The treatment of patients with hypothalamic hamartomas, epilepsy and behavioural abnormalities: facts and hypotheses

André Palmini, Eliseu Paglioli-Neto, Jose Montes*, Jean-Paul Farmer*

From the Porto Alegre Epilepsy Surgery Program, Hospital São Lucas da PUCRS, Porto Alegre, Brazil; *Department of Neurology and Neurosurgery, Montreal Children's Hospital, McGill University, Montreal, Canada

ABSTRACT – The growing interest in the association between hypothalamic hamartomas (HH), epilepsy and behavioural abnormalities witnessed in recent years, has led to significant progress regarding the clinical presentations, pathophysiology and management of this entity. Patients with these lesions may occupy different points within a spectrum of severity of the epileptic and behavioural disorder, and may dynamically progress toward more malignant epilepsies with time. The role of the subcortical lesion in the generation of the gelastic seizures has been established, and encouraging results have been obtained with surgical resection, destruction or disconnection of the hamartoma. The present work highlights several aspects that should be taken into account for the selection of medical and surgical treatment for individual patients. We conclude with a reflection on what we still do not understand as regards in the genesis and surgical management of the neuropsychiatric disabilities related to this disorder.

KEY WORDS: hypothalamic hamartoma, epilepsy, gelastic seizures, surgical treatment, surgical strategies, behavioural abnormalities

Correspondence:
André Palmini,
Serviço de Neurologia,
Hospital São Lucas da PUCRS,
Avenida Ipiranga 6690, 90610-000,
Porto Alegre, RS, Brazil.
Phone/Fax: + 55 51 3339 49 36;
E-mail: apalmini@uol.com.br

Patients with HH have been recognized for a long time, and are now identified by magnetic resonance imaging (MRI) [1-3]. The most common scenario is that of a child or adolescent with gelastic and other types of partial and generalized seizures and variable degrees of cognitive and behaviour abnormalities, whose evaluation shows the characteristic diencephalic lesion. Gelastic attacks are not specific to patients with HH, and can also occur in partial epilepsies originating from temporal or frontal lobe regions [4, 5]. However, sudden attacks of 'mechanical laughter' in children or adolescents with cognitive and behavioural impairment should prompt a search for a HH [2, 3, 5-8].

The clinical spectrum of manifestations associated with HH has been enlarged considerably since the initial reports on the syndrome [3]. A group of patients with HH and precocious

puberty but who do not have epilepsy, or who have only rare seizures [9-11] has been recognized. Recent reports also describe patients with mild epilepsy characterized by a 'pressure to laugh' and other partial seizures, easily controlled by antiepileptic drugs (AEDs) [12]. Another category includes patients with a somewhat more severe epileptic disorder characterized by gelastic, partial and generalized seizures, who do not have a catastrophic course and whose seizures may be, at least partially, responsive to AEDs [13-15]. The need to devise therapeutic options for children and adolescents who have gelastic and other, much more malignant partial and generalized seizure types, and in addition present with progressive cognitive and behavioural abnormalities [16-18] remains essential. We have recently suggested that the high seizure frequency and the severity of the associated behavioural and cognitive decline should prompt the inclusion of this form of presentation of the HH syndrome in the group of the surgically remediable, catastrophic epilepsies of childhood [16], in which extremely frequent seizures, related to destructive, malformative or inflammatory disorders, are responsible for a progressive encephalopathy with delays or arrests of development, cognition, motor function and behaviour [17-19]. Mechanisms of plasticity cannot drive functional compensation unless the lesion is resected. Such catastrophic syndromes are now regarded as surgically remediable [20], and several lines of evidence suggest that the earlier the surgical intervention to control the seizures and to remove the continuous epileptic activity, the better the final developmental outcome [21]. We believe that the most severe forms of the syndrome of HH and refractory seizures should be regarded as a form of 'non-hemispheric', surgically remediable, catastrophic epilepsy [16]. Since recognition of a catastrophic epilepsy of childhood is a call to neurological and neurosurgical action, patients with HH and intractable seizures should be managed without undue delay, by specialized epilepsy care units.

