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Critical Review

Hypothalamic Hamartoma and Seizures: A Treatable Epileptic Encephalopathy

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Summary: Hypothalamic hamartomas may be associated with gelastic seizures, focal seizures, and a generalized epileptic encephalopathy, with severe seizures and cognitive and behavior decline. Despite earlier views to the contrary, good evidence now exists that all these clinical features are caused, directly or indirectly, by the hamartoma. Resection of these lesions was long regarded as too hazardous and unlikely to benefit seizure control. It is now clear that hypothalamic hamartomas can be effectively treated with a variety of surgical approaches with sustained seizure control and often seizure freedom. Qualitative observations suggest that behavior and cognition also improve with treatment, but quantitative validation is required. The specific approach should be tailored according to the surgical anatomy of the lesion and the experience of the surgeon. Choices include a transcallosal approach (good for intraventricular lesions), a pterional approach (useful for interpeduncular lesions), a transventricular endoscopic approach, or destruction of the lesion with radiofrequency probes or gamma knife radiosurgery. The previously dismal outlook for children with severe seizures associated with this lesion has now dramatically changed. These insights may have implications for other epileptic encephalopathies of childhood.

The generalized epileptic encephalopathies of childhood, typified by the Lennox–Gastaut syndrome, are important and distressing disorders to treat. The association of damaging tonic and atonic seizures ("crash helmet epilepsy"), with frequent cognitive decline and behavioral abnormalities, is an all too familiar scenario for treating physicians. Complete, or even adequate, control of seizures is rarely achieved. The outcome in adult life is generally that of continuing seizures associated with intellectual and social disability. Such epileptic encephalopathies have a wide variety of causes including developmental abnormalities and perinatal and early childhood insults (1). Hypothalamic hamartoma is a rare cause (2), but provides singular insights into the pathophysiology of such epileptic encephalopathies (3).

In the last few years, a paradigm shift has occurred in the understanding of the pathophysiology and management of epilepsy associated with these lesions. It is now clear that it is a treatable epileptic encephalopathy. Collation of clinical research results from centers around the world investigating this rare disorder at a recent meeting in Montreal suggested that the lessons learned from studying this remarkable epilepsy syndrome will lead to significant improvement in management. This has major implications for the relatively small numbers of children with this condition, but it also has wider implications for understanding the generalized epileptic encephalopathies. Strong evidence now exists that removal, destruction, or disconnection of the hamartoma leads to remarkable control of the seizures, as well as to improvement in behavior and probable cessation of cognitive decline.

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CLINICAL SPECTRUM OF THE SYNDROME

The classic presentation of this disorder is well known: gelastic seizures begin in infancy, often in the neonatal period, and are followed some years later with the development of seizures with focal motor features and autonomic manifestations such as flushing and cardiorespiratory changes. Partial seizures, suggestive of temporal or frontal lobe origin, also may occur. In many children, a generalized epileptic encephalopathy develops, with tonic and atonic seizures, slow spike-and-wave discharges on interictal EEG, intellectual deterioration, and sometimes with marked behavioral disturbances including rage attacks. In a proportion of children, precocious puberty also develops, but this feature is independent of the epilepsy (2,5).

With increased awareness of this syndrome, and improvements in magnetic resonance imaging (MRI), a milder spectrum of disorders has been recognized, sometimes with apparent onset later in childhood or in adolescence. Laughing seizures can be subtle and at times may manifest with peculiar symptoms such as a "pressure to laugh." The lack of interictal EEG abnormalities, or even changes during ictal EEG, can lead to misdiagnosis of such cases (6). The lesions vary in size, and small lesions can be easily missed on MRI unless the hypothalamic region is specifically scrutinized (Fig. 1).

Pathology and etiology

High-resolution MRI scans show no other abnormalities in nearly all cases. Because the symptomatic generalized epilepsies had been conceptualized as resulting from diffuse grey matter dysfunction, previously it was thought that diffuse macroscopic or microscopic dysgenetic changes must accompany these hamartomas to account for the generalized epileptic encephalopathy (3). This view now appears to be incorrect and, in the majority of cases, the hypothalamic lesion is the sole lesion. Although rare cases are found in which other cortical abnormalities are present, these are not epileptogenic, underscoring the significance of the hypothalamic hamartoma in the generation of seizures.

