Neurosurgical treatment of hypothalamic hamartomas causing precocious puberty

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Five children, three girls and two boys, were treated for precocious puberty secondary to hypothalamic hamartoma by resection of the hamartoma. The patients' ages at onset of pubertal development ranged from 6 to 19 months. The hamartomas ranged in size from 6 to 10 mm; four were pedunculated, one was sessile, and all were located below the tuber cinereum. The hamartomas were excised via a right subtemporal approach, with transection at the inferior surface of the hypothalamus; two were adherent posteriorly to the basilar artery and brain stem, and the adhesions were divided. Postoperatively, three children exhibited a transient oculomotor paresis and one other child required eye-muscle surgery. The symptoms and signs of precocious puberty completely regressed postoperatively in all patients. Preoperative hormone assays of testosterone, luteinizing hormone, and follicle-stimulating hormone were within the pubertal range in all five children; postoperative assays fell to prepubertal levels. The children have been followed for 0.5 to 10.5 years (mean 5.0 years) postoperatively, without evidence of recurrence of precocious puberty. One child has begun spontaneous puberty at a normal age. It is concluded that complete resection of hypothalamic hamartomas causing precocious puberty is curative.

KEY WORDS · hamartoma · precocious puberty · hypothalamus · endocrinology

Hypothalamic hamartomas are rare lesions that have been diagnosed more frequently since computerized tomography (CT) and magnetic resonance (MR) imaging have been available. They are midline spherical masses that typically lie below the tuber cinereum. They range in size from 0.5 to 4.0 cm, but most are less than 1.5 cm in diameter. They may be pedunculated or sessile. Histologically, they are composed of disordered neurons resembling those of the hypothalamus, glial cells, and myelinated tracts that may connect with the hypothalamus. Some hypothalamic hamartomas cause precocious puberty.

Surgical treatment of hypothalamic hamartomas causing precocious puberty has usually been unsuccessful. Although occasional cases of successful resection have been described, in 1983 Alvarez-Garrojo, et al., wrote, "very few cases of precocious puberty due to hypothalamic hamartomas have been reported, and surgical treatment appears to be of little benefit for the sexual syndrome." As recently as 1989, Burton, et al., stated, "Current data do not support a primary role for surgery in the treatment of hypothalamic hamartomas."

We have successfully treated five children with precocious puberty secondary to hypothalamic hamartomas by resection of the hamartomas. We report the operative rationale and techniques, as well as the hormone levels and responses before and after treatment.

Case Reports

Case 1

This 9-month-old boy presented with pigmented Tanner stage 2 pubic hair, a husky voice, acne, and increased musculature. His penis and testes were enlarged, his gonadotropin levels were pubertal before and after gonadotropin-releasing hormone (GnRH) stimulation, and his testosterone values were in the adult male range. A CT metrizamide cisternogram obtained when he was 21 months old demonstrated a pedunculated mass below the tuber cinereum.

The mass was approached via a right subtemporal craniotomy (Fig. 1). There were fine arachnoid adhesions between the mass and the adjacent oculomotor nerve and posterior communicating artery. The adhesions were divided and the stalk was transected at its apex. The boy had no postoperative complications and was discharged on the 5th postoperative day. Postoperatively, his growth decelerated to normal, and the signs of precocious puberty had completely regressed within 6 months. The 7-mm hamartoma contained se-
cretory neurons, an ependymal cell-lined tubule, and scattered bundles of myelinated nerve fibers. There were GnRH granules present in neurons and axons of the hamartoma and in axons in the stalk. The endocrine results and pathology have been reported in detail previously. The patient entered puberty at the age of 10.5 years and his puberty has progressed normally.

Case 2

This 19-month-old boy presented with acne, Tanner stage 2 pubic hair, muscularity, height greater than the 95th percentile, and enlargement of his penis and testes. Assays revealed follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels in the pubertal range both before and after GnRH stimulation (Fig. 2). A CT scan showed a nonenhancing mass below the tuber cinereum, and an MR image revealed a 6-mm sessile mass (Fig. 3).

A right subtemporal craniotomy was performed. There were fine arachnoid adhesions between the mass and the oculomotor nerve and posterior communicating artery. More dense adhesions were present between the posterior surface of the mass and the basilar artery and anterior surface of the brain stem. The adhesions were divided and the mass was transected flush with the floor of the hypothalamus. The mass was a hamartoma containing secretory GnRH granules.

