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Hamartomas and epilepsy: clinical and imaging characteristics

B. DIEHL[†], R. PRAYSON[‡], I. NAJM[†] & P. RUGGIERI[§]

Departments of [†]Neurology, [‡]Pathology and [§]Neuroradiology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Correspondence to: Dr Beate Diehl, The Cleveland Clinic Foundation, Department of Neurology, 9500 Euclid Avenue, MB 655, Desk 890, Cleveland, OH 44195, USA. *E-mail*: diehlb@ccf.org

Purpose: Cerebral hamartomas are lesions marked by a disorganized arrangement of mature neural elements and represent a rare cause of medically intractable focal epilepsy. We present the clinical presentation and imaging findings of this rare entity.
Methods: History and neurophysiological studies of 14 patients with pathologically confirmed hamartomas who had surgery for intractable focal epilepsy were reviewed. MRIs were available for review in 10 patients.
Results: The lesions were most commonly located in the temporal and frontal lobes. Seizure semiology was concordant with the anatomic location of the hamartoma in all patients. Nine of the thirteen patients (69%) with the hamartoma confined to one lobe had interictal spikes and sharp waves at the corresponding electrodes. The ictal pattern was confined to the same lobe of the hamartoma in five of nine patients with ictal recordings. Although imaging characteristics were variable, all patients had signal increase on T2-weighted images and 50% of them had mild mass effect. Neocortical involvement was present in the majority of patients (7/10), blurring of the gray/white matter interface was seen in seven patients. Five of those seven patients were found to have associated cortical dysplasia by pathology.
Conclusion: Hamartomas represent a rare entity and may cause devastating epilepsy. Imaging characteristics are difficult to distinguish from those of some other developmental tumors. Hamartomas are frequently associated with microscopic cortical dysplasia (CD), thus underlining their malformative etiology.

Key words: epilepsy; EEG; hamartoma; magnetic resonance imaging; cortical dysplasia.

INTRODUCTION

Cerebral hamartomas are defined as lesions composed of disorganized but mature cells, mostly a combination of neuronal or ganglion cells, glial cells and blood vessels. They represent a rare cause of medically intractable focal epilepsy. In pathological series of patients operated on for epilepsy, between 2.8[1] and 3.2%[2] of all patients had glioneural hamartomas.

The MR-imaging characteristics are not well defined, mostly because hamartomas represent a rare entity. The objective of the study was to better characterize the imaging findings and clinicopathological correlation in patients with chronic epilepsy secondary to pathologically proven hamartomatous lesions.

METHODS

We retrospectively reviewed 14 patients who underwent surgery for epilepsy between 1991 and 1999 with a histological diagnosis of hamartomas. Presurgical assessment of all patients included history, physical examination, neuropsychological testing, prolonged video-EEG telemetry and MR-imaging. The MRI studies were performed on a 1.5T MR (Vision, Siemens, Erlangen, Germany) system using a conventional, circularly polarized head coil. Sagittal T1, coronal conventional spin-echo T2, coronal MPRAGE (magnetization-prepared rapid gradient echo) and axial FLAIR or spin-echo T2 images were obtained. MRI scans were reviewed by two experienced raters (PR and IN). The histological criteria for diagnosis and detailed

Table 1:

