The Histopathology of Hypothalamic Hamartomas: Study of 57 Cases

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Abstract

Hypothalamic hamartomas (HHs) are rare developmental tumors that cause seizures or pituitary axis dysfunction, usually beginning in childhood. We analyzed HH tissue from 57 patients whose tumors were resected through recently developed transcaldosal interforniceal and transventricular endoscopic surgical approaches. All cases were composed of abnormally distributed but cytologically normal neurons and glia, including fibrillary astrocytes and oligodendrocytes. Neuronal elements predominated in most cases, but a relative increase in astrocytic elements was seen with increasing age. All had various sized nodular foci of neurons as well as areas of diffusely distributed neurons with interspersed glial cells. Smaller neurons predominated, and most cases had only a few interspersed large ganglion cells. Immunohistochemistry demonstrated extensive production of synapse-associated proteins. Immunohistochemistry for phosphorylated and nonphosphorylated neurofilament and α-intermixin demonstrated staining patterns consistent with mature neurons. In contrast to cortical dysplasia, atypical large ganglion-like balloon cells were almost never seen. In summary, although their number and distribution vary, mature smaller neurons were the most prominent and most consistent histologic feature of HH. Nodules of these small neurons were a universal feature of the microarchitecture of HH lesions associated with epilepsy. Characterization of these neurons may aid in understanding the mechanism of seizure development in HH.

Key Words: Gelastic seizures, Hypothalamic hamartoma, Intractable epilepsy, Precocious puberty.

INTRODUCTION

Hypothalamic hamartomas (HHs) are congenital, nonprogressive, tumor-like masses that arise from the ventral hypothalamus and tuber cinereum (1). HH lesions associated with epilepsy are relatively uncommon, with a prevalence of about 1 affected patient in 200,000 children and adolescents (2). There are 2 different primary subgroups of HH: Parahypothalamic (pedunculated) tumors project below the hypothalamus, and intrahypothalamic (sessile) lesions have a broad base of attachment that includes the lateral walls of the third ventricle (3–5).

The pedunculated form is primarily associated with pituitary axis dysfunction, specifically central precocious puberty. It is rarely associated with epilepsy. In contrast, intrahypothalamic tumors are consistently associated with neurologic symptoms, including epilepsy, cognitive impairment, and psychiatric disturbance (6–8). However, their natural history appears to be quite variable. Many of these patients become symptomatic during infancy or even during the neonatal period with gelastic (laughing) seizures (9). Seizures associated with HHs are usually refractory to antiepilepsy medications. Most of these patients undergo a deteriorating course and later develop multiple seizure types, progressive cognitive impairment, or worsening psychiatric symptoms (6–11). Central precocious puberty occurs in about 40% of patients with the intrahypothalamic form of HH (12).

Most HHs are sporadic; however, approximately 5% are associated with the Pallister-Hall syndrome, an autosomal dominant syndrome that includes HH and skeletal dysmorphisms, among other developmental anomalies (13–15). The Pallister-Hall syndrome is associated with a germ-line defect in the GLI3 gene (16–18). The genetics of the sporadic lesions remain unknown.

Until recently, resective surgery for HH was often discouraged because its efficacy for seizure control was relatively poor and its risk of complications was high (19). Even so, a sizable number of publications, most relating the surgical outcome of HH resection, have at least mentioned the neuropathologic features associated with HH and epilepsy (3, 20–40). Most of these publications consist of single case reports and the description of the pathology tends to be minimal. Consequently, major texts provide only limited descriptions of the histologic features of HH associated with epilepsy.

The HH itself is intrinsically epileptogenic (41–44). For patients with refractory epilepsy, successful surgical resection of the HH through a transcaldosal interforniceal or transventricular endoscopic approach can lead to complete seizure control or to a significant reduction in the frequency of seizures (45, 46). As a center where these procedures are
performed, the Barrow Neurological Institute has acquired a large series of patients who have undergone surgical resection of HH. We present the histologic consistencies and differences among 57 HHs associated with refractory epilepsy. In addition to morphologic features, immunohistochemical expression of neuronal differentiation and maturation markers were analyzed. The morphologic data were correlated with clinical presentation and imaging findings.

