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Hemimegalencephaly: clinical implications and surgical treatment

C. Di Rocco · D. Battaglia · D. Pietrini · M. Piastra · L. Massimi

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Abstract
Introduction Hemimegalencephaly (HME) is a quite rare malformation of the cortical development arising from an abnormal proliferation of anomalous neuronal and glial cells that generally leads to the hypertrophy of the whole affected cerebral hemisphere. The pathogenesis of such a complex malformation is still unknown even though several hypotheses are reported in literature.
Background HME can occur alone or associated with neurocutaneous disorders, such as neurofibromatosis, epidermal nevus syndrome, Ito's hypomelanosis, and Klippel–Trenonay–Weber syndrome. The clinical picture is usually dominated by a severe and drug-resistant epilepsy. Other common findings are represented by macrocrania, mean/severe mental retardation, unilateral motor deficit, and hemianopia. The EEG shows different abnormal patterns, mainly characterized by suppression burst and/or hemihypsarrhythmia. Although neuroimaging and histologic investigations often show typical findings (enlarged hemisphere, malformed ventricular system, alteration of the normal gyration), the differential diagnosis with other disorders of the neuronal and glial proliferation may be difficult to obtain in some cases. Hemispherectomy/hemispherotomy is the most effective treatment to control seizure, and it also seems to provide good results on the psychomotor development when performed early, as demonstrated by the literature review and by the personal series reported here (20 children). The surgical therapy of HME, however, is still burdened by a quite high complication rate and mortality risk.

Keywords Hemimegalencephaly · Hemispherectomy · Drug-resistant epilepsy · Epileptic outcome

C. Di Rocco (✉) · L. Massimi
Pediatric Neurosurgery, Catholic University Medical School,
Largo A. Gemelli, 8,
00168 Rome, Italy
e-mail: cdirocco@rm.unicatt.it

D. Battaglia
Child Neuropsychiatry, Catholic University Medical School,
Rome, Italy

D. Pietrini · M. Piastra
Pediatric Intensive Care Unit,
Catholic University Medical School,
Rome, Italy

Introduction

Hemimegalencephaly is a rare congenital developmental malformation of the brain characterized by the anomalous and dysplastic hypergrowth of one cerebral hemisphere or some of its lobes [4, 29, 62]. The term "hemimegalencephaly" (HME) was introduced by Sims in 1835 [70] to describe the case of a female patient whose left cerebral hemisphere occupied about two-thirds of the whole intracranial volume.

Although uncommon, HME is a subject of debate among genetists, neuropathologists, pediatricians, and pediatric neurologists concerning the clinical characteristics, the natural history, and the pathogenesis of such a complex alteration of the brain development, which is surprisingly limited to one cerebral hemisphere and involving neural migration, differentiation, and proliferation at the same time. Pediatric neurosurgeons consider the condition a challenge, as it requires an early diagnosis and an early surgical indication in the majority of the children to prevent the damage associated to the nearly constant and precocious evolution toward a catastrophic epilepsy. The surgical management may be difficult and needs the combined efforts of the neurosurgeon, the pediatric anesthesiologist, and the intensive care specialist.

Background

HME is commonly defined as a congenital and dysplastic malformation of the brain due to an abnormal growth of one hemisphere [4, 29]. The current classification [5, 48] numbers HME among the *malformations due to abnormal neuronal and glial proliferation*, together with tuberous sclerosis and focal cortical dysplasia with balloon cells. Besides the hamartomatous hypertrophy of one hemisphere, HME malformation consists of a complex alteration of the cortical development [10, 62] where the anomalies of neural proliferation would represent the primary event and the alterations of neural cell migration the secondary phenomenon [30]. Usually, there is an inverse relationship between the enlargement of the affected hemisphere and the severity of its malformation. More severe alterations as agyria and wide gliosis of the white matter are, in fact, more commonly detected in relatively less enlarged hemispheres, whereas milder anatomical anomalies (polymicrogyria with a normal white matter) are found in grossly enlarged cerebral hemispheres [48]. Some authors support the hypothesis that HME is a malformation involving all the brain, though significantly more evident on one side, on the basis of histological features [40], neurophysiological observations [55], and the findings of functional neuroimaging investigations [single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance (MR) spectroscopy] [39, 61, 72].

