Introduction

Hypothalamic hamartoma (HH) is not an everyday diagnosis for child neurologists or even for those specializing in pediatric epilepsy. However, as I hope the following pages will attest, it is a subject worthy of the reader’s time and consideration. HH is certainly a catastrophic disorder for many of those born with one. The last 10 years have shown a new way forward for the treatment of these lesions, which has made working with these children and their families a particularly gratifying experience. Previously (and sometimes even today), families were told that this is an untreatable disease and that nothing could be done. These new developments in HH treatment are the primary focus of this issue.

HH is also a critically important human model for some of the key issues, questions, and controversies in epileptology, particularly as they relate to catastrophic epilepsy of childhood, an umbrella term that includes much more common entities such as infantile spasms and the Lennox-Gastaut syndrome. HH is the premier human model for subcortical epilepsy. It is also an excellent model for studying poorly understood and even somewhat controversial phenomenon such as secondary epileptogenesis (the process by which seizures begin to arise independently from brain regions not involved in the original pathological process) and epileptic encephalopathy (the multifactorial process in which children with epilepsy suffer cognitive and behavioral deterioration, in part due to seizure activity). Although the natural history for HH is extraordinarily variable from patient to patient, it offers the opportunity to observe secondary epileptogenesis and epileptic encephalopathy in children with a single causative lesion, where the rest of the brain (including cerebral cortex) is most likely normal at birth.

Lastly, tissue that is surgically resected from HH patients with epilepsy offers the opportunity to study intrinsically epileptogenic human tissue. Presumably, the cellular and molecular mechanisms responsible for seizures are unique to each pathology. However, observations in one disease may offer insights that help to explain other, more common conditions. As with all research with human epileptic tissue, the lack of true controls is a challenge. However, investigation of secondary epileptogenesis, where the rest of the brain (including cerebral cortex) is most likely normal at birth.

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Lastly, tissue that is surgically resected from HH patients with epilepsy offers the opportunity to study intrinsically epileptogenic human tissue. Presumably, the cellular and molecular mechanisms responsible for seizures are unique to each pathology. However, observations in one disease may offer insights that help to explain other, more common conditions. As with all research with human epileptic tissue, the lack of true controls is a challenge. However, investigation of surgically resected human tissue, coupled with the more rigorous experimental approach that is possible with animal models, is necessary to understand the basic mechanisms of why seizures occur. In this issue, Kristina Fenoglio and her coworkers at the Barrow Neurological Institute in Phoenix review their laboratory findings to date.

HH occurs in two distinct flavors. The first, consisting of HH lesions that are pedunculated (parahypothalamic), are attached to the inferior surface of the hypothalamus or tuber cinereum (often with a narrow stalk or base of attachment). These HH lesions usually present with central precocious puberty only and infrequently have epilepsy, cognitive impairment, or behavioral problems. These patients are treated medically with gonadotropin-releasing hormone agonists, do not require surgery, and are not further discussed in this issue.

The second type is the realm of the pediatric neurologist, neurosurgeon, neuropsychologist, and child psychiatrist. These patients have the so-called sessile type of HH (intrahypothalamic), usually with a broad base of attachment and usually (but not always) with some portion of that base of attachment to the walls of the third ventricle above the normal position of the floor of the third ventricle. These lesions are usually associated with epilepsy, which proves itself to be refractory to medication management, and are likewise associated with cognitive impairment and organic behavioral disturbance. Unfortunately, for a significant subset of patients, perhaps 50%, these are clearly progressive clinical features, with worsening of the seizure disorder and, coincident with this, cognitive decline and deterioration in behavior. Psychiatric problems can ultimately be the single most disabling aspect of this disease for the patient and family and are typically characterized by mood disturbance and rage behaviors.

Recently, we have a better handle on exactly how often these problems occur. Brandberg and colleagues in Sweden have been able to define the prevalence of HH associated with epilepsy in children and adolescents within their study population as 1 in 200,000.

The single most important teaching point about HH is the extreme variability of the syndrome. The HH lesions themselves commonly range in size from that of a pea to that of a plum. The vast majority of HH patients have no other cerebral pathology as seen by high-resolution magnetic resonance imaging, but 2 to 4% do. Gelastic seizures commonly may begin in the first month of life, whereas an occasional HH patient may first begin to have gelastic seizures during early adulthood. Later seizure types are variable, including
partial seizures that are phenotypically consistent with either
temporal or frontal lobe origin or seizure types that pheno-
typically suggest generalized events, including drop attacks,
tonic seizures, and infantile spasms. Cognitive testing in-
cludes HH patients within the broad range of normal (but
usually with at least some deficits in specific domains such as
attention and episodic memory) to those who are too im-
paired to be tested with the commonly used scales. Half of the
HH patients will experience some cognitive deterioration
(early onset of seizures is a major risk factor), but the other
half will have a stable developmental profile. Although com-
mon threads quickly emerge, each of these patients has a
unique story. In this issue, Harvey and Freeman from the
Royal Children’s Hospital in Melbourne review the clinical
and electroencephalographic features of seizure activity in
HH patients, whereas Prigatano of Barrow discusses recent
findings on the neuropsychological profile of patients with
refractory epilepsy.

The remainder of this issue is devoted to the new develop-
ments in treating HH (which, unfortunately, do not yet in-
clude antiepilepsy drugs). Each of the authors is an expert in
the treatment of HH and refractory epilepsy with their chosen
modality, and it is only natural that each author will be an
advocate for their individual approach. Prospective, random-
ized trials of similar patients would, of course, be required to
completely resolve the issues with respect to superiority in
efficacy and in the adverse event profile. However, such stud-
ies are not likely to be performed in the foreseeable future
because of the relative rarity of the disease and the expense of
such a trial. On the other hand, it is increasingly clear that the
treatment of HH associated with refractory epilepsy is not a
“one-size-fits-all” scenario. The question needs to be re-
framed as to which modality is superior for what patient,
considering the anatomic features of the HH lesion and the
severity and pace of deterioration, of the patient’s seizures,
and comorbid cognitive and behavioral problems.

Regis and colleagues from Timone Hospital in Marseilles
present the experience of their group with gamma knife ra-
diosurgery. Schulze-Bonhage and Ostertag of University
Hospital Freiberg discuss the therapeutic option of interstitial
radiosurgery for HH. The experience with surgical resection
of HH is then presented for two different operative ap-
proaches. Rosenfeld, now at The Alfred Hospital of Monash
University in Melbourne, discusses the experience of his
group with transcallosal, interforniceal resection. Finally, Ng
and Rekate present the Barrow experience with transven-
tricular endoscopic resection.

I wish to thank each of the authors for their contribution to
this issue of Seminars in Pediatric Neurology. Individually,
and collectively, they are a scholarly (and surprisingly punc-
tual) group.

John F. Kerrigan, MD
Guest Editor

References
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