Postoperative Craniopharyngioma in a 10-Year-Old Girl Presenting with Central Precocious Puberty, Central Diabetes Insipidus, and Growth Hormone Deficiency

Nyoman Ananda Putri Prashanti1*, Putu Wahyu Dyatmika Tanaya1, I Wayan Bikin Suryawan1

1Department of Pediatric, Wangaya Regional General Hospital, Denpasar, Indonesia

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*Corresponding author:
Nyoman Ananda Putri Prashanti
E-mail address: prashantiananda@gmail.com

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ABSTRACT

Background: Hypopituitarism is the most common endocrinology complication of postoperative craniopharyngioma. However, we found a 10-year-old girl with a history of postoperative craniopharyngioma presenting with central precocious puberty (CPP), central diabetes insipidus (CDI), and growth hormone deficiency (GHD). Case presentation: A 5-year-old girl experienced breast growth followed by menstruation six months later. The patient’s weight was 19 kg (weight-for-age: P25-P50), height was 109 cm (height-for-age: P10-P25), and good nutritional status (Waterlow 90%). The stage of pubertal development was M2P2. There was a history of craniopharyngioma, and it was resected at the age of 2 years. After surgery, the patient developed CDI and has received desmopressin. No new tumour growth was found from evaluation with periodic MRIs every three years. After CPP was established, with increased serum levels of LH, FSH, and estradiol, GnRH agonist therapy was given at 100 mcg/kg BW every month. During five years of follow-up, the patient experienced clinical and laboratory improvement. However, the growth is only 3-4 cm/year (<P3) with short stature (height-for-age: <P3) and overweight. Low levels of IGF1 and GH were found in the stimulation test results, so the diagnosis of GHD was confirmed. The patient will receive growth hormone therapy and is expected to reach her potential genetic height (148.5 - 165.5 cm). Conclusion: Even though the craniopharyngioma tumour has been resected and no recurrence has occurred, it is crucial to evaluate the hormones produced by the pituitary thoroughly.

1. Introduction

Craniopharyngioma (CP) is a benign brain tumor that originates from the remnants of Rathke’s pouch cells and is further classified as adamantinomatous type or squamous papillary type.1 CP is a very rare tumor and can occur in children or adults. An epidemiological study of the Central Brain Tumor Registry in the United States (Momin et al.) found the incidence of craniopharyngioma was 0.16 cases per 100,000 people with a peak age of 5-9 years and 55-69 years.2 Despite being histologically benign neoplasia malformations (WHO grade I), CPs create considerable morbidity and mortality due to the aggressive behavior of the tumor, resulting in infiltration of surrounding brain structures (hypothalamus, pituitary, and optic nerve) and sometimes obstructing the third ventricle, as well as by the treatment-related damage to the hypothalamo-pituitary structures and functions.3

Postoperative complications of craniopharyngioma include fluid-electrolyte disturbances, hypopituitarism, increased cardiovascular risk, hypothalamic damage, hypothalamic obesity, visual and neurological deficits, impaired bone health, cognitive function, and central diabetes insipidus (CDI).3,4,5 Additionally, there may be changes in thyroid-stimulating hormone, triiodothyronine, thyroxine, prolactin, follicle-stimulating hormone,
luteinizing hormone, and cortisol levels. Surgery for craniopharyngioma can aggravate endocrine dysfunction, and routine hormone therapy may be necessary after the operation. Usually, signs of hypopituitarism are common clinical symptoms of craniopharyngiomas, both at diagnosis and after surgery. However, apart from signs of hypopituitarism (central diabetes insipidus and growth hormone deficiency), we also found early activation of the hypothalamic-pituitary-gonadal (HPG) axis, specifically central precocious puberty in a 10-year-old girl with a history of post-operative craniopharyngioma.