Postoperatively, the boy was normal except for a right-sided ptosis and oculomotor paresis; he was discharged on the 5th postoperative day. The ptosis resolved in 2 months and the exotropia improved but required extraocular muscle surgery 6 months postoperatively. The signs of precocious puberty began to regress within 2 months after surgery, and growth rate and hormone values normalized. The patient has been followed for 4 years with no recurrence of pubertal signs.

Case 3

This 6-month-old girl presented with breast development, menses, Tanner stage 2 pubic hair, excessive muscularity, and parental complaints of an “adolescent personality.” Gonadotropin levels were pubertal (Fig. 2). Magnetic resonance imaging demonstrated a pedunculated mass below the tuber cinereum (Fig. 4). The patient was treated with daily GnRH analog injections for 18 months. Menses ceased and hormone levels

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![Graph showing the plasma luteinizing hormone (LH) levels measured by fluorometric assay before and after gonadotropin-releasing hormone stimulation (at 0 minutes) in three patients with hypothalamic hamartomas (Case 2, closed triangles; Case 3, closed squares; Case 4, open squares). For comparison, the mean ± standard error of the mean for responses in 10 patients with idiopathic central precocious puberty (open triangles) are shown.](image)

![Case 2. Nonenhanced short-TR magnetic resonance images, sagittal (left) and coronal (right) projections, demonstrating an isodense mass (arrows) below the hypothalamus and immediately below the tuber cinereum.](image)
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![Fig. 4. Case 3. Nonenhanced magnetic resonance images, sagittal (left), coronal (center), and axial (right) views, demonstrating an isodense pedunculated mass (arrows) below the hypothalamus.](image)

normalized, but her adolescent personality and muscular physique persisted.

The mass was resected via a right subtemporal craniotomy. Fine adhesions around the hamartoma were lysed, and the stalk was divided at its apex. Postoperatively, the child had a mild right ptosis and oculomotor paresis which resolved within 3 months. Menses ceased without postoperative GnRH analog, her "adolescent personality" passed, muscularity regressed, and FSH, LH, and estradiol levels returned to normal. She has been followed for 3 years without recurrent symptoms or signs.

**Case 4**

This 6-month-old girl presented with breast development, menses, an excessive appetite, height above the 95th percentile, and muscularity; her parents complained of her "adolescent personality." Serum LH and FSH levels were pubertal (Figs. 2 and 5). An MR image demonstrated an 8-mm pedunculated mass below the tuber cinereum, and she was treated with monthly injections of depot GnRH analog for 1 year. Menses ceased and breast development regressed, but she retained her "adolescent personality" and muscularity.

A right subtemporal craniotomy was performed. Fine adhesions were present around the hamartoma, and the posterior surface of the mass was quite adherent to the anterior surface of the pons (Fig. 6). The adhesions were lysed, the stalk was divided at its apex, and the hamartoma (Fig. 7) was removed. Histologically, the

![Fig. 5. Case 4. Graphs showing serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels measured by fluoroimmunoassay before and after gonadotropin releasing hormone (GnRH) stimulation (at 0 minutes). Closed squares depict basal responses before treatment, open squares show suppression to a hypogonadotropic state during GnRH analog therapy and closed triangles show a typical prepubertal response after surgical resection.](image)

![Fig. 6. Case 4. Drawing showing a pedunculated hypothalamic hamartoma below the hypothalamus (bottom), with adhesions to the pons. The dissector is between the oculomotor nerve and the posterior communicating artery. The basilar artery and trochlear nerve lie posteriorly (right). The inferior aspect of the hamartoma lies just below the edge of the tentorium (top).](image)
hamartoma contained a tubule lined by ependymal cells, apparently a primordial diverticulum from the third ventricle, as well as GnRH-containing granules within neurons and axons (Fig. 8).

Postoperatively, mild ptosis and exotropia resolved within 3 months. The patient had no postoperative menses, her adolescent-type personality and muscularity regressed within 3 months, and the other stigmata of precocious puberty resolved. Serum LH and FSH values returned to normal (Fig. 2). She has been followed for 15 months without recurrence of puberty.

