Hypothalamic hamartomas (HHs) are rare congenital nonneoplastic malformations of the posterior hypothalamus that primarily present in the pediatric population. Presenting features of HHs may include precocious puberty, gelastic seizures (ictal laughter), behavioral dysfunction, and mental retardation. The reported incidence of HH in the pediatric population is approximately 1 case in 200,000 persons.3 However, an autopsy study by Sherwin et al. documented these lesions in 21.5% of consecutively investigated brains.48 Pedunculated lesions are typically associated with precocious puberty, whereas sessile types are more closely related to seizures, as noted by Boyko et al.7 Hypothalamic hamartomas are congenital heterotopic malformations consisting of dysplastic neurons clustering in nodular foci. They do not undergo neoplastic transformation.

They typically occur as small solid masses. Rare cases of giant HHs (diameter > 30 mm) have been reported and, very rarely, cystic changes and calcification have been described. Alves et al. found that giant HHs, as compared with smaller lesions, have a lower frequency of precocious puberty and similar frequency of seizures.2 The mechanism of cyst formation in HH is unclear and believed to be related to ischemic change followed by liquefactive necrosis within the lesion. The pathophysiology behind the clinical presentation of precocious puberty seen in HH is still uncertain. Case reports have demonstrated abnormally secreting hormonal cells within the hamartoma itself, such as luteinizing hormone (LH).24 Nishio et al. demonstrated lowered levels of both LH and LH-releasing hormone in patients postoperatively.18 Some researchers believe that it is the presence of an abnormal afferent neuronal network linking the HH to the hypothalamus that stimulates hypothalamic hormonal secretions. Others have suggested that it is the mechanical compression of the hypothalamus by the lesion that impairs the gonadotropin-secreting cell-inhibiting mechanism. These latter two hypotheses may also explain the underlying etiology of the epileptogenicity that can be associated with HH. To date, only Voyadzis...
et al. have demonstrated corticotropin-releasing hormone (CRH) immunostaining in an HH.46

We report the first case of a symptomatic HH with a solid CRH-positive component and associated tumor cyst in an 18 month-old girl presenting with central precocious puberty. We discuss the pathological features of this hamartoma along with approaches to its resection and management. The patient had complete remission of precocious puberty and no recurrence of the suprasellar mass on long-term follow-up.

Case Report

History and Examination. An 18-month-old girl presented with the early onset of thelarche at the age of 10 months, pubarche at 11 months, and menarche at 16 months. She had two episodes of irregular menses, each lasting 2–3 days. She had no headache, excess irritability, nausea or vomiting, visual abnormalities, weakness, or seizures. She was born via normal spontaneous vaginal delivery to a healthy primigravida. Birth weight was 8 lbs 14 oz, and APGAR scores were 10/10. Her developmental milestones were precocious. She sat at age 3 months and was walking and talking at age 8 months. On general examination she was a healthy-appearing girl with breast buds and genital hair (Tanner Stage II). Neurological examination was normal.

Endocrine workup showed an elevated estradiol level of 2.6 ng/ml (normal < 1.5 ng/ml). Baseline LH was 0.7 μIU/ml with a delayed level of 15.8 μIU/ml after stimulation of gonadotropin-releasing hormone. Following CRH stimulation, baseline follicle-stimulating hormone was 1.5 μIU/ml with a delayed level of 4.3 μIU/ml, and baseline cortisol was 4.5 µg/dl with a delayed level of 18.8 µg/dl. Serum thyroxine, thyroid-stimulating hormone, and prolactin levels were normal. Magnetic resonance imaging showed a suprasellar cystic mass with a small, nonenhancing solid component laterally on the left side close to the oculomotor nerve (Fig. 1). Bone age testing according to the standards of Greulich and Pyle49 showed advanced bone age corresponding to that of a girl 11 years old. Ultrasonography examination showed fully developed bilateral ovaries.

Operation. The patient underwent a right pterional craniotomy and microsurgical removal of the suprasellar mass. A suprasellar cystic mass was identified in the opticocarotid triangle. There was a small solid mass attached to the cyst on the left side (Fig. 2). The cyst was aspirated, and the fluid appeared slightly straw colored. The cystic and solid masses were removed via microdissection, working between the right optic nerve and carotid artery. The surgery was uncomplicated.

