrium concentration to be reached). Thyroid hormone levels are followed particularly closely in children less than 2 years old since hypothyroidism may lead to slowed mental development.

A significant number of children receive anticonvulsant medications after treatment of craniopharyngioma. Many of the anticonvulsant medications interfere with thyroid function tests. Isojarvi et al. showed that the free and total T4 levels were low and T3 and TSH levels were within normal range in men treated with carbamazepine. Clinically, the patients with low thyroid hormone levels were euthyroid [28]. In their publication in JAMA, Surks and DeFesi [29] demonstrated that when undiluted serum is used and free T4 and T3 levels are measured via ultrafiltration assays, the levels are within normal limits. Thus, dialysis or ultrafiltration assays of free T4 should be employed instead of the more common and more rapid analogue methods.

For treatment of hypothalamic or pituitary hypothyroidism, the synthetic form of L-T4, levothyroxine sodium, is administered orally once daily. Intravenous doses should be approximately one half to three fourths of the oral dose. In patients with deficiencies of both TSH and ACTH, hydrocortisone replacement should precede replacement of L-thyroxine. L-Thyroxine increases the metabolic clearance of glucocorticoids and may lead to adrenal crisis if L-thyroxine replacement precedes that of hydrocortisone.

ACTH deficiency

The signs and symptoms of ACTH deficiency may be subtle. Anorexia, nausea, hypoglycemia, poor weight gain, and/or easy fatigability may be seen. During times of stress, ACTH deficiency may lead to hypotension and death. Diagnosis of ACTH deficiency may be established by finding subnormal 8 AM plasma cortisol levels in association with nonelevated levels of ACTH. Insulin-induced hypoglycemia may be used for diagnosis in borderline cases, keeping in mind the contraindication of insulin use for this purpose in patients with a history of seizures. The low-dose ACTH stimulation test may be helpful in diagnosis of ACTH deficiency, but its use in this setting is controversial. A peak cortisol response less than or equal to 18 μg/dl is considered as ACTH deficiency.

ACTH deficiency was reported in 25–71% of children at presentation with craniopharyngioma [2, 5]. Postsurgery, Lyen and Grant [30] demonstrated that 72% of the children had impaired ACTH function after provocative testing.

It is recommended that those children with history of cranial surgery, irradiation, or tumors, especially those with craniopharyngioma, should be tested for ACTH deficiency annually for up to 10–15 years. A baseline AM cortisol level should be obtained. If the baseline cortisol level is low, then a stimulation test should be considered [31].

Failure to treat ACTH deficiency may be lethal. Since ACTH deficiency may develop during surgery in those patients not deficient preoperatively, all patients with craniopharyngioma should be treated with stress doses of glucocorticoids immediately prior to surgery. Patients receiving dexamethasone for surgical purposes do not require additional steroid coverage since the doses are virtually always many times greater than the physiological doses [32].

In ACTH-deficient children, the replacement dose of hydrocortisone is age-dependent. In young children, the appropriate replacement dose is as low as 6 mg/m^2 body surface area. The replacement dose is 9 mg/m^2 in older children and adolescents [33, 34]. The maintenance dose of hydrocortisone should be changed as children grow and gain weight. Even slight underdosing or overdosing of the glucocorticoid replacement may be complicated by side effects. Overdosing may lead to signs and symptoms of Cushing syndrome and can lead to growth deceleration. Underdosing may lead to the problems of adrenal insufficiency. Hydrocortisone is dosed three times daily and is preferred in children since it is somewhat less likely to restrict growth than are longer-acting glucocorticoid preparations.

During surgery, the stress dosing for hydrocortisone is approximately three to ten times the physiological dose. Recently, the stress of surgery has been decreased due to improved techniques in anesthesiology, to better anesthetic, analgesic, and muscle-relaxant medications, and to better understanding of intraoperative fluid and electrolyte management [35]. Commonly, preoperative hydrocortisone is administered intravenously in a dose of 100 mg/m^2 body surface area. This dose can be repeated at 8- to 12-h intervals and tapered at a rate determined by the postoperative clinical course.

It is common practice to triple the maintenance dose of glucocorticoids during febrile illness and during times of fluid loss. In patients under stress unable to take oral glucocorticoids, intramuscular hydrocortisone could be given in the following doses: 25 mg in young children, 50 mg in older children, and 100 mg in adolescents. These doses of hydrocortisone may be used intravenously as preoperative stress doses. They can be repeated at 8- to 12-h intervals and tapered at a rate determined by the postoperative clinical course.