Case 5

This 20-month-old girl had developed breasts and menses at the age of 1 year, and soon thereafter had body odor, increased muscle bulk and height, and pubic hair. Her physical examination revealed Tanner stage 3 breast development, clitoral hypertrophy, and a vaginal discharge. She had a severe iron deficiency anemia from menstrual blood loss. Basal LH and estradiol levels were elevated, as was the LH response to GnRH. An MR image demonstrated a 7-mm pedunculated mass of brain signal intensity below the tuber cinereum.

The hamartoma was excised via a right temporal craniotomy. Oculomotor electromyograms were monitored during resection of the hamartoma. The apex of the stalk was located behind the origin of the posterior communicating artery; the artery was retracted, with some vasospasm, and the stalk was transected at its junction with the hypothalamus. Postoperatively, the patient had mild ptosis, no extraocular muscle paresis, and a transient left arm paresis. Menses ceased and the other stigmata of puberty resolved within 3 months. The LH levels were normal 3 months postoperatively.

Discussion

Precocious Puberty

Puberty commences because of the resurgence of the episodic release of GnRH

which differentiates first
during fetal life, persists into neonatal life, then normally down-regulates until the usual age of puberty. The mean age for onset of puberty in girls is 10.0 to 10.5 years, but the range extends as young as 8 years. In boys, the mean age at onset is 12 years, and the range extends as young as 9.5 years. Precocious puberty, then, is the occurrence of puberty in girls aged less than 8 years and in boys aged less than 9.5 years.

In addition to the development of pubertal sexual characteristics, children with precocious puberty often present with prominent skeletal and muscular features, complaints of teenage behavior, tall stature for their age, and an accelerated growth rate. If skeletal maturation progresses more rapidly than appropriate, height potential is lost. In rapidly progressing sexual precocity, premature epiphysial fusion may lead to an unusually short adult stature. Treatment of precocious puberty is aimed: 1) to stop untimely pubertal development, not because such development is physically harmful, but to avoid the psychosocial consequences thereof; and 2) to slow the rapid growth and skeletal maturation to avoid tall stature in childhood, early growth cessation, and short stature in adulthood.

Precocious puberty may have peripheral or central causes. Peripheral causes include those conditions in which sex steroid stimulation is via a mechanism other than GnRH-stimulated pituitary gonadotropin secretion. These include an excess of androgen in untreated congenital adrenal hyperplasia, steroid-producing neoplasms of the ovary, adrenal, or testes, and forms of autonomous gonadal function such as familial male precocious puberty or the McCune-Albright syndrome. Treatment of peripheral forms is aimed at removing or blocking the underlying pathophysiology. Central causes result in physiologically normal but early puberty as a consequence of episodic GnRH, LH, and FSH secretion. Underlying abnormalities resulting in central precocious puberty include disorders that affect the hypothalamus such as arachnoid cysts within the third ventricle, trauma, septo-optic dysplasia, neurophakomatoses, irradiation, neoplasms, and hamartomas.

Children with central precocious puberty have pubertal or adult levels of LH, FSH, and estradiol or testosterone, and pubertal or mature responses to GnRH stimulation. Treatment should result in cessation of GnRH-stimulated pituitary gonadotropin secretion.

Hypothalamic Hamartomas

Some neurons within hypothalamic hamartomas contain GnRH granules.9,10,11,12 Hamartomas apparently act as independent neurosecretory organs, releasing GnRH granules that cross axons and continue up into the tuber cinereum, where they are released into the hypophyseal-portal circulation. Neurons within the hamartoma that contain GnRH are apparently outside normal neurophysiological regulation and act as independent episodic pulsatile secretory units.

Hamartomas have been detected with increased frequency since the availability of CT and MR imaging studies. Before 1980, approximately 37 cases of hypothalamic hamartomas causing precocious puberty had been reported.10,11 Since 1980, at least 56 cases have
been reported. On CT scans, hypothalamic hamartomas are isodense nonenhancing masses, usually less than 2 cm in diameter and located below the hypothalamus. They are frequently attached to the hypothalamic by a stalk or pedicle and have been reported to lie free in the interpeduncular fossa or within the hypothalamus. They rarely calcify. Not all hypothalamic hamartomas are detected by CT.