The pathogenesis of HME is still unknown [2, 48]. The presence of a triploid–diploid mosaicism, postulated in the past by some authors [10, 49] on the basis of a possible increased DNA/RNA content in the anomalous neurons, has not been confirmed [76]. However, the somatic mosaicism of the primitive neuroectoderm could explain the association of HME with some neurocutaneous syndromes [52]. Due to the lack of hyperploidy [4], other authors [14, 48] hypothesized that an unknown etiologic factor acting during the second trimester of the fetal life, can result in an altered axonal development (molecular, receptor, and cell membrane damage) with impairment of the axonal proliferation and migration and subsequent accumulation of inert neurons. The early occurrence of injury would lead to the involvement of both glial and neuronal elements, whereas a later one would prevent the correct development of the neurons only [52].

Incidence

In spite of the lack of epidemiological studies, HME has to be considered a rare pathological entity [43, 62], equally distributed among the two sexes or with a mild prevalence for males [7, 76]. The data provided by recent studies suggest a prevalence of 1–3 cases/1,000 epileptic children and 1–14% among those with cortical development abnormalities [41, 64]. In spite of its rarity, HME accounts for a significant proportion of surgically treated cases, especially when considering series of patients who underwent hemispherectomy/hemispherotomy for intractable epilepsy. Actually, in these series the condition may account even for up to 30 to 50% of the cases [15, 25, 42, 57].

Clinical classification

HME can be clinically classified in three main variants [29]. The *isolated* form represents the classic and most common type. It shows a sporadic distribution among the population and does not present any cutaneous or systemic involvement; its prognosis depends on the severity of associated epilepsy and neurological deficits. The second type, the *systemic* form, is characterized by the association with partial or total hemigigantism and/or several neurocutaneous syndromes [56, 79]. The prognosis varies according to the clinical features. Rarely, a mendelian transmission has been reported. As to the epileptic manifestations, there is no significant difference between the isolated and the systemic variant [59, 81]. The last and less frequent form, the so-called *total hemimegalencephaly*, involves, besides the affected cerebral hemisphere, the homolateral cerebellum and brainstem [66].

Clinical findings

Macrocrania is the main characteristic of the hemimegalencephalic child and, in the isolated form, it may be the only sign to be obvious at birth or in the early postnatal period [29, 82]. Seldom, especially in cases of prenatal diagnosis, a cesarean delivery may be required because of the enlarged skull [14]. At physical examination, macrocrania appears to be asymmetric. Usually, signs and symptoms of raised intracranial pressure are absent [76], probably because of the progressive adaptation of the skull to the abnormally growing cerebral hemisphere.

Hemigigantism is the main extracranial finding in HME (Fig. 1). It can involve all the homolateral hemibody or, more commonly, a single body segment (usually the facial one) [24, 76, 82]. Hemigigantism can occur alone or in association with neurocutaneous syndromes such as neurofibromatosis I (NF-I), tuberous sclerosis, epidermal nevus syndrome, Ito's hypomelanosis, and Klippel–Trenonay–Weber syndrome [24, 36]. When associated to NF-I or tuberous sclerosis complex, the clinical course of HME seems to be less severe [76].

Epidermal nevus syndrome (ENS) is a sporadic neurocutaneous disorder characterized by the presence of congenital epidermal nevi and congenital brain, ocular and

muscoloskeletal malformations [2, 56] (Fig. 2). ENS actually does not represent a unique disorder but can be subdivided at least into six different syndromes, of which the most known are the *linear sebaceous nevus syndrome* and the *Proteus syndrome* [79]. The first one, also called Jadassohn's nevus syndrome, includes a typical triad–facial nevus, epilepsy and mental retardation-associated in a great proportion of cases, (up to 70% of subjects) to cranioencephalic malformations, such as macrocrania, HME, and hydrocephalus [78]. The Proteus syndrome is very heterogeneous as it depends on an alteration of all the three germinal layers. It is characterized by total or partial gigantism, epidermal nevi, deregulation of the fat tissue, and vascular malformations. HME is present in about 8% of cases [77, 79].

The association of HME to Ito's hypomelanosis or to Klippel–Trenonay–Weber syndrome is reported in the literature only in isolated cases [22, 73]. Ito's hypomelanosis is characterized by areas of hypopigmentation of the skin and systemic malformations, which may involve also the central nervous system (cerebral/cerebellar atrophy, ventriculomegaly, cortical dysplasia, HME) [3]. Klippel–Trenonay–Weber syndrome, besides the cerebral malformations, is characterized by a typical triad made up by the asymmetric growth of the limbs, malformations of the capillary vessels of the skin, and the abnormal development of the superficial and deep venous systems [9] (Fig. 3).