We will further discuss the medical and surgical management of patients with HH and epilepsy, emphasising the rationale for selection of specific surgical strategies to remove the lesion in patients with catastrophic epilepsy. The discussion will evolve from the milder to the more severe forms, addressing AEDs and psychopharmacological management, yet concentrating upon surgical strategies.

Hypothalamic hamartoma, epilepsy, and behavioural abnormalities: medical management

Patients with HH and epilepsy whose seizures are reasonably well controlled with AEDs or that do not have a catastrophic evolution have been reported [12-15, 22]. These are usually adult patients with gelastic and complex partial seizures beginning in childhood, without progression to symptomatic generalized epilepsy. Sturm *et al.* [12] reported on three patients who had 'pressure to laugh' and other partial seizure types. Complex partial and simple motor seizures remained reasonably well controlled with carbamazepine and/or lamotrigine; generalized seizures were not an issue, and only the episodes of 'pressure to laugh' ('embryonic' forms of gelastic seizures) were refractory to medication, recurring many times a day. The common denominators in these patients were (i) the presence of very small (about 0.5 mm) hypothalamic hamartomas; (ii) normal interictal and ictal EEGs; and (iii) normal development and behaviour. Other authors also report on patients who have medically refractory gelastic and complex partial seizures, however in these patients, AEDs significantly reduce seizure frequency to a point that many can lead reasonably normal lives [13, 14]; [Palmini *et al.* unpublished observations].

Still other patients may have a transient, favourable response to AEDs, but eventually become refractory and may progress to a more severe form of epilepsy. We have recently re-examined a 4 year-old girl referred to us with a 1.2 cm HH and delayed language development. She started with giggling attacks during infancy, and evolved with complex partial and head dropping attacks, which were reasonably well controlled with carbamazepine until age 3. However, seizures recurred and she now has gelastic, complex partial and head dropping seizures daily, despite high dosages of carmabamazepine and clobazam. The interictal EEG during the period in which she had mild, weekly attacks on carbamazepine monotherapy is shown in *figure 1*. It is possible that the delayed language development and the markedly abnormal EEG predicted worsening of the epileptic picture with time. We suggested that valproic acid be added to the AED regimen and discussed the surgical alternative at length.