These lesions are usually sporadic and have no known etiology. However, hypothalamic hamartomas also are part of the Pallister–Hall syndrome, in which associated polydactyly and a bifid epiglottis are seen in about half the cases. Inheritance is autosomal dominant, with essentially complete penetrance. Mutations in the *Gli3* gene have been found in the majority of families (7,8). The *Gli3* gene encodes a transcription factor in the sonic–hedgehog pathway that has an essential role in embryogenesis (9). In the initial description of Pallister–Hall syndrome, the cases were quite severe and usually lethal. It is now recognized that a wide clinical spectrum exists, with most cases being relatively mild, and some showing just polydactyly. Indeed, seizures are reported in only ~15% and are generally regarded as mild. Although the pathology in Pallister–Hall syndrome was initially described as a "hamartoblastoma," it appears that the lesion is similar if not identical to that seen in sporadic hypothalamic hamartoma cases. Why the epilepsy syndrome seems to be milder in Pallister–Hall syndrome and whether the usual sporadic cases result from somatic mutations in *Gli3* remains to be determined.

Neurophysiology

In the typical severe cases of hypothalamic hamartoma, an association is seen with slow spike–wave with or without multifocal (typically frontal or temporal) epileptiform abnormalities (3–5). Additionally, some seizures can closely resemble complex partial seizures of temporal or frontal origin on clinical and ictal EEG criteria. Even on

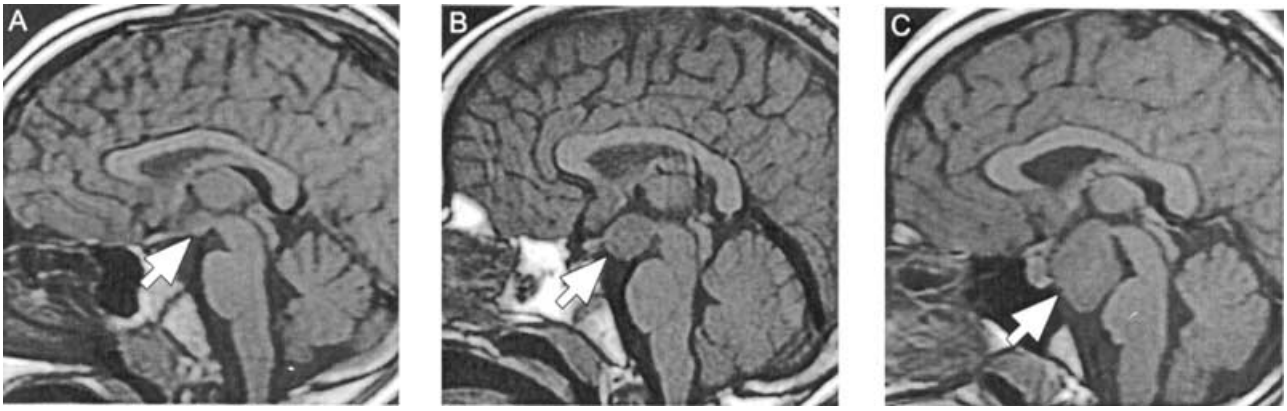

FIG. 1. Sagittal magnetic resonance imaging (MRI) scans showing hypothalamic hamartomas of different sizes. **A:** A small lesion in the third ventricle (8 mm diameter) in a 10-year-old girl seen with gelastic seizures at age 2 years. Such lesions can be easily missed on a cursory examination of MRIs. **B:** An intermediate lesion (17 mm diameter) in a 5-year-old boy seen with neonatal-onset gelastic seizures, followed by complex partial and tonic–clonic seizures and associated with developmental delay and aggressive and autistic behavior. **C:** A large lesion protruding well down into the interpeduncular and prepontine cisterns (34 mm maximum diameter) in a 14-year-old girl seen with gelastic and complex partial seizures associated with mild intellectual and memory impairment, but no behavioral disturbance.

ictal recordings with depth electrodes, the cortex can appear to be site of origin of seizures, but cortical resection is uniformly ineffective in treating the seizures (10).