FIGURE 1. (A) Coronal T2 fast spin echo (FSE) magnetic resonance imaging sequence demonstrating a type I hypothalamic hamartoma (HH) lesion (arrow). This patient has a history of intractable epilepsy and central precocious puberty. Note the broad base of attachment to the underside of the hypothalamus, a common finding in type I cases with epilepsy. (B) Coronal T2 FSE sequence with a type II HH lesion (arrow). (C) Coronal T2 FSE sequence with a type III HH lesion (arrow). This lesion attaches both above and below the floor of the third ventricle. (D) Coronal T1 sequence with a type IV (or “giant”) HH lesion. This particular lesion has bilateral attachment to the hypothalamus (arrows). HH classification according to Delalande, Fohlen, and colleagues (47, 48).

TABLE 1. Delalande Classification of Hypothalamic Hamartoma (HH) Anatomic Subtypes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Number of Cases</th>
<th>HH Lesion Volume (mean [range] cm³)</th>
<th>Bilateral Attachment (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HH attachment below the floor of third ventricle (parahypothalamic)</td>
<td>5</td>
<td>1.83 (0.08–5.31)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>II</td>
<td>HH attachment wholly within the third ventricle (intra-hypothalamic)</td>
<td>31</td>
<td>1.40 (0.13–11.81)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>III</td>
<td>HH attachment above and below the floor of the third ventricle (intra-hypothalamic)</td>
<td>14</td>
<td>3.29 (0.53–10.23)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>IV</td>
<td>Giant HH lesions (intra-hypothalamic)</td>
<td>7</td>
<td>10.32 (8.15–15.70)</td>
<td>7 (100)</td>
</tr>
</tbody>
</table>
Finally, the implications of the pattern of neuronal maturation and differentiation in regard to possible mechanism(s) of seizure development were considered.

**MATERIALS AND METHODS**

Tissue was obtained from 57 patients who underwent resection of an HH between 2003 and 2004 at the Barrow Neurological Institute of St. Joseph’s Hospital and Medical Center (Phoenix, AZ). HH was confirmed microscopically in all 57 patients, of whom 17 were female (30%) and 40 were male (70%). At surgery, their ages ranged from 8 months to 55.9 years (median age, 9.5 years). The median age of the female patients was 9.2 years (range, 2.3–55.9 years), and the median age of male patients was 10.1 years (range, 8 months to 37.5 years).

The volume and classification of the HH were determined before surgery by the use of a standardized magnetic resonance (MR) imaging protocol (46). Anatomic features of the lesions were categorized according to the HH classification system proposed by Delalande and colleagues (47, 48). The Delalande classification scheme assigns type I for HH lesions with a horizontal plane of attachment inferior to the floor of the third ventricle, type II for lesions within the third ventricle and with a vertical plane of attachment, and type III for lesions with both vertical and horizontal planes of attachment that span the floor of the third ventricle. Type IV are “giant” hamartomas. Type I corresponds most closely to the parahypothalamic subgroup, whereas types II to IV correspond to the intrahypothalamic subgroup. Representative examples of types I through IV are shown in Figure 1A–D.

Most (52 of 57, 91%) of the HHs were of the intrahypothalamic type (Delalande subtypes II–IV), whereas only 5 (9%) were parahypothalamic (Delalande subtype I) (Table 1). These type I lesions tended to have a broad base of attachment to the inferior surface of the posterior hypothalamus. For the entire series, the mean volume of the HH lesions was 3 cm$^3$ (median 1.29 cm$^3$; range, 0.08 cm$^3$–15.70 cm$^3$).

In 49 patients (86%), the age at seizure onset was 1 year or less and was 1 month of age or less in 31 patients (54%). At some time during their clinical course, all 57 patients had gelastic seizures. In 55 (97%) patients, this was the initial seizure type. At surgery, 41 patients (72%) had multiple seizure types, whereas 16 (28%) had only gelastic seizures. All patients had epilepsy that was refractory to medical management (failure of at least three medications): 49 (86%) experienced multiple daily seizures, and the remainder had multiple seizures each week.