2. Case Presentation

A 5-year-old Balinese girl came to the pediatric endocrinology clinic because she experienced breast growth followed by menstruation 6 months later. Height growth is said to be more rapid in the last 6 months (but not measured). There was a history of craniopharyngioma (Figure 1), and it was resected at the age of 2 years. After surgery, the patient suffered from central diabetes insipidus and received desmopressin until now. The patient was born at term by caesarean section with a birth weight of 3500 grams and a body length of 52 cm. There is no exposure to exogenous hormones. The patient is the second child, and the patient’s older brother is healthy. There is no history of precocious puberty in the family. On physical examination, it was found that the patient’s weight was 19 kg (weight-for-age: P25-P50), height 109 cm (height-for-age: P10-P25), and good nutritional status (Waterlow 90%). The stage of pubertal development is M2P2. No enlargement of the thyroid gland was found on palpation. The results of the examination found an increase in serum levels of LH, FSH, and estradiol, 11.4 mIU/mL, 8.73 mIU/mL, and 23 pg/mL, respectively. No abnormalities were found in the results of the blood electrolyte examination. No new tumor growth was found from evaluation with periodic MRI every 3 years (Figure 2). So, the diagnosis of central precocious puberty was confirmed. Then, the patient was given GnRH agonist therapy at 100 mcg/kgBW every month.

During the 5-year follow-up period, the patient experienced clinical improvement as indicated by the absence of menstruation again, and breast growth and pubic hair were normal for age (M2P1), and laboratory examinations showed a decrease in LH, FSH, and estradiol levels. However, CDC 2000 growth curve shows a height growth rate of only 3-4 cm/year (<P3) and below genetic height potential (Figure 3). The patient had normal body proportions. No neurological abnormalities were found. Low levels of IGF1 (78 ng/mL) and GH were found from the results of the stimulation test (respectively from the 1st to 4th stimulation; 0.37/0.1/0.79/0.16 ng/ ml). Examination of thyroid hormone levels showed subclinical hypothyroidism (TSHs 2.81 mIU/L; FT4 0.63 ng/dL), so the diagnosis of growth hormone deficiency was confirmed. The patient received growth hormone therapy (started at 0.025 mg/kg/day) and levothyroxine (2.7 mcg/kg/day) and was expected to reach her potential genetic height (148.5 - 165.5 cm). We have obtained consent from the patient’s parents to publish their child’s case to the general public.

3. Discussion

Craniopharyngiomas (CP) are intracranial tumors often seen in the sellar or parasellar region that is derived from Rathke’s pouch. Although they are histologically benign, they can be aggressive by infiltrating the local region. CP count for up to 10% in pediatric tumors and are rarely found in adults. Furthermore, based on the Central Brain Tumor Registry in The United States, the incidence rate is 0.16 per 100,000 persons, with incidence peak at 5 until 9 years or 55 until 69 years. Clinical manifestations often found in CP are usually related to their aggressive behaviour on vital structures of the brain (nervus opticus, hypothalamus, pituitary gland). Visual disturbance, growth hormone deficiency, headache, and vomiting are the most frequent symptoms found in CP.
Figure 1. MRI of the head showing images of (a) T2 sagittal section, (b) contrast T1 axial section, (c) T1 axial section, (d) contrast T1 coronal section. An intrasellar cystic mass was seen measuring 2.22 x 2.93 cm, which extended suprasellar with sellar balloning. When administering contrast, it is not a visible enhancement.

Figure 2. The latest MRI of the head shows images of (a) T2 sagittal section, (b) contrast T1 axial section, (c) T1 axial section, and (d) contrast T1 coronal section. There was no visible residual mass.

Figure 3. Stature-to-age growth chart (CDC 2000). It shows that the patient experienced deficient height growth every year. At the age of 10 years 6 months, she was considered short stature (<P3). It also represents the patient’s height growth below her potential genetic height (148.5 - 165.5 cm).
Morphologically and molecularly, CP can be classified into Adamantinous Craniopharyngioma (ACP) and Papillary Craniopharyngioma (PCP). ACP is precipitated by somatic mutation in CTNNB1 and accumulation of β-catenin. However, PCP shows a somatic mutation in BRAFV600E. ACP can be found at any age and is more common than PCP. Magnetic resonance imaging (MRI) and computed tomography (CT) can be used to diagnose CP; however, MRI is still the gold standard because it can see the tumor and vital structures of the brain more clearly.\textsuperscript{1,3,7}