Patient #	Location of lesion	Age at onset	Age at surgery	sz semiology	sz frequency	Interictal epileptiform abnormalities	Ictal abnormalities	Surgery	Outcome at time after surgery
1	Left temporal[a]	20	22	Complex partial (automotor) sz-GTS	2–3 per month	Left mesial temporal SW	Left temporal	Left temporal lobectomy	I (1 year)
2	Right frontal[a]	11	33	Abdominal aura-complex partial (bilateral asymmetric tonic) sz	Clusters, 90 per day	Right frontal spikes and SW	Non-localizable	Right frontal lobectomy	I (5 years)
3	Right hemisphere[a]	1	6	Tonic (bilateral asymmetric tonic) sz-complex partial (automotor) sz. Seven years later: psychicaura-tonic (left face tonic) sz	3–4 per day	Surface EEG: no epileptiform abnormalities	Surface EEG: suppression right fronto-parietal region PEG: orbital, anterior and mesial frontal region after surgery: right fronto-temporal	Right frontal lobectomy	IV (8 years) continues sz arising from right frontal region (about 2 per day)
4	Right frontal[a]	2	8	Complex partial (automotor) sz	1 per day	Right > left frontal SW	Lateralized right hemisphere	Right frontal lobectomy	I (6 months)
5	Right frontal[a]	26	32	Simple partial sz with motor symptoms-version (left versive sz)-GTS	1 per month	Right frontal SW	None recorded	Right frontal lobectomy	I (4 years)
6	Left frontal[a]	2	14	Simple partial sz (non-specific aura)-simple partial sz with motor symptoms (bilateral arm tonic-right arm clonic)	6–8 per day	Left frontal > right frontal SW	Left fronto-central	Left frontal lobectomy	I (1 year)
7	Left occipital[a]	13	27	(1) Complex partial (dialeptic) sz; (2) psychic aura-visual aura-complex partial (automotor) sz	1 per day	Left temporal SW	Left parietooccipital Invasive recording: left occipitotemporal	Left occipital lesionectomy	I (1 year)
8	Left temporal[a]	13	17	Abdominal aura-complex partial (automotor) sz	2–3 per week to 3–4 per day	Left temporal SW	Regional left temporal or lateralized left hemisphere	Left temporal lobectomy	IV (died in status 2 years later)
9	Left temporal[a]		38	Aura-complex partial (automotor) sz	2 per week	Left temporal SW	None recorded	Left temporal lobectomy	No follow-up available
10	Right temporal[a]		25	Olfactory aura-complex partial (automotor) sz	3–4 per month	Normal	No recording	Right temporal lobectomy	I (4 years)
11	Right temporal	10	30	Complex partial (automotor) sz	2–3 per day	Right temporal SW	Obscured	Right temporal lobectomy	I (9 years)
12	Right temporal	22	29	Auditory aura-complex partial (automotor) sz-GTS	2 per week	Bitemporal SW, right > left	None recorded	Right temporal lobectomy	I (1 year)
13	Left frontal	2	15	(1) Simple partial sz with motor symptoms (bilateral arm tonic-right face clonic sz); (2) complex partial (automotor) sz-GTS	5–7 per week	Left frontal spikes	Lateralized left hemisphere	Left frontal lobectomy	IV (died in status 2 years after surgery)
14	Left temporal	16	31	Complex partial (automotor) sz	2–3 per month	None	None recorded	Left temporal lobectomy	I (2 years)

[a] Imaging reviewed, see Table 2. SW: sharp wave; GTS: generalized tonic-clonic seizure; sz: seizure. In parenthesis: semiological seizure classification if different from International classification.

pathology of some of the patients was described previously[3].

RESULTS

Clinical and neurophysiological data

The hamartomas were localized in one lobe in 13 of the 14 patients, 7 were in the temporal, 5 in the frontal lobe and 1 in the occipital lobe. Please see Table 1 for detailed clinical data. None of the patients had the clinical features of tuberous sclerosis and none had multiple brain lesions identified on MRI.

Mean age of seizure onset was 11.1 ± 7.9 years, mean age at surgery was 23.4±10 years. Seizure semiology was concordant with the anatomic location of the hamartoma in all patients. Seizure frequency was variable (one to five seizures per day in seven patients, two to four per week in three patients, one to four per month in four patients). Interictal EEGs revealed epileptiform activity in all but three patients. Nine of the thirteen patients (69%) with the hamartoma confined to one lobe had interictal spikes and sharp waves at the corresponding electrodes. Two of those thirteen patients had no interictal epileptiform activity, one patient with temporal lobe epilepsy had bitemporal spikes, one patient with frontal lobe epilepsy had bifrontal spikes. Ictal recordings were obtained in nine patients. The ictal pattern was confined to the same lobe of the hamartoma in five patients, lateralized to the ipsilateral hemisphere in two patients, non-localizable in one patient, or obscured by artifact in one patient.

Neuropsychological testing revealed comprehensive IQs from 76 to 113 (median 93). Two patients were described as mentally retarded without detailed neuropsychological testing. Neurological examination was abnormal in two patients concordant with the lesion.

Postoperative seizure outcome was good in 10 patients (seizure free at 6 months to 9 years after surgery). One patient was lost in follow-up, three had recurrent seizures despite gross removal of the hamartoma as evidenced by postoperative MRI. Two patients died in status epilepticus several years after their surgery at ages 17 and 19 years, respectively.

MR imaging characteristics

MRI scans of 10/14 patients were available for review, findings are displayed in Table 2. The lesions were located in the mesial temporal lobe in four patients (see Fig. 1), and in the frontal lobe in four patients (see Fig. 2). One patient had an occipital hamartoma and another one had more widespread right hemispheric involvement.

On T1-weighted images, the lesion was isointense to gray matter in six patients, hyperintense in two and hypointense in two. On T2-weighted images, all patients had signal increase (non-homogeneously in five). Of the nine patients who received gadolinium, two patients showed mild enhancement. Cysts were present in two patients. Mild mass effect was seen in five patients. Neocortical involvement was present in the majority of patients (7/10), blurring of the gray/white matter interface was seen in seven patients. Five of those seven patients were found to have associated cortical dysplasia by pathology.