Nineteen patients (33%) had a history of central precocious puberty. Five (9%) had Pallister-Hall syndrome, and one had Mohr syndrome (oral-facial-digital syndrome type II). Thirty-nine patients (68%) exhibited mental or developmental retardation. Other than the HH, congenital brain abnormalities were apparent on MR imaging in only 1 patient (congenital hydrocephalus, periventricular nodular heterotopia, and suspected hamartoma of midbrain tectum). Seven patients (12%) had undergone previous treatment directed at the HH (prior surgical biopsy or subtotal resection in 3, Gamma Knife radiotherapy in 3, and stereotactic thermoablation in 1).

Routinely processed, 4-μm, paraffin-embedded sections from all 57 cases were stained with hematoxylin and eosin. For the first 27 cases, or as noted, histochemical and immunohistochemical analysis was performed for markers of neuronal differentiation, maturation and structural proteins, glial differentiation, and cellular proliferation. The immunohistochemical analysis was performed on 4-μm sections using the Ventana Nexus immunostainer (Ventana Medical Systems, Tucson, AZ). The reaction product was visualized with diaminobenzidine. Negative control sections were processed identically with omission of the primary antibodies. Table 2 lists the antibodies used and specific stained sections from all 57 cases were stained with hematoxylin and eosin. For the first 27 cases, or as noted, histochemical and immunohistochemical analysis was performed for markers of neuronal differentiation, maturation and structural proteins, glial differentiation, and cellular proliferation. The immunohistochemical analysis was performed on 4-μm sections using the Ventana Nexus immunostainer (Ventana Medical Systems, Tucson, AZ). The reaction product was visualized with diaminobenzidine. Negative control sections were processed identically with omission of the primary antibodies. Table 2 lists the antibodies used and specific staining conditions. Luxol fast blue (LFB) stain was used to demonstrate myelin. Normal control hypothalamus was obtained at autopsy from 4 patients aged 2, 6, 13, and 35 years, respectively.

Statistical analysis was performed with SAS Learning Edition 2.0 with Enterprise Guide 2.1.40. Categorical variables were analyzed with a chi-square test. When samples were smaller than 5, the Fisher exact test was used instead. The Wilcoxon test was used to analyze continuous

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**TABLE 1.** Histopathology of Hypothalamic Hamartoma

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Dilution</th>
<th>Antibody Retrieval</th>
<th>Control</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFAP</td>
<td>Prediluted</td>
<td>Heat-induced epitope retrieval (citrate buffer)</td>
<td>Normal cortex</td>
<td>Dako (Carpinteria, CA)</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Prediluted</td>
<td>Heat-induced epitope retrieval (citrate buffer)</td>
<td>Normal cortex</td>
<td>Dako (Carpinteria, CA)</td>
</tr>
<tr>
<td>SNAP25</td>
<td>Prediluted</td>
<td>Heat-induced epitope retrieval (citrate buffer)</td>
<td>Normal cortex</td>
<td>Novocastra (Newcastle Upon Tyne, UK)</td>
</tr>
<tr>
<td>Neurofilament phosphorylated</td>
<td>Prediluted</td>
<td>None</td>
<td>Normal cortex</td>
<td>Cell Marque (Hot Springs, AR)</td>
</tr>
<tr>
<td>Neurofilament nonphosphorylated</td>
<td>1:10</td>
<td>Heat-induced epitope retrieval (citrate buffer)</td>
<td>Normal cortex</td>
<td>Chemicon (Temecula, CA)</td>
</tr>
<tr>
<td>α-Intemexin</td>
<td>1:10</td>
<td>Heat-induced epitope retrieval (citrate buffer)</td>
<td>Normal cortex</td>
<td>Novocastra</td>
</tr>
<tr>
<td>Ki-67/MIB-1</td>
<td>1:50</td>
<td>Heat-induced epitope retrieval (citrate buffer)</td>
<td>Lymph node</td>
<td>DAKO</td>
</tr>
<tr>
<td>CD68</td>
<td>1:100</td>
<td>Ventana cell conditioning solution</td>
<td>Lymph node</td>
<td>DAKO</td>
</tr>
</tbody>
</table>

GFAP, glial fibrillary acid protein; SNAP25, synaptosomal-associated protein.
variables. Logistic regression was performed for multivariate analysis using a backward, stepwise subtraction. Significance was established as $p < 0.05$.