There are no studies specifically addressing the issue of AED management in patients with HH. The choice of medication should be tailored to the type of seizures, EEG abnormalities, and severity of the condition in individual patients along the clinical spectrum mentioned above. However, patients may move along the spectrum of severity of the disorder, and the need for a dynamic view to management should be kept in mind. Thus, in patients with only gelastic and focal motor or complex partial seizures, associated with predominantly focal EEG abnormalities, AEDs with proven efficacy in partial and secondarily generalized seizures like carbamazepine and lamotrigine may be appropriate choices, as well as other drugs with similar pharmacodynamics (eg., phenytoin, oxcarbazepine). Clobazam or clonazepam may be added in patients with only partial response. In contrast, in patients presenting with a symptomatic generalized epilepsy [3, 17, 18, 23], medical management should aim to control tonic, tonic-clonic and atonic seizures, including drop attacks [13]. EEG abnormalities are usually more severe,
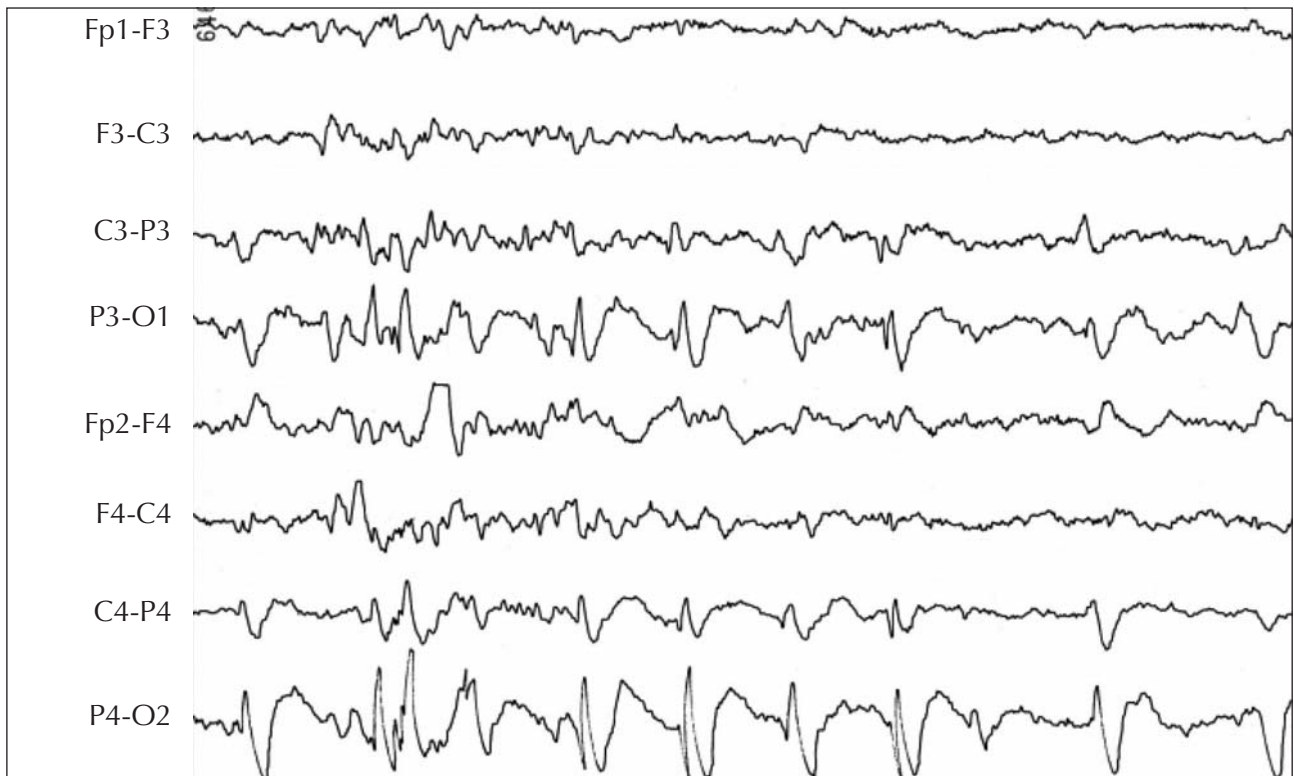
Figure 1. *Sleep interictal EEG section of a 2 y, 9 m old girl, with gelastic and other seizure types adequately controlled with AEDs. Note the abnormal background rhythms and bilateral epileptic discharges with posterior predominance.*

with generalized, irregular slow spike and wave complexes [17, 18, 23, 24]. Valproic acid, clonazepam, nitrazepam, and topiramate are the AEDs that should be considered, in variable associations with other drugs. However, the need for a combination of drugs should not progressively lead to an irrational polytherapy.

The management of the behavioural abnormalities in patients with HH has also not been specifically addressed. The use of typical or atypical neuroleptics complemented, as needed, by trazodone or lithium has been our basic approach. Several of the AEDs used by these patients could have a favourable impact on behaviour, but the usually poor medical control of the aggressiveness attests to the general medical intractability of the catastrophic side of the syndrome.

Hypothalamic hamartoma and epilepsy: surgery *not* directed at the hamartoma

Seizure semiology, as well as scalp EEG, depth EEG from cortical regions, and metabolic (fluoro-deoxy-glucose [FDG]-PET) studies have suggested that seizures in patients with HH may result from associated cortical abnormalities. Focal cortical hypometabolism in PET and focal cortical seizure onsets recorded by intracranial EEG [25]

have suggested that the main generators were indeed in the cortex. However, cortical resections targeted at these sites have uniformly failed [25-27].