Reports of the MRIs of the remaining four patients were reviewed, three had temporal masses, one frontal. All had increased signal in T2-weighted images. Enhancement was present in one of two patients who had gadolinium administered.

Table 2:

Patient #	Location	T1	T2	Enhancement	Cysts	Mass effect	Neocortical involvement	Gray/white blurring
1	Left amygdala, extending into hippocampal body	Isointense	⇧	Yes	No	Yes	Yes	Yes
2	Right mesial frontal	⇧	⇧	No	No	No	Yes (dysmorphic gyri)	Yes
3	Right hemisphere	Isointense	⇧ (NH)	Not given	Yes	No	Yes (variable gray matter thickness)	Yes
4	Right frontal pole	Isointense	⇧	No	No	No	Yes	Yes
5	Right anterior frontal	⇩	⇧ (NH)	No	No	No	Yes (dysmorphic gyri)	Yes
6	Left inferior frontal sulcus	Isointense	⇧	No	No	No	Yes (dysmorphic gyri)	Yes
7	Left occipital	Isointense	⇧ (NH)	No	No	Yes	Yes	Yes
8	Left hippocampus	Isointense	⇧ (NH)	No	Yes	Yes	No	No
9	Left amygdala	⇧	⇧	No	No	Yes	No	No
10	Right anterior and mesial temporal	⇩	⇧ (NH)	Yes	No	Yes	No	No

NH: non-homogeneous.

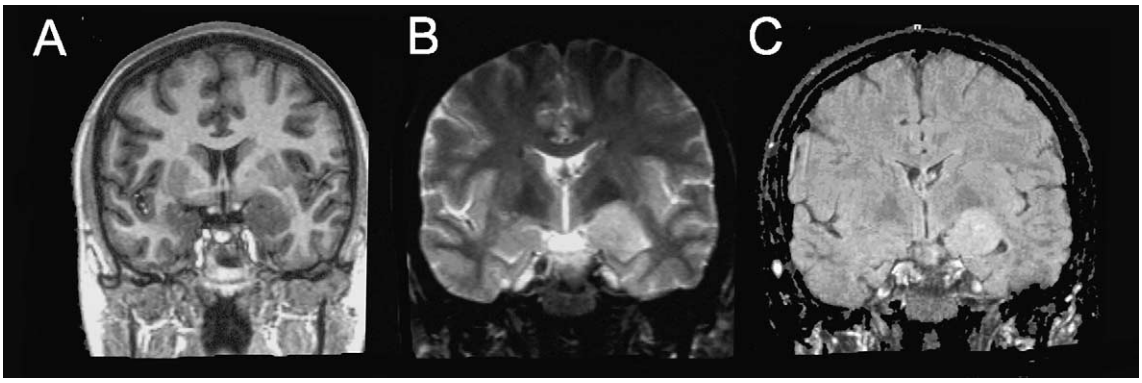

Fig. 1: MRI of a 22 years woman with intractable temporal lobe epilepsy secondary to a hamartoma. The patient had two to three complex partial seizures per month with rare secondary generalization since the age of 19 years. The MRI shows a mass in the left amygdala and hippocampal body. Signal characteristics are: isointense on T1 (*A*), hyperintense on T2 and FLAIR (*B* and *C*).

