Hypothalamic hamartomas are rare nonneoplastic lesions originating from the tuber cinereum or mamillary 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 HH. At referral, MR imaging revealed a huge solid-cystic HH broadly based on the tuberomammillary region and 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 transcallosal 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 were 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 (leuprolelin 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, transcallo-
sally, 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 pos-
terior 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 fur-
ther 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 sei-
zure 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 addi-
tional endocrinological disturbance has been diagnosed.

Discussion

Studies relating to the neuropathology and neurobiol-
ogy of the HH are limited. Immunohistochemical stud-
ies reveal positive staining for neuronal markers, including
neuron-specific enolase, synaptophysin, and neurofilament
protein, supporting a neuronal phenotype of a great pro-
tortion of the cells. A detailed analysis of HH cell char-
acteristics, with respect to the normal hypothalamic cy-
toarchitecture and immunohistochemistry, demonstrated
neuronal elements predominating in most cases and a rela-
tive increase in astrocytic elements with increasing age.4
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 associ-
ated 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.8 The reported prevalence of chil-
dren and adolescents affected by an HH has been reported
to be 1 in 200,000.2 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.14 No clinical data were reported.
The size of these lesions ranged from 0.5 to 1.5 mm in di-
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 perforat-
ing hypothalamic artery.14

The mechanism of HH development is still not under-
stood, but several hypotheses exist. One hypothesis is that
the hamartoma may result from ectopic localization of
otherwise relatively normal cellular elements. This mis-
placement could be related to defects in cell-cell recogni-
tion 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 them-
selves intrinsically abnormal, potentially expressing more
primitive cell markers, including tumoralike or stem cell-
like phenotypes. No data are available at that time to sup-
port 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 underly-
ing 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 pos-
ted by Prasad et al.12 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.3

In the postnatal course, the enlargement of the ham-
artoma 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.4 In our

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**Fig. 1.** Axial T2-weighted MR images depicting the large cystic tumor component with space-occupying effect and compres-
sion of the left cerebellar hemisphere and dislocation of the brainstem. Also apparent is mild hydrocephalus with widening of the
lateral ventricles and the third ventricle.
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 transcaldosal 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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