Munari [26], Kahane [27] and colleagues have shown that different types of seizures in patients with HH originated from different regions of the brain. Using stereo-EEG, they inserted depth electrodes in both cortical and hypothalamic targets, and showed that gelastic attacks indeed originated from the hamartoma, while generalized tonic seizures, potentially leading to drop attacks, had a multifocal neocortical onset. Nonetheless, in these and other patients [16, 24, 27-29], a sizable resection, destruction or disconnection of the HH led to complete or very significant alleviationof these major attacks, demonstrated to originate from neocortical sites. Thus, seizures in patients with HH and epilepsy either originate in the HH [26, 27, 29] or originate in cortical structures but have a close pathogenetic relationship to the diencephalic lesion [26, 27]. These latter seizures, when refractory, have been proven to be controlled only through resection, destruction or disconnection of the hamartoma. Why should resection of the subcortical lesion alleviate generalized attacks, demonstrated to originate in the cortex, is not clear. In all likelihood, mechanisms of secondary epileptogenesis are involved. It has been hypothesized that the cortical regions generating seizures in patients with HH

are in a "*dependent phase of secondary epileptogenesis*", as suggested by Morrell for bitemporal foci [17, 18, 30]. This hypothesis could also explain why some patients do not improve even after removal of the hamartoma, in that dependency versus independency of the cortical focus from the primary hypothalamic lesion may hold the key to surgical success following resection of the lesion.

Hypothalamic hamartoma and epilepsy: surgical results when targeting the lesion

Several lines of evidence have converged to modify the concepts involved in the surgical management of patients with catastrophic epilepsies and HH. The momentum for the change was kindled by the disappointing results obtained with cortical resections [25] and also by reports appearing in the early 90s demonstrating that favourable results could be obtained with resection of the subcortical lesion [9, 31,32]. However, greater interest for the lesional approach followed the demonstration by depth EEG and ictal SPECT that gelastic attacks originated in the HH [16, 26, 27, 29, 33]. Thus, the surgical strategy for patients with HH became the resection, destruction or disconnection of the lesion, and several reports on series of patients treated this way are available [16, 24, 34-36].

We and others have recently reported on 13 patients followed for many years, in whom the HH was resected through the pterional or subfrontal route [16]. They all had severe epilepsy, cognitive impairment and behavioural abnormalities. On the basis of pre- and post-operative MRI, lesion removal was rated as total in two patients, subtotal in seven, and partial in four. Eight of the nine patients (88%) in whom complete or subtotal resection of the hamartoma was feasible had a complete or greater than 90% control of the major generalized tonic-clonic seizures or drop attacks, while none of the four who had only a partial resection had a good result. Five patients were re-operated upon, two of whom had additional resection of the lesion, and the other three had alternative procedures, including a stereotactic lesion of the mammillo-thalamic tract, gamma-knife surgery or implantation of a vagus nerve stimulator. Those patients having additional resection of the lesion and the one with interruption of the mammillo-thalamic tract had significant, additional improvement. Taking into account both the first and second surgical procedures, 11 of the 13 patients (84%) were either seizure-free or had a greater than 90% reduction in the frequency of *major* debilitating attacks. Minor attacks, including gelastic and complex partial seizures persisted in most patients although with reduced frequency. Even though only two patients were free of all seizure types, the gains related to the control of the severe attacks (generalized and drop) had a major impact on the quality of life. In addition, all 13 patients had a most significant improvement in behaviour and cognition as rated by parents and

teachers. Occasionally, aggressive or hyperactive behaviour persisted to a minor degree, but this was still compatible with productive relationships with family and peers. Post-operatively, three patients had an anterior thalamic and one a capsular infarct, which left only minimal long-term deficits. Despite a favourable outcome, this rate of surgical complications attest to the delicate balance involved in the decision to operate on these patients. Lesion location, in relation to the interpeduncular fossa and to the walls of the third ventricle, correlated with the extent of excision, seizure control and complication rate. Resection was more extensive with a lower rate of complications when the lesion extended into the interpeduncular fossa, in comparison to patients in whom the hamartoma was fully contained within the hypothalamus.