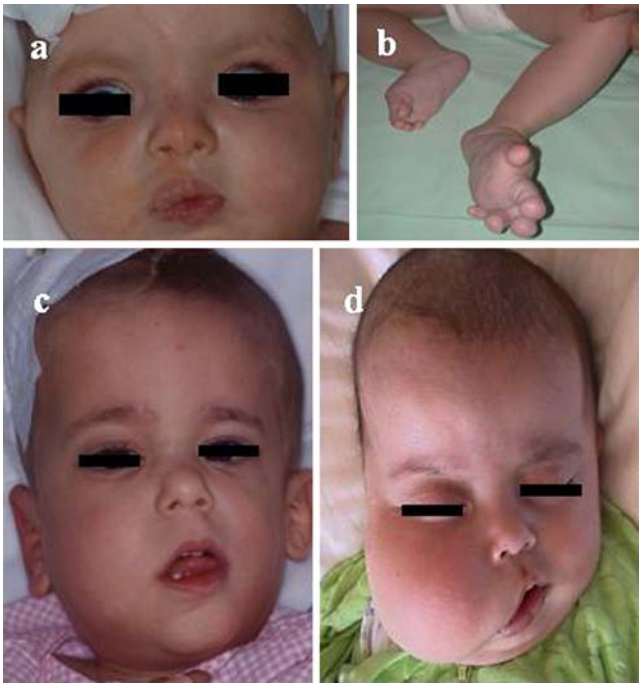

Fig. 1 Spectrum of hemigigantism in HME. The hemihypertrophy can involve an entire hemibody or be limited to just a segment: the right lip (**a**), the left inferior limb (**b**), the right hemiface (**c**, **d**). Note the association of partial hemigigantism with an epidermal nevus (**a**) and a lipoma of the cheek (**d**)

Fig. 2 Epidermal nevi (**a**, **b**); linear sebaceous nevi (Jadassohn's nevi) (**c**, **d**)

Neurological features

Psychomotor retardation, contralateral motor deficit, and epilepsy represent the classic neurological triad of HME. This triad presents a variable clinical expression in the different patients, ranging from mild to severe degree [24, 82]. Though a few cases with normal psychomotor development, mild or absent motor deficits, and seizures controlled by antiepileptic drugs (AEDs) have been reported [4, 32], in most subjects HME is characterized by a severe neurological disorder and progressively increasing seizure frequency, which may lead to precocious death in status epilepticus in some unoperated patients [14, 24, 50].

Mild to severe psychomotor retardation is a common finding depending on the anatomic anomalies of the affected hemisphere and the compensative role of the contralateral one [4, 6, 7, 43]. Furthermore, it is affected by the length of the epileptic history and the response to AEDs [6, 24, 25, 50]. Similar considerations apply to the focal neurological deficits. They are usually represented by slowly progressing hemiparesis and hemianopia, contralateral to the malformed hemisphere, and, less frequently, cranial nerve deficits [4, 14, 24, 43, 76]. Hemianopia, which is different from hemiparesis/hemiplegia, is often difficult to demonstrate especially in younger patients [82]. Cranial nerve deficits, generally optic nerve atrophy and/or