RESULTS

The HHs were composed of abnormally distributed but cytologically normal neurons and glia. In most cases (33 of 57, 58%), neuronal elements predominated. In many cases (24 of 57, 42%), however, glial elements were prominent or even preponderant. Every case had multiple discrete nodular foci of neurons separated by areas with diffusely distributed neurons interspersed with glial cells. The nodular pattern predominated in 39 of 57 (68%) cases, whereas 18 of 57 (32%) cases demonstrated a predominantly diffuse architecture (Fig. 2A–C).

The glial cells were usually distributed diffusely, either individually or interspersed with neurons. Only rarely were discrete nodules of glial cells present. The preponderant glial cells were small fibrillary astrocytes with oblong or, less commonly, round nuclei and either a small cap of eosinophilic cytoplasm or polar glial processes (Fig. 3). Scattered oligodendrocytes were present but recognized less frequently than the astrocytes.

The presence of microglia was evaluated using CD68 immunohistochemistry. Although scattered microglia were present in all cases, the glial-rich regions were confirmed as being predominantly glial, and no consistent association was seen between microglial number and HH pattern.

The size of the neuronal nodules ranged from $<10$ to hundreds of neurons. The larger nodules were the most common. The cellularity of the nodules also varied. Most nodules were highly cellular with the neurons situated almost back-to-back. In some, however, the neurons were widely spaced (Fig. 4A–D). Almost all of the nodules were composed primarily of small-to-intermediate sized neurons. A few larger neurons were visible in a minority of nodules (Fig. 5). A single small nodule of large ganglion cells was

**FIGURE 2.** (A) In most cases various sized nodules of small neurons predominated, with diffusely scattered small neurons and astrocytes between the nodules. Hematoxylin and eosin (H&E), original magnification: 100×. (B) In some cases, nodularity was limited with larger numbers of diffusely distributed neurons. H&E, original magnification: 400×. (C) Glial (astrocytic) elements were prominent or even preponderant in a significant minority of cases. H&E, original magnification: 200×.

**FIGURE 3.** The glial cells predominantly resembled fibrillary astrocytes with either bipolar processes or a small cap of eosinophilic cytoplasm. The nuclei ranged from round to oblong. Hematoxylin and eosin, original magnification: 400×.
found in only 1 case. The diffusely distributed neurons were also predominantly small. In contrast, most nuclei in the normal hypothalamus are composed of nodules of large ganglion cells (Fig. 6).

The neurons consistently demonstrated a “mature” pattern of neurofilament (NF) expression. Whereas non-phosphorylated NF was present in cell bodies and diffusely in neuronal processes, phosphorylated NF was seen only in scattered processes. The mature axonal marker α-internexin demonstrated a pattern of reactivity similar to that of phosphorylated NF (Fig. 7A, B). In contrast to cortical dysplasia, atypical large ganglion-like balloon cells were identified as a rare finding in only one case.

In all cases, the stroma resembled neuropil and had a fine spongiform quality, particularly within nodules (Fig. 8). Synaptosomal-associated protein-25 and synaptophysin immunohistochemistry demonstrated diffuse production of synapse-associated proteins similar to normal gray matter both within nodules and in diffuse areas (Fig. 9). Within the HH, LFB stain showed only occasional randomly distributed myelinated axons in the nodules or diffuse areas (Fig. 10). In
contrast to normal hypothalamus, well-organized tracts of axons were never present except at the periphery of the lesions. It was unclear whether these tracts were a part of the hamartoma or represented the interface with native hypothalamus. For comparison purposes, an internuclear region of normal hypothalamus (LFB stain) is shown in Figure 11. The distribution of phosphorylated NF-positive axons was similar to that of myelinated axons seen with the LFB stain.