Since the completion of that study [16], we have operated upon several additional patients, taking into account the lessons learned from the original retrospective series and also the technical proposition by Rosenfeld *et al.* [24], demonstrating that the HH could be effectively approached by a transcallosal, interforniceal route (that is, 'from above', instead of 'from below'; see also Harvey *et al.* in this issue). The rationale for the choice of the resective strategy is discussed thereafter. The merits and difficulties involved with gamma-knife surgery [35], complete surgical disconnection of the lesion [28, 36], as well as with stereotactic thermocoagulation or radiofrequency ablations [24, 29, 37], are reviewed elsewhere in this issue.

Choosing the direct operative approach: 'from above or from below'?

Size and location of the hamartomatous lesion may help decide the type of direct surgical approach. When the HH is small, surgical difficulties relate to the preservation of surrounding hypothalamic structures, which have not been displaced by the lesion. Internal decompression of the lesion does not provide a safe 'surgical corridor'. Many delicate arteries surround the hamartoma and should be dissected and preserved. When the lesion is too large, it may displace the hypothalamus, blurring the boundaries between the lesion and the normal structures. The location of the lesion in regard to the hypothalamus, the interpeduncular cistern, and the third ventricle is another important issue. When discussing surgical strategy, we refer to the anatomical plane at the level of the optic tracts as a dividing line: when the hamartoma is above this plane, we find it difficult to perform a sizable resection through the pterional route, and these lesions probably should be approached "*from above*", preferably through Rosenfeld and Harvey's transcallosal – interforniceal route [24] *(figure 2)*. In contrast, we think that hamartomas predominantly located below the level of the optic tracts are better approached through the pterional route (that is, "*from below*"), which offers a more direct view of the lesion *(figures 3 and 4)*.
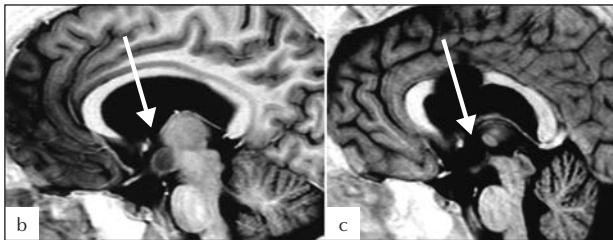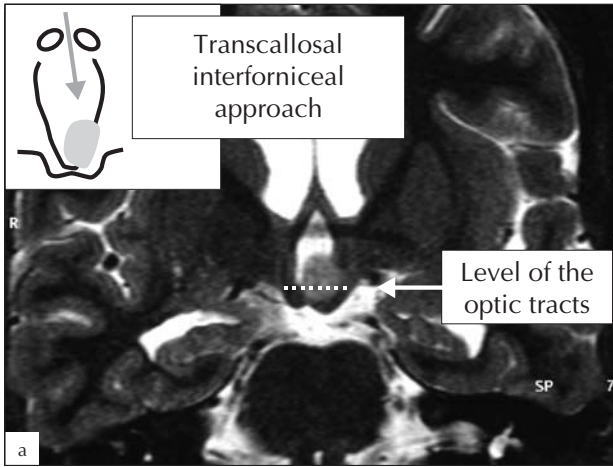
Figure 2. *The transcallosal-interforniceal approach for lesions above the level of the optic tracts, as depicted in (a). Pre- and post-operative views through sagittal MRI sections show virtually complete elimination of the lesion -arrows in (b) and (c).*
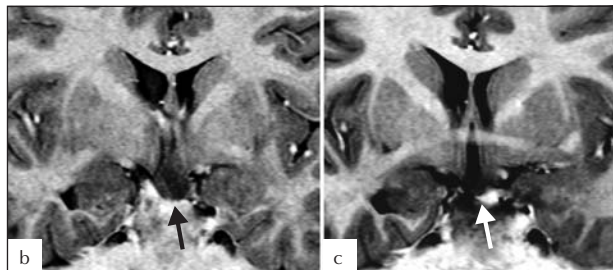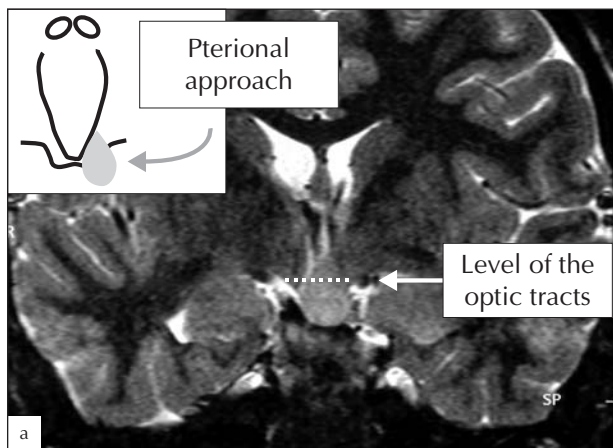