Now overwhelming evidence exists that the hamartoma itself is the source of the gelastic or dacrystic seizures, as well as the site of origin of the focal seizures with secondary spread to frontal and temporal cortex. This evidence includes direct invasive EEG recordings and stimulation of the hamartoma (11–14), ictal single-photon emission computed tomography (SPECT) studies (14,15), and the successful treatment of these seizures by removal, destruction, or disconnection of the hamartoma (see later). This conclusion may now seem obvious, but a strong historical bias was seen against this view. Deep midline structures were not thought to be important in the genesis of either focal or generalized seizures after the rejection of the classic "centrencephalic" hypothesis of generalized epilepsy that was proposed in the 1950s (16–19).

The genesis of slow spike-and-wave discharges and the associated tonic and atonic seizures in these patients also has been a mystery. Recent evidence shows that, unlike the laughing seizures and focal seizures, they do not arise directly from the hamartoma. Direct simultaneous recordings from the hamartoma and frontal cortex during surgery suggest that the slow spike–wave cortical discharges do not originate in the hamartoma (20). Moreover, postoperatively, tonic and atonic seizures may "run down" progressively after removal of the hamartoma, suggesting that they are the result of secondary epileptogenesis, rather than the hamartoma being the direct source of the discharges and associated seizures (20). The interpretation of secondary epileptogeneis is in keeping with the natural history of the slow spike-and-wave discharges and associated seizures; they are not present at the clinical onset of the epileptic syndrome but develop years after, in some but not all cases (3,5).

Treatment

Treatment of the focal seizures and of tonic and atonic attacks is at best moderately successful with conventional antiepileptic drugs (AEDs); gelastic seizures are resistant to all currently available medications. Some patients on very mild end of the spectrum of this disorder may tolerate the gelastic seizures, achieve acceptable control of focal seizures with AEDs, and lead productive lives (6), but the impact of medical treatment on the more severe cases is disappointing.

A few case reports or small case series of improvements in seizures with surgical treatment (21–23) were reported. Because of the technical difficulties in surgery, removals were often incomplete. Some of the earlier reported "successful" cases had very short follow-up with unpublished later relapse. Now sufficient experience from around the world suggests that long-lasting control of seizures can be effected by complete removal, destruction, or disconnection of the hamartoma. This has become possible because of improvements in imaging and in technical aspects of the surgery. The debate has now shifted to the best means of treatment with a variety of surgical approaches and the possibility of destruction of the lesion with radiofrequency probes or gamma knife surgery.

The traditional approach to these lesions has been pterional; this lateral approach may be suitable for lesions protruding into the interpeduncular cistern. Lesions associated with the epileptic encephalopathy usually extend up into the third ventricle and are difficult to excise completely with safety by the pterional approach because of the proximity of the circle of Willis, third nerve, and brainstem. A recent series reported a >90% reduction in major seizures and drop attacks in 11 of 13 cases, but minor attacks persisted in all but two. Four small strokes occurred, all with good recovery, and four third-nerve palsies, with full recovery in three (24).

A transcallosal approach reaching the lesion from above through the third ventricle has now been performed with low morbidity in >20 cases, and the long-term results from this procedure appear to be excellent (20,25,26). Dissection of the hamartoma from the wall of the third ventricle and infundibulum or mammillary bodies may be achieved in selected patients under direct vision without causing significant hypothalamic symptoms of disturbed thirst, appetite, temperature regulation, sleep, or behavior. The major concern with this approach is that it may damage the fornices, leading to memory impairment. Alternative ablative surgical approaches include a more anterior approach through the lamina terminalis or radiofrequency destruction of the lesion by using a transventricular endoscopic probe (27–29). At present the experience and results of these approaches are not so favorable as those of the transcallosal approach, but morbidity is low. Alternatively, the lesion can be disconnected, with or without partial removal (30). The exact surgical anatomy of each case would determine the safest and best approach. All forms of surgery can be associated with transient diabetes insipidus, but no other major endocrinologic or hypothalamic complications have emerged as hazards of these procedures.

Destruction of the lesion by focused ionizing radiation (gamma knife) is an attractive approach that does not require conventional surgery, and a large series is accumulating from the center in Marseilles (31–33). Although a delayed response to gamma knife treatment (4–6 months) is expected, early results suggest an excellent seizure response. However, results in terms of long-term seizure freedom are not clear. Some have concerns about the long-term effects of radiation in the hypothalamic region, but, so far, no adverse consequences have emerged.

