Hypothalamic hamartomas are rare nonneoplastic lesions originating from the tuber cinereum or mammillary bodies. They often present in early childhood with either precocious puberty and/or medically refractory seizures. Gelastic seizures are the hallmark of these lesions, which have been shown to have intrinsic epileptogenicity. Most HHs are sporadic lesions and 10% are part of a multiple malformation syndrome. In 2 large series reported by Freeman et al. and Arita et al. the mean size of the HHs was 19 and 17.9 mm, respectively. Very few cases of giant HHs have been reported. We describe a case of a patient harboring an enormous solid-cystic HH, the size and extension of which seem unique in the literature and potentially raise further questions about the origin of these lesions.

Case Report

History and Examination. This 8-month-old boy presented with enlarged head circumference, precocious puberty, and delayed development. After fetal ultrasound detection of hydrocephalus at 20 weeks age of gestation, fetal MR imaging revealed a solid-cystic mass originating from the floor of the third ventricle, suggesting an enormous HH. At referral, MR imaging revealed a huge solid-cystic HH broadly based on the tuberomammillary region extending down to the lower clivus, with the cystic component displacing the brainstem and left cerebellar hemisphere. The dimension of the solid component was $2.7 \times 4.5$ cm (width $\times$ height). The cyst further extended through the posterior tentorial notch into the velum interpositum and both lateral ventricles with associated hydrocephalus (Figs. 1, 2A, and 3). Neither the solid nor cystic parts had increased disproportionally to brain growth up to the time of referral.

Operation. We performed a transcaldosal partial resection with the aim of decompressing the aqueduct and establishing communication of the cyst through the solid part of the HH to the basal cisterns (Figs. 2B and 4). The abducent nerves were found to be tightly adherent to the lesion. The resection and fenestration of the solid part was restricted to the median portion toward the foramen magnum. Because the patient did not have seizures, we did not attempt a disconnection. The treatment of hydrocephalus seemed successful and the precocious puberty was effectively treated with a gonadotropin-releasing hormone analog (leuprolin acetate, Takeda Pharma).

Second Operation. One year later, seizures developed that were refractory to medical treatment; the patient experienced frequent gelastic fits and a developmental de-
lay. We decided to undertake a reoperation, transcallosally, with the objective now to disconnect the HH. The dorsal displacement of the brainstem and the hamartoma did not allow a safe total disconnection of the most posterior parts abutting the mammillary bodies (Fig. 2C), but a 50% decrease in seizure frequency was achieved immediately after disconnection. Two weeks after the second operation the boy developed hydrocephalus and a ventriculoperitoneal shunt was inserted.

Postoperative Course and Third Operation. The further development of the boy was quite satisfying and he reached the milestones with a delay of 1–2 months. With increasing seizure frequency 2 years later the boy again experienced a regression in speech development. A third transcallosal operation was performed to complete the disconnection (Fig. 2D). A significant reduction of seizure frequency was achieved (1 episode per month while receiving anticonvulsive medication). The 7-year-old boy still exhibits signs of a severe attention deficit and a delay in speech and motor development. At this time, no additional endocrinological disturbance has been diagnosed.

Discussion

Studies relating to the neuropathology and neurobiology of the HH are limited. Immunohistochemical studies reveal positive staining for neuronal markers, including neuron-specific enolase, synaptophysin, and neurofilament protein, supporting a neuronal phenotype of a great proportion of the cells. A detailed analysis of HH cell characteristics, with respect to the normal hypothalamic cytoarchitecture and immunohistochemistry, demonstrated neuronal elements predominating in most cases and a relative increase in astrocytic elements with increasing age. The hamartomas showed various-sized nodular foci of neurons as well as areas of diffusely distributed pattern. Most HHs are sporadic, and only about 10% are associated with the Pallister-Hall syndrome or other syndromic entities including McKusick-Kaufman syndrome, Bardet-Biedl syndrome, oral-facial-digital syndrome Type 6, and Waardenburg syndrome. The reported prevalence of children and adolescents affected by an HH has been reported to be 1 in 200,000. However, an autopsy study in 1962 demonstrated hamartomatous malformations adjacent to the mammillary bodies in 26 (21.5%) of 121 consecutively investigated brains, indicating that clinically silent HHs may be underreported. No clinical data were reported. The size of these lesions ranged from 0.5 to 1.5 mm in diameter at the base of the lesion. Of note, the authors of the aforementioned study described these lesions as nodules composed of compact and loose glial tissue containing ganglion cells, which were all directly related to a perforating hypothalamic artery.