Figure 3. *The pterional approach for lesions below the level of the optic tracts, as depicted in (a). Arrows in (b) and (c) show pre-and post-operative views of the hamartoma.*
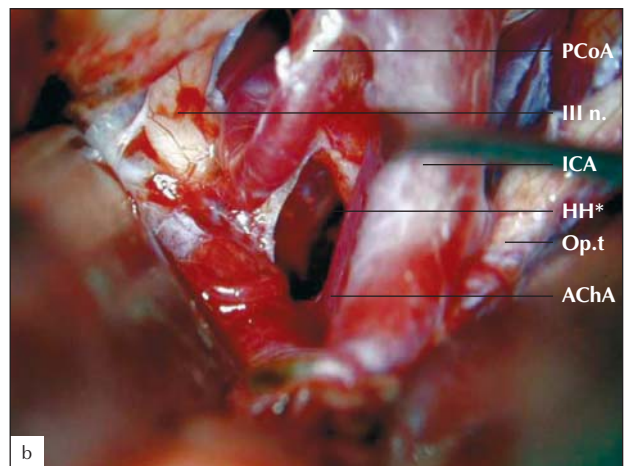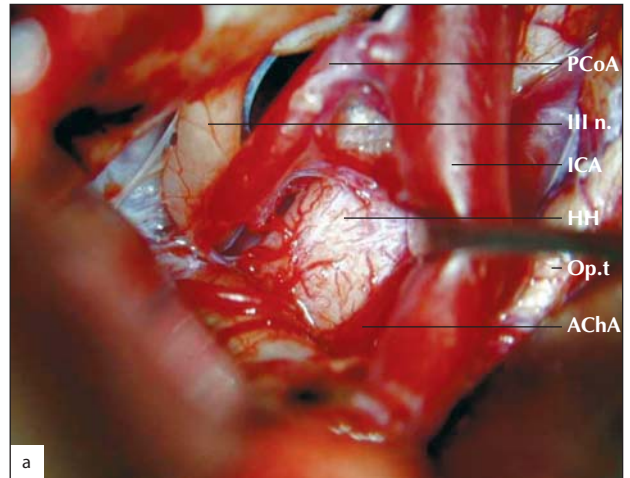

Figure 4. *Intra-operative views of the structures surrounding the hamartoma, both before (a) and after (b) resection of the lesion. PCoA = posterior communicating artery; IIIn = third cranial nerve; ICA = internal carotid artery; HH = the hypothamalic hamartoma; HH* = bed of resection of the hamartoma; Op. t = optic tract; AChA: anterior choroidal artery.*

Surgical treatment of HH and epilepsy: what more do we need to know?