Postoperative Course. The patient made a smooth postoperative recovery. Repeat MRI confirmed total resection of the suprasellar mass. Her precocious puberty gradually resolved. Breast buds began to noticeably decrease in size 2 weeks after surgery. She remained prepubertal at the time of her most recent follow-up examination at age 9 years. Repeat MRI at that time showed no evidence of a residual or recurrent mass (Fig. 3).

Cytology of the cyst fluid was negative for malignant cells. On pathological examination, the lesion showed nodular aggregates of neurons and glial cells with abundant neuropil. The surface of the lesion resembled the normal superficial molecular layer of the cortex. The thin membranous component of the lesion showed glial cells and scattered neurons and was lined by a layer of flattened or cuboidal cells (Fig. 4A–D). Immunohistochemical staining for SMI-33 showed neuronal cell bodies within the nodular mass and scattered cell bodies within the membranous component. Scattered axons positive for SMI-34 appeared within the nodular mass and membranous tissue. Glial fibrillary acidic protein was positive within the membranous tissue as well as the nodular mass. Ki 67 was negative within the nuclei of the lesion. Immunostaining for tau, ubiquitin, and alpha-synuclein were negative, supporting the diagnosis of HH.

Corticotropin-releasing hormone immunoreactivity was identified in the solid part of the resected specimen (Fig. 4E and F). The Immunohistochemistry Laboratory of University Hospitals Case Medical Center performed the immunostaining technique. Briefly, unstained 4-μm sections were prepared from paraffin blocks and baked for 30 minutes at 60°C in a Boekel Lab oven. The slides were deparaffinized, and antigen was retrieved manually for anti-corticotropin factor developed in rabbit (CS5348, Sigma). The slides were then processed using a Bond automated immunostainer. The slides were incubated in primary antibody and subsequently counterstained with hematoxylin onboard the automated instrument. The slides for anti–corticotropin-releasing factor mouse monoclonal antibody (ab35748, Abcam) were processed using a Bond automated immunostainer. The slides were deparaffinized, and antigen was retrieved, and the slides were incubated in primary antibody and subsequently counterstained onboard the automated instruments. We used placenta as a control, as we had technical difficulties with the autopsy paraventricular nucleus and because it was easy to obtain. Corticotropin-releasing hormone is expressed in the placenta, particularly late in pregnancy, and offers a suitable control for CRH immunostaining in tissue specimens.

Discussion

Radiological Findings in HH

Cystic HHs have been infrequently reported in the neurosurgical literature.57 Multiplanar multispectral MRI techniques have become the gold standard in identifying and classifying HH. On CT, HHs are identifiable as non–contrast-enhancing isodense lesions located posterior to the infundibulum and extending into the interpeduncular, prepontine, and posterior suprasellar cisterns.52 Rarely, calcification can be identified within the hamartoma.59

Cystic Changes in HH

Cystic changes in HHs have been reported infrequently in the neurosurgical literature,57 with the possible etiology as ischemia and liquefactive necrosis. Sai Kiran et al.52 proposed bleeding as a possible etiology for cyst formation. In a developmental sense, this hypothesis seems to
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favor the abnormal proliferation theory responsible for the cystic degenerative process involved in giant cystic HHs as reported by Prasad et al.42 The vascular etiology of cystic changes could be related to the anatomical proximity of a perforating hypothalamic artery described by Sherwin et al.48 Dorfer et al. proposed that factors determining cystic degeneration include a delicate balance between growth of the mass and the angiogenic potential providing perfusion.12 Moreover, Koutcherov et al. suggested a developmental vicinity to normal hypothalamic cell lines, which enter a proliferative phase of normal development between the 25th and 41st day after conception; hence, a true HH would not show this progression.26