Hypothalamic hamartomas are well demonstrated on T1-weighted (short TR) images, however, on long TR images, the hamartoma is poorly distinguished from cerebrospinal fluid in the suprasellar cisterns. Sagittal and coronal images clarify the attachment of the hamartoma to the hypothalamus and do not demonstrate the oculomotor nerve or adhesions between the hamartoma and the brain stem. A pedunculated mass below the hypothalamus in a child with precocious puberty is probably pathognomonic of a hamartoma; a sessile mass in such a child is more often a hamartoma than a glioma.

Gelastic seizures have been reported in some children with hypothalamic hamartomas and occasionally in children with hypothalamic hamartomas causing precocious puberty. The seizures have been improved but not cured by resection of the hamartoma. None of our patients had gelastic seizures.

Medical Treatment

Medical treatment of hypothalamic hamartomas causing precocious puberty and other forms of central precocious puberty has improved dramatically in the past decade due to the availability of long-acting GnRH analogs. Since pulsatile GnRH release, producing intermittently high levels with intervening low levels, is necessary to initiate and continue puberty, continuous pituitary stimulation by either GnRH or GnRH analog will maintain persistently high GnRH levels and inhibit gonadotropin secretion, and puberty ceases. Clinically, GnRH analog has been administered for 13 years without side effects and no sequelae of long-term administration are anticipated. However, it is expensive (at least $3,600 per year) and, as suggested by the cases presented in this paper, may not reverse the musculature, increased appetite, and “adolescent personality.” Parents of a child with precocious puberty may therefore face the prospect of continuous expensive medical therapy as well as having a “teenager” with symptoms of premenstrual syndrome, mood swings, irritability, and a voracious appetite for 10 years or more before normal puberty is reached.

Surgical Treatment

The reported neurosurgical experience in treating hypothalamic hamartomas causing precocious puberty has not been good. In a 1990 review of treatment options for these children, Starckes, et al., reported that, of the 33 cases treated surgically since 1958, 27 had undergone subtotal resection, with clinical and hormonal regression in only one. Of the six who received total resection, only three had arrested puberty. Since that review, Boyko, et al., reported relief of precocious puberty in three children by excision of pedunculated hamartomas. The neurosurgeon cannot be sure that the resection is total since residual GnRH-secreting neurons can persist within the hypothalamus, particularly in sessile lesions. No postoperative MR images have been reported for children with persistent precocious puberty after apparently total resections.

Surgical Approach

Although hypothalamic hamartomas have been excised via frontal, pterional, and subtemporal craniotomies, the subtemporal approach is probably preferable. The posterior surface of the hamartoma was adherent to the anterior brain stem or basilar artery in two of our cases; lysing those adhesions would have been difficult from a pterional approach. Adhesions to the basilar artery have been observed by others. Theoretically, pedunculated hamartomas could be treated by simply dividing their stalk at the apex, leaving the hamartomas in place. We have always removed the hamartomas in order to study the histology and immunopathology. Although there are reports of free hamartomas, we infer that they were attached by small...
stalks; no unattached hamartomas have been demonstrated by high-quality MR images.

The risk of postoperative oculomotor paresis due to nerve manipulation during hamartoma management may be reduced by intraoperative monitoring of oculomotor electromyograms. They were monitored in Case 5, helped to minimize nerve manipulation, and the child had no postoperative extraocular muscle paresis. The hamartoma stalk is intimately related to the basilar artery and the posterior communicating-basilar artery junction; arterial manipulation may induce vasospasm and cause neurological deficits. The microneuroanatomy is rarely as straightforward as suggested by MR images or diagrams.

Conclusions

Based on the patients presented in this report, surgery is an appropriate treatment option for children with precocious puberty secondary to hypothalamic hamartomas who otherwise face years of GnRH administration; this alternative should be considered if the MR images indicate a strong likelihood that the hamartoma can be excised. There are instances in which surgery, although technically possible, would be inappropriate. For example, one of our patients, an 8-year-old boy with precocious puberty secondary to a pedunculated hypothalamic hamartoma, was not treated medically or surgically because he was near the normal age for puberty and had a projected adult height of 176 cm (only 1 cm less than his father’s height).1 We conclude that complete resection of hypothalamic hamartomas that cause precocious puberty is a reasonable therapeutic option, with acceptable morbidity and a strong likelihood of endocrine cure.

References


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