Despite recently accumulated knowledge, several issues still need clarification. One point is why subtotal or apparently complete resection of the lesion may have a greater impact on the major seizures than on the minor attacks. It is possible that minor gelastic and complex partial seizures would still occur if any amount of hamartomatous tissue is left in place, which is a common occurrence in the face of the lack of a clear anatomical plane between the hamartoma and the surrounding hypothalamic tissue.

Furthermore, we do not know why some patients reported in different series fail to improve despite similar extents of resection. Extent of resection or disconnection is a major determinant of the surgical outcome, and limited resections could explain less satisfactory results in some pa-

tients [2, 13, 21]. However, this is apparently not a universal explanation, as illustrated by at least two cases. Pascual-Castroviejo *et al.* recently reported a 24 year-old man [38] who had the classical picture of catastrophic epilepsy related to HH: refractory partial and generalized seizures, cognitive deterioration and behavioural abnormalities. Their *figure 3* depicts only a modest resection of the anterior portion of the HH, in spite of which the patient is completely seizure-free, much improved from behavioural and cognitive standpoints, and close to complete AED withdrawal. A 12 year-old girl whom we evaluated and operated upon twice illustrates the opposite situation. When first seen, she had a catastrophic picture, characterized by intense aggressiveness and impulsive behaviour, prolonged trains of generalized slow spike and wave complexes associated with mental clouding, as well as frequent falls and generalized tonic-clonic seizures. Gelastic attacks represented the least of her problems. The hamartoma and the MRI pictures of the two operations are illustrated in *figure 5*. The lesion was initially approached through a transcallosal-interforniceal route, with attempts to spare the mammillary body *(figure 5b)*. She had an excellent course for a few weeks, being seizure-free and much more alert. Seizures gradually returned to the preoperative frequency, and she was evaluated again a year later in view of another operation. MRI showed that resection had been almost complete, except for the ipsilateral mammillary body *(figure 5b)*. We hypothesized that the transitory improvement after the first resection was due to post-operative swelling, functionally interrupting the spread of epileptic activity through the mammillothalamic tract. Once the swelling subsided, ictal activity originating (probably) within the mammillary body could have led to seizure recurrence. We then resected the mammillary body through a pterional route *(figure 5c)* and obtained a remarkable control of seizures and behavioural improvement in the first month after operation. However, exactly as after the first procedure, seizures and behaviour progressively deteriorated again after the first postoperative month. Cognitive problems and aggressive behaviour persisted, and improvement was obtained some months later after the institution of a ketogenic diet. Since the hamartoma was apparently entirely resected *(figure 5c)*, we can speculate that in some patients with HH, the neurobiology of the epilepsy and the behaviour abnormalities transcends the anatomic boundaries of the lesion. We do not know whether such patients develop an *independent stage* of secondary cortical epileptogenesis [17, 18] or if something else accounts for the failure to obtain seizure control following virtually complete resection of the hamartoma. The contrast between these two patients challenges our understanding of this disorder and of the intricate relationships between cortical and subcortical regions in the production of epilepsy and abnormal behaviour. □
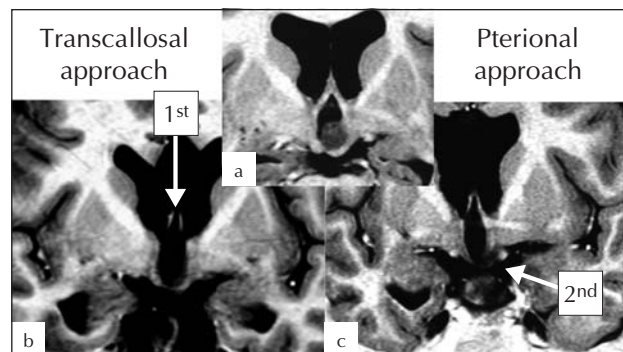

Figure 5. *Sequential surgical approach to a girl with catastrophic epilepsy and HH. The lesion is seen in* (**a**), *the subtotal resection after the first operation (through the transcallosal interforniceal route) is shown in* (**b**), *and further destruction of the left mammillary body through the pterional route is seen in* (**c**).

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