The majority of individuals diagnosed with craniopharyngioma (CP) often exhibit deficiencies in pituitary hormones at the time of diagnosis, a phenomenon more prevalent in children than adults. Approximately 70% of children with CP experience a deficiency in growth hormone (GH), followed by gonadotropin deficiency (51.7%), central diabetes insipidus (CDI, 28.6%), thyroid-stimulating hormone (TSH) deficiency (21.9%), and adrenocorticotropic hormone (ACTH) deficiency (12.5%).\textsuperscript{3,8} To manage CP patients effectively, it is essential to conduct a comprehensive assessment of pituitary function and blood chemistry. Addressing central adrenal insufficiency and central hypothyroidism with appropriate hormone replacement therapies (HRTs) prior to surgery is recommended. Additionally, correction of diabetes insipidus or other fluid-electrolyte disturbances, if present, is crucial.\textsuperscript{3}

The complications of craniopharyngioma discussed here focus on both immediate postoperative endocrinological complications and long-term complications. Immediately after surgery, electrolyte disturbances are observed in 27% of cases, particularly in patients undergoing transcranial approaches.\textsuperscript{3} Preoperatively, CDI may be present in 16–55% of patients, increasing to 90% postoperatively in CP cases.\textsuperscript{9,10} Managing postoperative polyuria and polydipsia can be challenging, requiring close monitoring of fluid balance. The course of postoperative CDI may be transient, permanent, or part of a triphasic pattern. Cerebral salt wasting (CSW) is another condition causing hyponatremia after neurosurgery, with mechanisms involving disruptions in neural input to the kidney and central release of a natriuretic factor.\textsuperscript{3}

The long-term prognosis and successful management of craniopharyngioma depend on achieving a balance between tumor control (preventing recurrences) and minimizing treatment complications (hypothalamic-pituitary dysfunction).\textsuperscript{3} Although long-term survival rates are high, the quality of life and neuropsychological function are often impaired, mainly due to the close proximity to critical brain structures. Following CP surgery, around 80–90% of patients develop panhypopituitarism, with up to three-quarters experiencing deficits in four or more hormones.\textsuperscript{11} Pituitary hormone deficiency rates appear higher in patients who underwent transcranial surgery compared to transsphenoidal surgery. The 10-year follow-up probabilities for deficiencies in growth hormone, FSH/LH, ACTH, TSH, and diabetes insipidus are 88%, 90%, 86%, 80%, and 65%, respectively.\textsuperscript{3,12}

Despite a high survival rate (92%) in CP, the quality of life is often compromised, primarily due to hypothalamic obesity (HOb), which can reach a severe obesity rate of 55%. The standardized mortality ratio in childhood-onset CP is 17%, with obesity being a major contributor. Early recognition and management of HOb are crucial. HOb is a form of obesity resulting from the disruption of hypothalamic centers regulating energy homeostasis.\textsuperscript{13}

Similar to simple obesity, the primary approach for managing hypothalamic obesity (HOb) involves lifestyle modifications. However, HOb tends to be less responsive to diet and exercise. Despite this, patients should still be encouraged to adopt a healthy diet and engage in physical activity. In some cases, pharmacological agents such as dextroamphetamine, ephedrine, octreotide, and melatonin have been employed in a limited number of patients, yielding varying degrees of success but generally modest outcomes.\textsuperscript{13} There is no consensus on the optimal therapeutic approach for CP treatment. Some experts advocate a conservative surgical strategy, such as
limited tumor resection followed by local adjuvant radiotherapy, cyst drainage to reduce neural compression, etc., aiming to minimize future hypothalamic dysfunction.\textsuperscript{14,15} Above, several endocrine complications that may arise after craniopharyngioma surgery have been outlined. CP typically disrupts pituitary function in children, leading to growth retardation and failure to reach puberty, which are the predominant endocrine disturbances. The occurrence of precocious puberty after the removal of craniopharyngioma is very rare. In this case, in addition to hypopituitarism, complications of CP can include precocious puberty. This has also been reported in several case studies.\textsuperscript{16-18}

4. Conclusion
Apart from hypopituitarism, post-operative craniopharyngioma can also cause endocrine abnormalities in the form of central precocious puberty. Endocrine disorders in CP patients should be evaluated thoroughly, especially for hormones produced by the pituitary, even if the tumor has been resected and no recurrence has occurred.

5. References