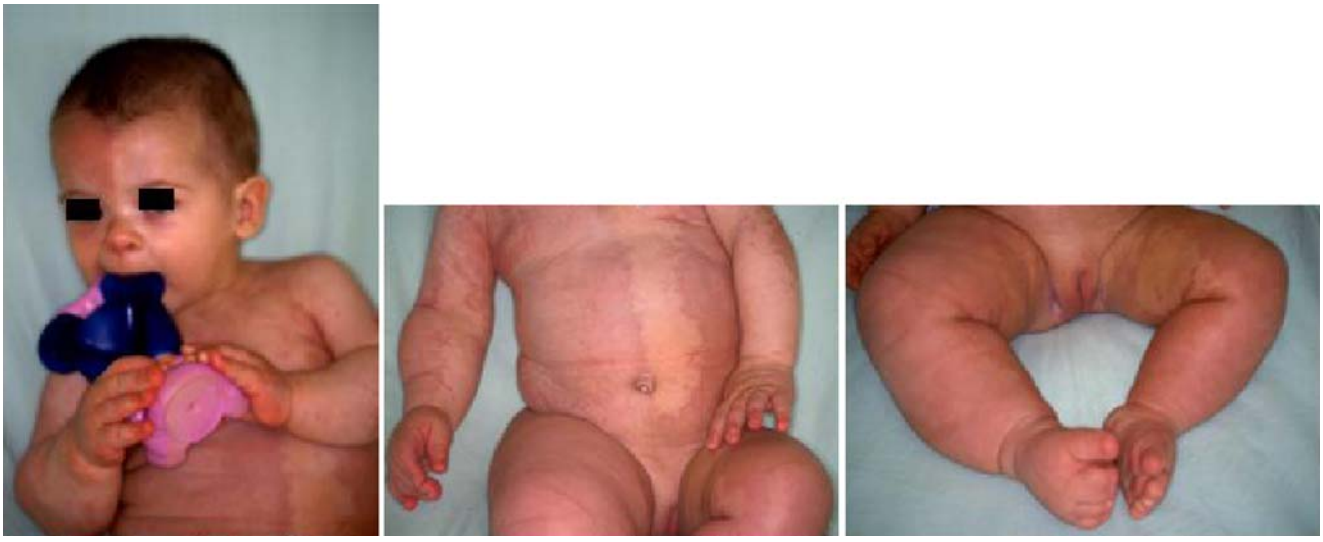

Fig. 3 Skin features of Klippel–Trenaunay–Weber syndrome in a child with hemigigantism of the right limbs

oculomotor nerves palsy, are usually determined by the primary neurological damage more than by an increased intracranial pressure [76].

Epileptic seizures represent the main manifestations of HME, seizures occurring in more that 90% of the patients [4, 24, 80, 82]. Their frequency supports a specific epileptogenicity of the malformed cerebral tissue, which may depend on alterations of the messenger RNA codifying for receptors of cerebral neurotransmitters, as glutamate and GABA [8], and/or on the synaptic activity of the anomalous neurons of the dysplastic areas that, therefore, could actively contribute to the epileptogenesis [30].

Seizures typically begin in the early postnatal period, often during the first days of life; rarely, the onset is after the sixth month of life [82]. The clinical semiology and the electrophysiological spectrum are rather heterogeneous [24, 46, 53, 54, 80]: motor partial seizures, tonic and atonic seizures, spasms and myoclonic jerks as well as early epileptic encephalopathy with suppression burst (Othahara syndrome), West syndrome, Lennox–Gastaut syndrome, partial epilepsy, and epilepsia partialis continua. Different types of seizures can be observed in the same patient. The most common clinical pattern is characterized by seizures partial at onset (seldom with secondary generalization), which, afterwards, tend to assume a different semiology [5]. Frequent but mild partial seizures (chewing automatisms, lateral eye deviation) or asymmetric spasms, prevalently involving the contralateral hemibody, are usually present during the first weeks of life [24, 46, 80]. In this period, also asymmetric or lateralized myoclonic jerks, prevalently involving the contralateral hemibody, may occur [83]. Negative myoclonus associated to Othahara syndrome has been reported as well [38]. Then, in particular after the completion of the first year of life, daily, severe partial motor seizures become prevalent, with or without persistence of clusters of asymmetrical spasms. When seizures evolve to constitute a syndrome, often they first correspond to the picture of the Othahara syndrome (suppression-burst and polymorphic seizures such as tonic, partial, and myoclonic seizures), usually after the third/fourth month of life. Later on, they correspond to the West syndrome, with asymmetrical spasms and hypsarrhythmia, and, after the first year of life, to the Lennox–Gastaut syndrome (tonic and atonic seizures and atypical absences); finally, they correspond to partial epilepsy or epilepsia partialis continua [54, 82].

The early resistance to the AEDs is to be regarded as the main characteristic of epilepsy in HME; such a feature is not rarely evident immediately after the onset or already in the very early phases of the epilepsy [4, 24, 43, 76, 80]. Such immediately occurring refractory response to AEDs could be explained on the basis of the intrinsic epileptogenicity of the dysplastic tissue of the malformed hemisphere, as suggested by microscopic (neuronal dysgenesis) and functional findings (continuous intercritic electric activity on the EEG, intercritic hyperperfusion at SPECT) [72]. The rapid evolution into catastrophic epilepsy justifies the need of an early surgical treatment.