Overall the consensus of the meeting was that the surgical approach must be tailored to the specific surgical anatomy of the hamartoma. The size and precise location

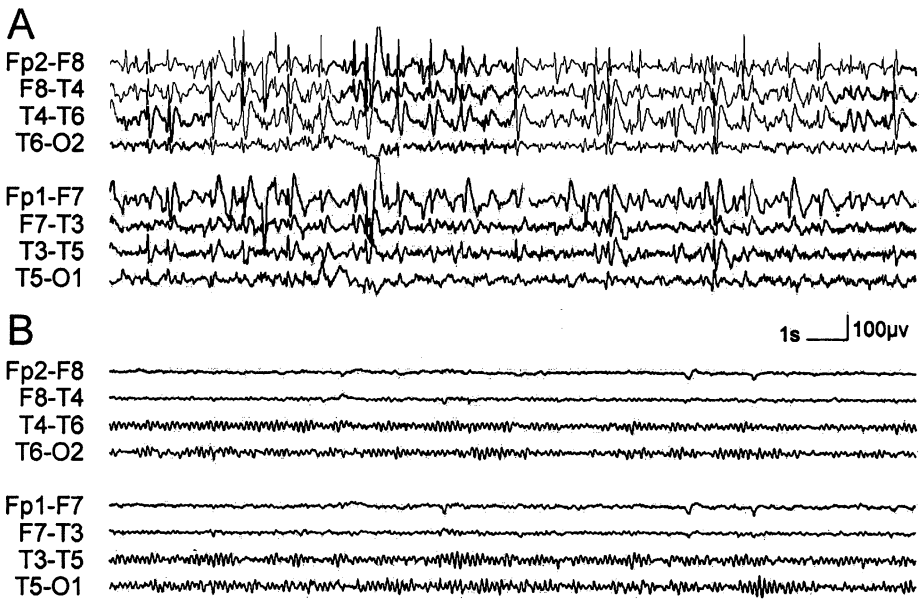

FIG. 2. EEGs in a 14-year-old girl who underwent transcallosal resection of a 20-mm diameter hypothalamic hamartoma associated with gelastic, complex partial, and tonic seizures, plus mild to moderate intellectual impairment. The preoperative record **(A)** shows frequent bilateral spike–wave and polyspike–wave discharges with no normal background activity. Three weeks after surgery, the record **(B)** shows normal background and no epileptiform discharges. The patient remains seizure free 11 months later.

of the lesions vary, and best results are obtained by surgeons with experience of these lesions and their complex surgical anatomy. The transcallosal removal and disconnection approaches now appear to be the techniques with the higher rates of success. At 1 year, ~90% of cases are free or essentially free of all seizures. Laughing seizures and focal attacks tend to cease in the immediate or early postoperative period, with tonic and atonic attacks sometimes persisting for a few weeks or months before "running down" (20,25,26). Marked behavioral improvement has been reported by many parents, but has yet to be objectively studied. Similarly, cognitive decline appears to stop, and freedom from seizures, with less medication, is associated with anecdotally reported improved school performance. The transventricular endoscopic approach combining disconnection, partial resection, or direct radiofrequency lesioning has, as would be expected, a low morbidity rate. At 1 year, ~70% of patients are seizure free or significantly better, with improvements in behavior and cognition. Finally, gamma knife has the lowest morbidity rate of all treatments with comparable seizure-free rates, but long-term safety data are lacking.

Implications for other epileptic encephalopathies

The effective treatment of the generalized seizures and generalized spike-and-wave discharges after removal of hypothalamic hamartomas (Fig. 2) raises the hope that these observations may have broader consequences for the understanding and treatment of commoner generalized epileptic encephalopathies. The lessons learned from this lesion are perhaps similar to the previous discoveries on the treatment of epileptic spasms. Infantile spasms were previously thought not to be surgically treatable, but a small percentage of such case have dysplastic lesions, particularly in the posterior cortex, that may be successfully treated by surgery with cessation of seizures and arrest of cognitive and behavioral decline (34). The story now seems to be similar for hypothalamic hamartomas—a focal lesion can cause generalized seizures and generalized EEG abnormalities. Whether imaginative approaches based on this insight can be applied to other epileptic encephalopathies is an area for future research. It would be hard to imagine a more important advance in epileptology than complete control of all "crash helmet" epilepsies.

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