In patients who have received glucocorticoids at a high dose for 7–10 days, abrupt discontinuation of the medication does not cause any side effects. However, when high-dose glucocorticoids are used for over 2 weeks, abrupt discontinuation may result in malaise, anorexia, nausea, headache, lethargy, and fever. These symptoms are due to delayed recovery of the hypothalamic–pituitary–adrenal axis. Patients who have been treated for longer periods of time with very high-dose glucocorticoids may experience symptoms of adrenal insufficiency despite receiving supra-physiological doses of glucocorticoid medications. These patients have the glucocorticoid withdrawal syndrome, a condition in which the glucocorticoid response mechanisms appear to be down-regulated. Although it may seem logical to decrease the pharmacological dose to physiological dose immediately, this may lead to signs and symptoms of glucocorticoid withdrawal syndrome. Therefore, the reduction in dose should be done slowly as dictated by the patient's symptoms.

ADH dysfunction

At diagnosis of craniopharyngioma, ADH deficiency is seen in 9–38% of the patients [2, 19]. Evaluation of the fluid and electrolyte status of craniopharyngioma patients is important since appropriate treatment of diabetes insipidus can minimize morbidity and, at times, mortality [30]. Among 59 children with craniopharyngioma, diabetes insipidus was a contributory factor in the death of five patients (approximately 8%) who died within the first 4 months of surgery.

Lyen et al. demonstrated postoperative diabetes insipidus in 76% of the children with craniopharyngioma. In another study, postoperative DI was as high as 93.8% [30].

The diagnosis of diabetes insipidus should include a history of fluid intake and output as well as laboratory assessment. Patients with hypothalamic diabetes insipidus experience persistent thirst, often preferring cold fluids throughout the day and night. They typically have sudden onset of these symptoms. Determination of the urine specific gravity, urine and serum osmolality, and serum electrolytes is the initial laboratory workup. The urine is dilute in the face of elevated plasma osmolality because of lack of antidiuretic hormone. In some cases, serum sodium and/or plasma osmolality are not elevated. If the results are equivocal, a water deprivation test is required for diagnosis of DI. During this provocative test, elevation of plasma hyperosmolality above 295 mosmol/kg would normally stimulate release of vasopressin, which would, in turn, increase urine concentration above 700 mosmol/kg. The diagnosis of diabetes insipidus is confirmed by the inability to concentrate urine despite elevation of the plasma osmolality.

In central diabetes insipidus, serum uric acid is elevated due to modest volume contraction and the loss of the action of vasopressin on V1 receptors in the kidney to increase urate clearance. Therefore, in patients with vasopressin deficiency, the uric acid level is high, often greater than 5 μg/dl [3].

In the postneurosurgical setting, the differentiation of central DI from polyuria resulting from the normal diuresis of fluids received intraoperatively is important. In both cases, a large volume (>200 ml m^{-2} h^{-1}) of dilute urine is seen. However, in patients with DI, the plasma osmolality is higher compared to patients undergoing postoperative diuresis. Central DI is likely if plasma osmolality >300 mOsm/kg is associated with urine osmolality less than approximately 700 mOsm/kg.

Due to the proximity of some craniopharyngiomas to the osmoreceptors for thirst in the hypothalamus, some patients develop abnormal thirst postoperatively comprising either polydipsia or adipsia. These patients are given an amount of fluid each day determined to be their usual fluid requirement. Additions or deletions from this usual fluid allotment are made by weighing the patient twice daily. If the patient's "good weight" (the weight at which serum Na is determined to be normal) is exceeded, then an amount of fluid is withheld which corresponds with the amount of weight gained. The adage, "a pint's a pound the world around," can be used to determine the relationship between weight deviations and changes in daily fluid amounts. Management of polydipsic patients is also challenging. DDAVP treatment is dangerous since continuous drinking may lead to water intoxication and significant hyponatremia. However, without treatment, polydipsia may interfere with daily activities.

Desmopressin acetate–DDAVP–is the mainstay of treatment in both acute and chronic central DI. DDAVP is a synthetic agonist of the AVP V2 receptor. It has two advantages over AVP (arginine vasopressin): longer half-life leading to longer duration of antidiuretic effect and the absence of the V1 activity (comprising elevation of arterial blood pressure). It is available in different preparations. The intranasal form is available either as an aqueous solution containing 100 μg/ml or as a nasal spray delivering a metered dose of 10 μg in 0.1 ml. Oral preparations are available in tablets containing 0.1 or 0.2 mg. In acute settings, the parental form of DDAVP containing 4 μg/ml should be used via the intravenous, intramuscular, or subcutaneous routes. The parenteral form is approximately five to ten times more potent than is the intranasal preparation. Increasing the dose of the parental or the intranasal preparations generally has the effect of prolonging the duration of antidiuresis.

Glucocorticoids have an inhibitory effect on the secretion of ADH. Conversely, ACTH deficiency exaggerates

release of ADH. Therefore, in patients with ACTH and ADH deficiency, untreated ACTH deficiency may mask the presentation of DI.