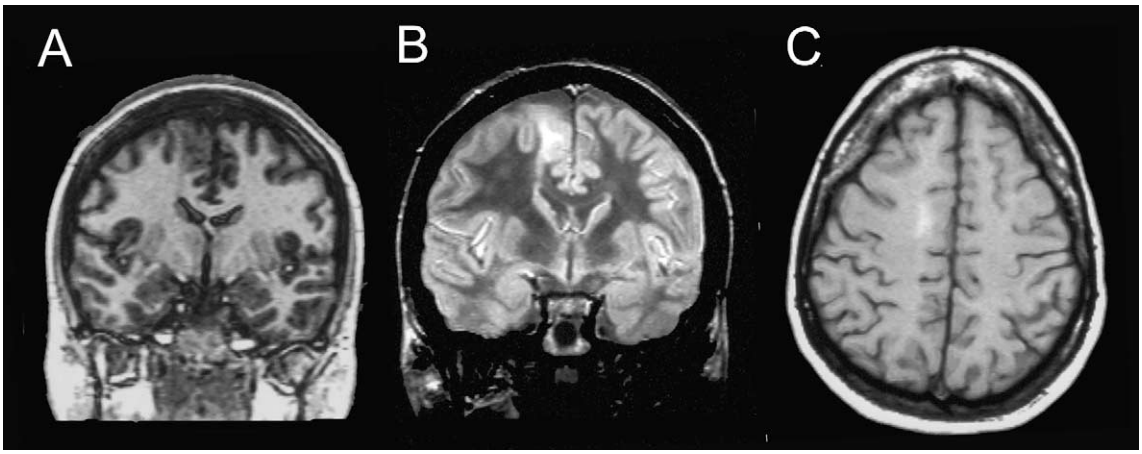

Fig. 2: MRI of a 33-year-old woman with bilateral asymmetric tonic seizures since the age of 11 years. The MRI shows a mass in the right superior frontal gyrus. Signal characteristics are: mildly hyperintense on T1 (*A* and *C*), hyperintense on spin-density (*B*).

Pathology results

As previously described, the pathological features included a circumscribed, disorganized collection of glial cells, primarily astrocytes[3]. Associated microscopic cortical dysplasia was found in seven patients.

Two patients died in status epilepticus: one patient died 3 years after left frontal lobe resection; pathology showed dysplasia of the remaining left frontal lobe. The contralateral frontal lobe, right parietal and left occipital lobes were normal. The second patient had a history of generalized status epilepticus prior to surgery. The pathological examination of frontal, temporal and parietal lobes revealed global ischemic changes and acute infarcts.

DISCUSSION

The nomenclature of malformative brain lesions has remained variable and the distinction between forms of glioneuronal malformations such as hamartomas, DNETs and gangliogliomas is not always clear[4–6]. Those lesions share the fact that they represent a tumor-like, not primarily neoplastic malformation. They are frequently associated with microscopic cortical dysplasia, thus underlining the malformative etiology[7].

Gangliogliomas and hamartomas both have mixed glial and neuronal cell elements and may have eosinophilic granular bodies, but the degree of cytological atypia is different. DNETs have a multinodular configuration, mostly consisting of oligodendroglial-like cells, whereas the hamartomas in this series consist of astrocytic cells. Given the similarities between those three lesions, it can be argued that they represent a spectrum and sometimes may be difficult to distinguish from one another.

Gomez-Anson *et al.*[8] described the imaging characteristics of two patients with temporal lobe hamartomas. One patient had a center of low T1 and T2 signal in the core of the lesion, and surrounding high

signal intensity. The second patient had an irregularly calcified, non-enhancing mass on CT, no MRI was done.

Most of our patients showed high signal on T2-weighted imaging with mild mass effect in 50% of cases. Gadolinium enhancement was rare. Signal characteristics on T1 were less homogeneous, however the majority of patients appeared isointense on T1. Gray white matter blurring was relatively frequent (70% of our patients). Seventy-one percent of those patients had associated cortical dysplasia, a known reason for loss of gray white matter differentiation on MRI[8, 9].

Nearly all of those lesions had the appearance of well-defined masses on MRI. Typical locations were the mesial temporal and frontal lobes. Cysts were seen, but less frequently than in other developmental tumors such as gangliogliomas. Since we did not review CT scans, we are not able to comment on the frequency of calcifications.

Raymond *et al.*[10] described imaging characteristics of fourteen patients with histologically proven DNETs. The lesions were located in the temporal lobe in 13 patients and in the cingulum in 1. Signal characteristics were hypointense on T1-weighted images in all but two patients, and hyperintense on T2-weighted images in all patients. Six of eight patients who received gadolinium had some enhancement, 5 of 14 had cystic component, and 6 had gray white blurring. These results are almost identical to the imaging characteristics of our patients with hamartomas. This may reflect the fact that DNET and hamartomas have many histological similarities.

The clinical spectrum included a wide range from clinically and developmentally normal individuals to mentally retarded patients. The epilepsy also ranged from rather infrequent seizures to devastating epilepsy with multiple daily seizures. Interictal and ictal activity was concordant with the tumor in the majority of cases. Outcome data in this study with 71% seizure freedom were comparable with other series[9]. The fact that two young patients died in status epilepticus years after surgery shows however the potential seriousness of the hamartoma-induced epileptogenicity and suggests an aggressive approach towards the treatment of these lesions. Further studies are needed to elucidate the cellular characteristics of these lesions and the mechanisms of hamartoma-induced epileptogenicity.

CONCLUSION

Hamartomas represent a rare entity and may cause devastating epilepsy. Imaging characteristics are difficult to distinguish from those of some other developmental tumors. Hamartomas are frequently associated with microscopic cortical dysplasia (CD), thus underlining their malformative etiology. Surgical resection will result in seizure freedom in the majority of cases (70%), however some patients may have recurrent seizures.

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