Neurophysiological aspects

The interictal EEG activity is invariably altered in HME, though with different patterns related to the age of the patients [53]. During the first weeks/months of life, the EEG shows an asymmetrical background activity and sporadic wide spikes and/or spikes–waves complexes usually confined to the malformed hemisphere [55, 80] (Fig. 4). Furthermore, two more specific patterns, the

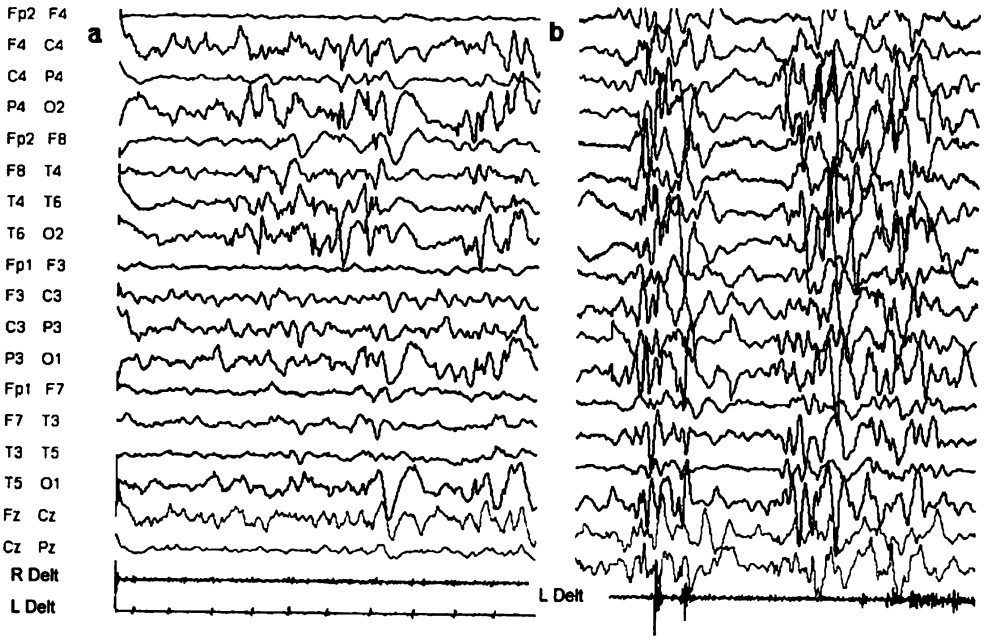

Fig. 4 Four-month-old boy affected by right HME. The presurgical EEG, performed when the child is awake, shows an asymmetric background activity with lower frequency on the right side and paroxysmal activity on the right central and posterior regions (**a**). The EEG pattern during sleep is characterized by diffuse discharges of spikes and spikes–waves fragmented by a depressed activity; some myoclonic jerks associated to the spikes are evident on the deltoid EMG (**b**)

unilateral suppression burst and the unilateral hypsarrhythmia (hemihypsarrhythmia) can be demonstrated at level a of the abnormal hemisphere even associated in the same patient [53, 55, 82]. The suppression burst is typically characterized by a high-voltage paroxysmal activity (burst) alternated to short periods of low-amplitude activity (suppression), this pattern generally being continuous either with the patient awake or asleep. The hemihypsarrhythmia typically includes multifocal and asynchronic paroxysmal elements over a very slow background activity. In the "modified" hemihypsarrhythmia, the abnormal activity is asymmetric and discontinued (Fig. 4). The suppression bursts can be detected in the early phases of the disease and, when associated to spasms or myoclonic jerks, they delineate the so-called Othahara syndrome [53]. Otherwise, they can start after a few months of disease to either disappear or develop in hemihypsarrhythmia, successively configuring a West syndrome [54].

After the first year of life and in case of drug-resistant epilepsy, the interictal EEG activity undergoes some variants and gets progressively worse, with the appearance of spikes/polyspike complexes, slow waves, and also rhythmic α-like activity [54, 55, 76]. Moreover, the parossistic activity becomes continuous at the level of the affected side, with possible diffusion to the contralateral hemisphere [55, 82]. Actually, bilateral interictal EEG anomalies are observed in hemimegalencephalic children much more than in patients with other epileptogenic lesions [27], thus requiring a careful and prolonged preoperative assessment to verify the unilateral onset of seizures. According to recent studies [72], the involvement of the "healthy" hemisphere is progressive and inevitable but can regress after an early surgical treatment.