The tumors were divided into groups based on estimates of the relative prominence of cell types (neuronal or glial predominant) and their distribution (nodular or diffuse). Despite this coarse semiquantitative classification, there were significant differences among the groups. There was an association between prominent neuronal nodularity and neuronal predominance. In 27 of the 39 tumors with prominent nodularity, neuronal elements predominated, compared with 6 of the 18 tumors with a diffuse distribution (p = 0.01). Similarly, 27 of the 33 neuronal-predominant tumors had prominent nodularity versus 12 of the 24 glial-rich tumors (p = 0.01).

Although neuronal-predominant HH lesions were seen at all ages, the prevalence of the neuronal-rich subtype decreased with age at time of surgery. The mean age at surgery was 10.5 years (±1 SD of 7.6 years) for the neuronal-predominant subgroup and 17.7 years (±1 SD of 12.4 years, p = 0.016) for the glial-predominant subgroup. The relationship between the microarchitectural pattern and age at surgery (nodular group mean age, 11.5 years; diffuse group mean age, 18.1 years) approached, but did not reach, statistical significance (p = 0.067).

The cellular predominance of the HH lesions was also associated with lesion volume. Neuronal-rich lesions had a mean volume of 1.88 cm$^3$ (range, 0.08–8.60 cm$^3$ ± 1 SD of 2.15 cm$^3$), and glial-rich lesions had a volume of 4.54 cm$^3$ (range, 0.25–15.70 cm$^3$ ± 1 S.D. of 4.73 cm$^3$; p = 0.027). (There was no correlation between age at time of surgery and HH lesion volume.) In multivariate analysis for the determinants of cellular predominance, the patient’s age at surgery and HH lesion volume correlated significantly with a glial tumor type (p = 0.026 and 0.025, respectively). Point estimates were 1.01 and 1.24 with r$^2$ = 0.212.

HH cellular predominance and microarchitecture showed no significant correlation with other clinical features, including gender, developmental retardation, or a history of central precocious puberty.

Six cases were associated with dysmorphology syndromes (5 with Pallister-Hall syndrome and 1 with Mohr syndrome). No consistent histologic differences were identified in this subset of patients compared with the HH patients as a whole. Interestingly, 2 full siblings with Pallister-Hall syndrome showed different microarchitectural patterns. A 12-year-old girl had a nodular, neuronal-predominant pattern, and a 10-year-old boy had a diffuse, glial-rich pattern.

Similarly, no differences were recognized in the 7 patients who had undergone prior treatment. This group

![FIGURE 6](image_url)

**FIGURE 6.** Section of normal hypothalamus (6-year-old boy) demonstrates typical clusters of large ganglion cells, a feature almost never seen in the hamartomas. Hematoxylin and eosin, original magnification: 100 ×.

![FIGURE 7](image_url)

**FIGURE 7.** (A) Non phosphorylated neurofilament (NF) was present in cell bodies and diffusely in neuronal processes. Original magnification: 200 ×. (B) Phosphorylated NF was seen only in scattered processes. Original magnification: 400 ×. Diaminobenzidine chromogen and hematoxylin counterstain.
included 3 patients who had undergone a previous subtotal resection of their HH, 3 patients treated with Gamma Knife radiotherapy, and 1 patient treated by stereotactic thermablation. The tumors in all 3 patients who underwent Gamma Knife radiotherapy were neuronal predominant. One patient, with a nodular, neuronal-predominant pattern, underwent HH resection at the age of 18.5 years and had undergone Gamma Knife radiotherapy with 17 Gy to the 50% isodose margin 15 months before surgery. The second patient, with a diffuse, neuronal-predominant pattern, underwent HH resection at the age of 27.4 years and had been treated with 12 Gy to the 50% isodose margin 4 years before surgery. The third patient, also with a nodular, neuronal-predominant pattern, had been treated with Gamma Knife radiotherapy twice and received 17 Gy to the 50% isodose margin at each treatment (total 34 Gy), 3.5 and 2 years before surgical resection, respectively (Fig. 12).