The cystic HHs reported in the literature have been seen mostly with giant lesions. The solid component of an HH is most often characterized on MRI as non–Gd-enhancing,7,10,53 mildly hyperintense relative to gray matter on T2-weighted imaging, and slightly hypointense to isointense relative to gray matter on T1-weighted imaging.6,7,9,10,20,30 In particular, T2-weighted imaging is important with respect to treatment, as it has the ability to distinguish HH from normal hypothalamus.21,46 Using MRI, authors have classified solid HHs as either pedunculated versus sessile or parahypothalamic versus intrahypothalamic.14 Pedunculated parahypothalamic HHs are lesions suspended from the floor of the third ventricle with minimal displacement of the third ventricle. These lesions are more likely to be associated with precocious puberty. Sessile intrahypothalamic HHs are more likely to be epileptogenic in nature, are involved or enveloped by hypothalamic tissue, and are more likely to distort the shape of the third ventricle. Magnetic resonance spectroscopy testing demonstrates that HHs have lower N-acetylaspartate and higher myoinositol concentrations as compared with those in normal thalamic gray matter and frontal lobe tissue. These two findings can be interpreted as indicating that HHs have neural loss and dysfunction with increased gliosis. These spectroscopic findings could help to explain the hyperintensity of HHs when studied with T2-weighted MRI, which can be indicative of increased glial tissue compared with normal gray matter.16,55 Several MRI reports on HHs have demonstrated variable myelin content, fibrillary gliosis, ischemic necrosis, and fatty changes, but calcification and cystic changes are extremely rare.42 Giant lesions have been shown to have a significant cystic component and present with precocious puberty or gelastic seizures. Some suprasellar arachnoid cysts also present with these symptoms.41 Surprisingly, there are anecdotal case reports on HHs associated with arachnoid cysts.17,23,31,36 Hence, it is important to distinguish a suprasellar arachnoid cyst from a cystic HH.

Hypothalamic Hamartomas and Precocious Puberty

Precocious puberty is defined as the appearance of physical and hormonal signs of pubertal development at a younger age than is considered normal: for females, before 6–8 years old; and for males, before the age of 9 years.51 In addition to the abnormal sexual development, other symptoms include prominent bone and muscular disturbances; accelerated growth rates can cause premature epiphyseal fusion leading to short adult stature. Central precocious puberty is gonadotropin dependent and caused by early

Fig. 1. Preoperative MR images. A: Axial T1-weighted section with contrast showing a suprasellar cystic lesion with a small lateral solid component (arrow). B: Axial T2-weighted section showing the suprasellar cystic lesion with CSF intensity and a small lateral solid component (arrow). C: Coronal T1-weighted section showing the cystic HH with a small solid component (arrow).

Fig. 2. Intraoperative images of cystic HH resection. A: Lesion visible through the right opticocarotid triangle. B: After resection of the hamartoma. C and D: Cyst wall and solid hamartoma specimen in two different views.
maturation of the entire hypothalamic-pituitary-gonadal axis. Precocious pseudopuberty is defined as conditions leading to the increased production of sex steroids independent of gonadotropin release.\textsuperscript{51} The etiology of central precocious puberty is predominately idiopathic (80\%–90\%). Mass lesions in the brain, CNS irradiation, and genetic abnormalities are responsible for the remaining cases. The common CNS lesions shown to cause precocious puberty are suprasellar arachnoid cysts and HHs.\textsuperscript{40}

Of the 46 cases of HHs studied by Lin et al., 41 (89\%) presented with symptoms of precocious puberty.\textsuperscript{28} Coons et al. at Barrow Neurological Institute reported on 57 cases of intractable epilepsy due to HH, 19 (33\%) of which had a history of precocious puberty.\textsuperscript{11} Arita et al. reported that 25 (83\%) of 30 cases of precocious puberty due to HH were parahypothalamic. Further regression analysis demonstrated that the presence of peduncles was highly correlated with precocious puberty (p = 0.0001).\textsuperscript{4} In a 72-case analysis, Freeman et al. found that precocious puberty was related to hamartoma size (p = 0.004), contact with the pituitary stalk (p = 0.01), and tuberal involvement (p = 0.04).\textsuperscript{14} Our patient had a solid component in the left opticocarotid cistern, far away from the parahypothalamic region. Like HH, arachnoid cysts in the hypothalamic region have been associated with multiple endocrinological abnormalities. Those in the suprasellar region rarely present with precocious puberty.\textsuperscript{8,52} In a series of 50 pediatric patients with arachnoid cysts, Onal et al. described only one case of early thelarche.\textsuperscript{18}

**Treatment of HH**

The treatment of HH can be medical or surgical. Since 1967, when Northfield and Russell\textsuperscript{37} first described the resection of HH for the treatment of precocious puberty, a multitude of surgical approaches and nonsurgical modalities have been used in the treatment of symptomatic HH. Apart from frontal, pterional, subtemporal, and transcallosal approaches and transventricular endoscopy, novel techniques, such as synchronous endoscopy and microsurgery, Gamma Knife surgery, radiofrequency ther-

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**Fig. 3.** Postoperative MR images on follow-up at 9 years. A: Axial T1-weighted section. B: Axial T2-weighted section. C: Coronal T1-weighted section. There was no reaccumulation of suprasellar cyst or recurrence of the solid component of the cystic HH.