The mechanism of HH development is still not understood, but several hypotheses exist. One hypothesis is that the hamartoma may result from ectopic localization of otherwise relatively normal cellular elements. This misplacement could be related to defects in cell-cell recognition and cell-matrix interference, which normally guides the cells’ neuronal migration along radial glial cells. The absence of the right migratory and proliferation stimuli might lead to an abnormal local brain structure.

A second hypothesis indicates that HH cells are positioned normally but have an abnormal proliferative potential. Immunohistochemical studies focusing on cell lineage may be capable of identifying cells that are themselves intrinsically abnormal, potentially expressing more primitive cell markers, including tumoralike or stem cell–like phenotypes. No data are available at that time to support either of these hypotheses.

At least in our case the large, predominately cystic lesion supports the notion of an abnormal proliferative tumorlike mechanism of origin. Factors determining cystic degeneration include the delicate balance between growth and its perfusion requirements with the underlying angiogenesis. Therefore, an at least temporary highly proliferative phenotype of the hamartoma cells might be the explanation for the large cystic HH in our case. This hypothesis of an ischemic degenerative process was posited by Prasad et al. in a report on 2 giant cystic HHs. In rare cases this proliferative phenotype may persist and result in a hypothalamic hamartoblastoma with more primitive and immature neuronal and glial elements, as described by Clarren et al.

In the postnatal course, the enlargement of the hamartoma is proportional with the normal brain growth, so that the lesion’s size does not change in relation to the rest of the brain. This growth pattern is further supported by the observations of a glial predominance with increasing age and a few MIB-1 proliferating glial cells in most of the histologically studied cases by Coons et al. In our
Giant solid-cystic hypothalamic hamartoma

The fact that true HHs never show progression would indicate that these cells only get proliferative stimuli during the proliferative phase of the normal hypothalamic development between the 25th and 41st day postconception, thereby suggesting their developmental vicinity to normal hypothalamic cell lines. The Gli3 transcription factor gene has been found to be mutated in some patients with HH associated with Pallister-Hall syndrome. With Gli3 being a downstream effector protein of the sonic hedgehog transduction pathway, HH could be related to the spectrum of sonic hedgehog–associated forebrain anomalies.

In addition to immunohistochemical and electrophysiological studies, molecular biology studies of HH will be essential to elucidate the mechanisms of development of these intriguing lesions.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Dorfer, Kasprian, Czech. Acquisition of data: Dorfer, Czech. Analysis and interpretation of data: Dorfer, Czech. Drafting the article: Dorfer. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Dorfer.

Fig. 2. Coronal and sagittal T2-weighted MR images displaying the solid tumor part as mainly isointense to gray matter–appearing mass, located ventrally to the brainstem. A: Images at presentation showing compression of the distal aqueduct by the solid component of the hamartoma anteriorly and the cystic component posteriorly, causing mild hydrocephalus. B: Images obtained after the first partial resection, decompression of the aqueduct, and communication of the cyst through the solid part of the HH to the basal cisterns. C: Images obtained after second surgery demonstrating right posterior parts of the hamartoma still connected to the hypothalamus (asterisk). D: Images obtained after third transcallosal operation demonstrated a completed disconnection.

Fig. 3. Sagittal postcontrast T1-weighted MR image. No enhancement is seen; the lesion is isointense to gray matter tissue.

Fig. 4. Hematoxylin and eosin–stained sections of the HH showing dysplastic neurons clustering in nodular foci. Original magnification × 10 (left) and × 20 (right).
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