Typically, HHs showed little proliferative activity. Rare MIB-1 reactive cells were present in 10 tumors, and no positive cells were seen in 17 cases. The scattered MIB-1–reactive cells tended to have glial morphology, but some appeared to be neuronal. One case had significant proliferative activity with an MIB-1–labeling index of 2.1%. The significance of this observation is uncertain because otherwise this case did not differ from the other hamartomas. Specifically, nothing else suggested a glial neoplastic process.

**DISCUSSION**

Because surgery in this eloquent region has been problematic, histologic descriptions of HHs are based on a small numbers of cases and do not address their varied patterns, noting only disorganized neurons and glia or a resemblance to native hypothalamus (3, 30, 39). This series of 57 cases, by far the largest analysis of these rare and unusual lesions, appears to be representative of HH patients with intractable epilepsy. Patients with precocious puberty alone were excluded. A retrospective review of the published literature on HHs associated with epilepsy identified 277 patients (7). The clinical manifestations of the patients in our series were similar to those summarized in this review. The only notable and unexplained difference is that the male-to-female ratio was 2:1 in our series, whereas no significant gender difference was found in the review. However, another published case series also found a male predominance (5).

Our series included primarily (52 of 57 cases, 91%) intrahypothalamic HH lesions (Delalande types II–IV) and included only 5 parahypothalamic (Delalande type I) HHs. Therefore, it may not represent the full spectrum of histologic patterns of this latter subset of HHs. All of our patients had intractable epilepsy, reinforcing the point that not all parahypothalamic lesions cause central precocious puberty alone. These Delalande type I lesions associated with intractable epilepsy had a broad base of attachment to the inferior aspect of the hypothalamus; they did not have a narrow peduncle, as is often the case with HHs in patients who have precocious puberty alone (4). However, we found no consistent differences in the histopathologic findings between intrahypothalamic (Delalande types II–IV) and parahypothalamic (Delalande type I) lesions. No extrapolation should be made to HH lesions associated with central precocious puberty alone (usually parahypothalamic), which are not represented in this series.

The lack of treatment changes in the 3 patients who underwent prior Gamma Knife radiotherapy must be viewed in the context that in all 3 patients, Gamma Knife treatment failed. Changes in pathology of HHs responding to Gamma Knife treatment are unknown.

HHs are composed of abnormally distributed but cytologically normal cellular elements. Although the neurons and glia of HHs are not cytologically atypical, neither are they typical of normal hypothalamus. The principal glial cells were oblong to spindle-shaped fibrillary astrocytes,
which are relatively inconspicuous in normal hypothalamus. Normal hypothalamus has prominent well-organized tracts of myelinated axons with numerous associated oligodendrocytes. In contrast, the oligodendrocytes of the hamartomas tended to be inconspicuous, and myelinated fibers were sparse and distributed haphazardly.

The small round neurons, which predominate in HH tissue, differ from the large ganglion cells that form major hypothalamic nuclei such as the supraoptic and paraventricular nuclei. These small neurons were present in clusters or nodules but also were scattered diffusely throughout the internodular regions of the hamartoma. Although this description is similar to that of native hypothalamus, the distribution and composition of the nodules were inconsistent and strikingly different from that of normal hypothalamus.

Almost all previous observers described combinations of mature neurons and glia. Neuronal immaturity has been described in HH lesions, but the basis for this assessment appears subjective (25, 49). Most concurred that neurons were the preponderant population. However, HH tissue specimens with few or no neurons have been described (24, 28). Several reports have described the nodular or clustered distribution of smaller neurons (20, 35, 38, 39, 49), while others have noted diffusely distributed cells (22, 23, 28). The latter pattern has sometimes been associated with a relative paucity of neurons (23, 28). The neurons have varied in size and shape. However, large neurons have been reported as being preponderant in only three reports (22, 34, 35).