As is true with adrenal insufficiency, hypothyroidism impairs the kidneys' ability to excrete water. Therefore, in patients with anterior pituitary deficiency and DI, either ACTH deficiency or TSH deficiency may foster urinary concentration. Once these deficiencies are replaced, patients may develop all of the clinical and laboratory features of DI.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may occur in some children postoperatively. This condition is typically characterized by low plasma osmolality and low serum sodium in association with inappropriately concentrated urine. Frequently, SIADH is quickly followed by DI. The time of onset of DI and SIADH does not seem to correlate with sex, age, body weight, location of tumor, or duration or extent of surgery [36].

The syndrome of inappropriate secretion of antidiuretic hormone has been reported in three children, ages 19 months, 5 years, and 7 years, as a presenting symptom of craniopharyngioma. In these cases, the excessive ADH secretion might be caused by the direct mechanical stimulation and/or ischemia of the osmoreceptor, the hypothalamic nuclei, or the posterior pituitary [37].

Weight changes

In a retrospective study of patients presenting with craniopharyngioma, anorexia was demonstrated in 11.4%, all of whom were males. Among the patients studied, 31.4% were noted to have vomiting. Vomiting was significantly more common in females (almost at a ratio of 1:10) [5]. In addition, nausea is seen in 43% of the patients as a presenting symptom [38].

In one study, weight gain was seen preoperatively in 5% of the patients. These preoperatively overweight children gained more weight posttreatment (BMI range from 32 to 35%) [27]. Posttreatment, 14% of the patients suffered from severe hypothalamic obesity [5]. Sorva [7] demonstrated that 3 months after treatment, obesity occurred in 57%, after 1 year in 62%, and after 5 years in 58%. These obese patients develop decreased satiety and lack of activity.

Severe obesity is a devastating late effect after cranial insult. It is a high-risk factor for morbidities such as diabetes mellitus, dyslipidemia, musculoskeletal problems, sleep apnea, depression, and social withdrawal. Studies in rats with ventromedial hypothalamic damage show excessive eating, rapid weight gain, and eventual hyperinsulinemia, insulin resistance, and glucose intolerance [39, 40]. Increased vagal tone is thought to lead to beta cell depolarization and increased insulin levels. A 19-year-old hypothalamic obese patient with a history of craniopharyngioma surgery at age 12 had decreased insulin secretion and weight loss following bilateral truncal vagotomy [41].

Treatment of hypothalamic obesity is a challenge. Octreotide, which inhibits the voltage-gated calcium channels of the beta cells of the pancreas, is used on a research basis for controlling obesity. Lustig et al. demonstrated that weight loss occurred in five of eight children, and weight stabilization was achieved in three. In these patients, no effect was seen within the first 2 months; weight loss occurred between 2 and 6 months after initiation of octreotide treatment. The two patients who used octreotide for a year showed increased weight loss [42].

Hyperphagia is the result of either tumor location or surgical intervention. Dextroamphetamine is a sympathomimetic amine that produces anorexia. Mason et al. [43] used dextroamphetamine to control obesity in five children who gained weight by 75% or more following surgical resection of craniopharyngioma. These children stabilized their weight during the medical treatment. Both neurosurgery and radiation treatment may cause defective short-term memory and limited concentration impairing learning capabilities [44]. Patients on dextroamphetamine experienced significant improvements in their ability to pay attention.

Prolactin

Increased prolactin levels were noted in 8–50% of the preoperative children with craniopharyngioma [5, 45]. Posttreatment, among 20 children, 3 had hyperprolactinemia, and the rest had normal levels [7]. Hyperprolactinemia likely results from disturbed secretion of the prolactin inhibiting factor due to hypothalamic damage. With hyperprolactinemia, amenorrhea–galactorrhea syndrome occurs and may present as the initial finding in females with craniopharyngioma [46].

Melatonin dysregulation

Melatonin is a pineal indoleamine produced by the pineal gland. It is mainly secreted during darkness. In children with craniopharyngioma, decreased nocturnal melatonin levels might lead to increased daytime sleepiness. In this study, nocturnal melatonin levels seemed to correlate with the degree of obesity [47].

Conclusion

In most patients with craniopharyngioma, endocrine dysfunction is present long before the diagnosis of the tumor. After treatment with surgery and/or irradiation, endocrine problems become a major cause of morbidity and mortality. Tomlinson et al. [48] studied the association between

premature mortality and hypopituitarism and showed that craniopharyngioma had mortality rates ten times greater than mortality in other causes of hypopituitarism. This excess mortality might be the result of hypothalamic damage and of resulting metabolic derangement. Even if hormone levels seem to be adequate in the short term after treatment, deficiencies may develop over years and need to be monitored closely.

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