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mocoagulation, and interstitial radiosurgery, have been attempted with varying degrees of success.3,5,25,39,40,54

The surgical management of HHSs can be extremely cumbersome. Most neurosurgeons have adopted the transcallosal or transventricular endoscopic approach for HH resection. The advantage of the transcallosal approach is that it offers an excellent surgical view while allowing one to debulk and/or disconnect the HH as well as spare the mammillary bodies, pituitary stalk, and optic chiasm.1 Unlike the basal approaches, the transcallosal approach does not interfere with blood vessels and cranial nerves in the local area and allows access into the interpeduncular fossa and preopticine cistern. Complications from the transcallosal approach most commonly involve short-term memory difficulties.21 Hypothalamic obesity, partial or complete panhypopituitarism, asymptomatic hypernatremia, and overt diabetes insipidus have also been described.15,34 Transventricular endoscopic resection has been shown to be a good treatment option for small (<10 mm) intrahypothalamic hamartomas that exhibit attachment to only one wall of the third ventricle and with definite intraventricular extension.35,32,33,43,44 To perform an endoscopic procedure, a distance of at least 6 mm is needed between the lesion and the foramen of Monro to allow for safe passage of the endoscopic instruments within the third ventricle.1 Frameless stereotactic neuronavigation is helpful for an accurate approach to the foramen of Monro. Patients who undergo transventricular endoscopy, as compared with the transcallosal approach, have statistically shorter hospital stays and less morbidity.23

The novel combined endoscope-assisted microsurgical approach may be advantageous since it allows for two concurrent operative approaches. Possible benefits include increased protection and accessibility of critical neurovasculature as well as a reduction in overall operative time. Gore et al. used a right supraorbital craniotomy in conjunction with a left transcortical transforaminal endoscopic approach to remove a large HH attached to the right wall of the third ventricle extending into the chiasmat, interpeduncular, and prepontine cisterns.18 A subfrontal approach allowed for debulking of the lesion inferior to the hypothalamus, preserving the surrounding critical neurovasculature. However, further investigation is required to elucidate the indications for a synchronous endoscopic microsurgical approach for complex suprasellar lesions. There are also anecdotal reports of disconnection surgery in HH, for example using an endoscopic Suros variable aspiration tissue resector disconnecting the tumor from the medial hypothalamus successfully.27

Surgical approaches for mixed cystic and solid lesions can be appropriately modified with respect to the anatomical location of the hamartoma’s solid component. The surgical indication for mixed cystic and solid HH resection also depends on the surgical corridors available for decompression of the lesion-associated cyst. The surgical approach should be selected based on the expertise of each neurosurgeon and modified appropriately with endoscopic assistance as needed. If surgical morbidity is deemed too high, consideration should be given to long-standing medical therapy.

The reversal of precocious puberty following HH resection has been well documented in the medical literature. Albright et al. described 5 children with precocious puberty and HH who were successfully treated with resection.2 There was no long-term recurrence of symptoms, and pubertal development went on to occur normally. Steward et al. described 6 patients with precocious puberty and HH in whom resection reversed symptoms only temporarily.50 It has been shown that total resection of the HH is necessary for satisfactory endocrinological results. Therefore, lesions that are nonpedunculated are less likely to have positive surgical outcomes. Our case has shown CRH immunoreactivity in the solid part of the lesion; however, there are conflicting opinions on the role of CRH in the causation of precocious puberty in these patients.16,22,56

Conclusions

We report an unusual case of a predominantly cystic suprasellar HH in a toddler presenting with precocious puberty. This is the first reported case of a cystic HH with the solid component staining for CRH and the glial cyst wall verified by GFAP immunostaining. We highlight the importance of identifying the solid component of the lesion, regardless of how small it is, and emphasize the significance of differentiating a cystic HH from a suprasellar arachnoid cyst. Precocious puberty associated with a cystic HH can be a surgically curable condition. Surgery entails resection of the lesion. Cyst fenestration alone may miss the solid component of the lesion.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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