As part of their original description of the phenotype of Pallister-Hall syndrome, Clarren and colleagues provided a detailed neuropathologic study of three cases (13, 14). These three cases, all newborns, died from multiple congenital anomalies, which included large hypothalamic tumors. These authors suggested that “hypothalamic hamartoblastoma” exists as a separate entity from HH, based on the finding of more primitive or immature neuronal and glial elements that implied a neoplastic character. In our series, including 5 Pallister-Hall syndrome cases (age range, 4.2 to 18.5 years), we saw none of the primitive features described in these prior reports. However, the youngest patient in our series was 8 months old at surgery. Given that the relatively undifferentiated findings of “hamartoblastomas” have only been seen in neonatal cases, it is likely that the immature neuronal elements in these lesions are age-appropriate and reflect only the age of the patients (40, 50–52). Pending further investigation, we discourage the use of the term “hamartoblastoma” for these lesions.

We have observed a previously undescribed histologic heterogeneity among HH cases. Whereas the cellular elements of the tumors were consistent, there were significant differences in the relative numbers and distribution of the neuronal and glial elements among the cases. Despite this variation, several patterns were recognized. In most cases, small neurons predominated. The most common pattern demonstrated nodules of small neurons separated by irregularly distributed astrocytes and individual small neurons. In a few cases, neurons predominated but were more diffusely distributed. In a significant minority of cases, astrocytes were prominent or even preponderant. Not surprisingly, cases with a greater proportion of astrocytes also often had more diffusely distributed neurons. The characterization of nodularity and neuronal/glial ratios was intended to be descriptive and is semiquantitative at best. However, MR spectroscopic analysis of the hamartomas in 14 of our patients showed distinctively different spectral signatures between neuron- and glial-rich tumors (53). This consistent correlation between histology and MR imaging supports the admittedly imprecise histologic observation.

The specific microanatomy of the connection between the HH and the brain is unknown. The nature
of this connection is extremely important as the pathway of ictal spread and secondary generalization in seizure events originating in the HH. Earlier autopsy-based neuropathologic reports of cases with HH and epilepsy had the opportunity to evaluate the relationship of the HH to normal hypothalamus (20–27). Several authors note well-formed fascicles of myelinated axons at the periphery of the lesions, often running parallel to and traversing or merging with the interface with hypothalamus (20, 21, 25, 27). These reports implicated the mammillary bodies as the most obvious point of attachment, but more definitive studies bearing on connectivity were not performed (20, 23, 26).

HH cellularity appears to vary independently with both volume of the lesion and the patient’s age at surgery. Neuronal predominance was more likely to be seen in smaller lesions and in younger patients (size of the HH did not vary with age in our series.) Accordingly, the data suggest that one predictor of neuronal predominance is the size of the lesion at the time of birth. The basic mechanisms determining cellular differentiation and proliferation of HH lesions are unknown.

There also appears to be a second, possibly dynamic, determinant of the neuronal abundance in HH, with an increasing likelihood of glial predominance as age increases. During postnatal development, the size of an HH does not change in proportion to the rest of the brain (54, 55). Thus, their enlargement appears concordant with normal brain growth and not with a progressive mass lesion (54, 55). The increased proportion of astrocytes could reflect slow, ongoing proliferation—a few MIB-1–reactive proliferating cells were seen in most cases. This observation supports the fact that an increase in astrocytes is responsible for the gliarial (usually diffuse) architecture. Alternatively, the increased proportion of astrocytes could reflect neuronal loss, with or without astrocytic proliferation.

FIGURE 12. The findings in this patient who had previous stereotactic radiosurgery (treated twice with a total dose 34 Gy) were well with in the range of findings for untreated HH lesions. This neuronal-predominant case shows a typical nodule of smaller neurons. Hematoxylin and eosin, original magnification: 200×.

The natural history of epilepsy associated with HH is complex and highly variable across patients (8). The gelastic seizures, which are generated intrinsically from HH tissue, are usually the first type of seizure to occur in patients with HHs (9). Particularly when gelastic seizures develop during infancy, additional seizure types, often more disabling, may emerge in later childhood (6). With age, however, the frequency of gelastic seizures often decreases, or they stop as the patient ages, even as other seizure types continue (39). At least for some patients, these later seizures have been shown to arise from neocortical regions without involvement of the HH (11, 41, 56, 57). Could the decrease in gelastic seizures relate to the decreased proportion and possible loss of neurons in the hamartomas?

Tuberous sclerosis and focal cortical dysplasia are other hamartomatous/malformative entities associated with epilepsy. The pathology of these entities differs from that of HH in significant ways. Tuberous sclerosis is characterized by large, often dysplastic neurons with an immature neuronal phenotype (58). In contrast, the characteristic neurons of HH are small with typical cytologic features and a mature neuronal neurofilament expression. Rare cells resembling balloon cells were seen in only in one case, but an immature phenotype was never seen. Because HHs do not involve the cortex, they are difficult to compare architecturally with the subtypes of cortical dysplasias (CDs), all of which are characterized by abnormal organization of one or more cortical lamina (59–62). The absence of dysmorphic neurons and/or balloon cells differentiates HHs from Taylor-type focal cortical dysplasias (FCD) type IIA and IIB (63, 64). The absence of abnormally large and immature (but not otherwise dysmorphic) neurons in HH differs from FCD type IB (63).

Distinction of HH from the less severe forms of CD is more problematic, at least at the microscopic level. These pathologic entities include FCD type IA by the Palmini classification (63) and have been previously grouped under the term “microdysgenesis.” They are characterized by ectopically positioned neurons (most frequently in or adjacent to cortical layer I) and/or cortical dyslamination. As in HH, these neurons are not dysmorphic. An additional microscopic similarity to HH is the frequent presence of microscopic hamartomas (hamartia), consisting of clusters of smaller neurons and associated oligodendrogial-like cells. Whether shared microscopic features indicate a developmental relationship to microdysgenesis is not clear. However, microdysgenesis is essentially a cortical disorganization, with at most microscopic neuronal aggregates. A HH, in contrast, is a true mass lesion. Despite this significant difference, similarity in the origin of HH and CD would not be too surprising. The association of CD with low-grade glioneuronal neoplasms and quasi-neoplastic processes such as gangliogliomas and dys-embryoplastic neuroepithelial tumors is well known.

In common with a limited number of other pathologic lesions such as FCD and neuronal tumors, HH lesions are intrinsically epileptogenic (41–43). Preliminary findings based on microelectrode recordings in acutely dissociated single HH neurons and on HH neurons in slice preparation suggest that small HH neurons have intrinsic pacemaker-like
activity, a phenomenon not observed in other intrinsically epileptogenic tissues (65). A comprehensive model for the basic mechanisms of seizure onset in HH tissue remains to be developed. However, we believe that this model will need to incorporate the finding that small HH neurons reside in discrete clusters in HH tissue and that this microanatomy may act as the “functional unit” for seizure pathogenesis.

Summary/Future Directions

HHs have a unique set of histologic features that differ from those in other developmental causes of epilepsy such as tuberous sclerosis and FCD. The principal cells are small, apparently mature neurons whose size suggests that they may be interneurons. Initial studies of dissociated small HH neurons have demonstrated GAD-67 immunoreactivity, suggesting that these cells utilize γ-aminobutyric acid as a neurotransmitter (65). Further characterization of these neurons should provide insight into the development of seizures in patients with HHs and may ultimately provide a model for the intrinsic epileptogenesis of HH tissue.

Whereas the cells that compose HHs are consistent across tumors, their relative numbers and distribution are not. The likelihood of a neuronal-predominant pattern appears to decrease with age. Interestingly, the seizure pattern also changes with age. The characteristic gelastic seizures become less frequent or disappear altogether in some older patients, whereas the frequency of other seizure types with neocortical origin can increase. Quantitative analysis of the change in neuronal density with age may shed light on this phenomenon.

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