Neuroimaging

Current neuroimaging techniques with high sensitivity and specificity allow the correct diagnosis of cortical development malformations in up to 90% of cases [89]. The suspicion of HME can be raised during fetal life by ultrasounds, which are particularly useful for the neonatal screening [3, 14, 76]. MRI, however, is the gold-standard examination for HME for both the diagnosis and the surgical indications. When supplemented with angiographic sequences, MRI and CT scan supply important information about possible anomalies of the vascular structures, such as contralateral shift of the median venous sinuses, hypoplasia of the deep venous system, hypertrophy of the veins draining into the sagittal sinus, abnormal extension of the sylvian veins up to the longitudinal superior sinus, and arterial hypervascularization of the affected hemisphere [23]. MRI, as for the other techniques, may show some limitations related to the poor sensibility in detecting the gray/white matter ratio because of the still incomplete myelination, in the first months of life. "Functional" neuroimaging studies (brain SPECT or PET) usually complete the diagnostic workup by demonstrating the typical critic (hyperflow/hypermetabolism) and intercritic alterations (hypoflow/hypometabolism) on the malformed side as compared to the normal contralateral one [61, 72].

In almost all the cases, the malformed hemisphere presents an abnormal enlargement, from mild to remarkable, with possible contralateral shift of the midline (Fig. 5). The lateral ventricle of the affected hemisphere is abnormal for both size and shape. The morphological pattern is that of a straight frontal horn and a widely enlarged occipital horn [4, 23] (Fig. 5). However, a grossly normal or even

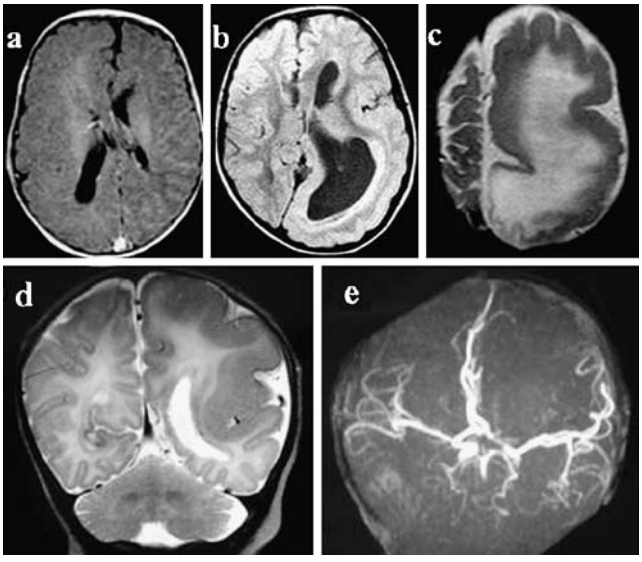

Fig. 5 Spectrum of various neuroimaging findings in HME. Hypertrophy of the right cerebral hemisphere associated with polymicrogyria, thickening of the cortical ribbon, poorly differentiated gray-white matter border, malformation of the homolateral ventricle in axial T1-weighted MR images (**a**); enlargement of the left hemisphere with typically malformed lateral ventricle (straight frontal horn, dilatation of the occipital horn), areas of grossly normal gyration (frontal lobe) alternated with dysplastic areas, lissencephaly, double cortex (axial FLAIR MRI) (**b**); markedly enlarged left hemisphere (note the asymmetry of the two hemicranium) with agyria/pachygyria and signal alterations of both gray and white matter (axial T2-weighted MRI) (**c**); left HME with pachygyria, atrophy of the temporal lobe, and enlargement of the lateral ventricle (coronal T2-weighted MRI) (**d**); and contralateral displacement of midline cerebral vessels (angio-MRI) (**e**)

small ventricular system may be observed [14]. The cortical mantle is characteristically dysplastic because of its increased thickness, poor differentiation from the white matter, and wide and shallow cortical sulci [23, 48]. Moreover, the normal gyral architectural pattern is nearly always further altered because of areas of agyria, pachygyria, micropolygyria, and lissencephaly, which may alternate with areas of normal gyration [43] (Fig. 5). Cumulated neuroradiological studies have confirmed that agyria is usually observed in slightly enlarged hemispheres, whereas the polymicrogyric pattern is found in huge hemispheres [14]. The dysplastic cortex shows a quite variable signal at MRI, usually being isointense (but also hyperintense or hypointense) on T1-weighted sequences and hyperintense or hypointense (seldom hysointense) on T2-weighted and proton density images. In most cases, the signal density varies according to different cerebral regions [89]. The white matter usually shows a low signal with focal areas of isointensity due to neuronal heterotopia and/or gliosis [48]. At spectroscopy MRI, a decreased N-acetylaspartate/creatine ratio can be found within the dysplastic areas [48]. The aforementioned radiological characteristics are similar to those of other disorders of the cortical development, such as multilobar cortical dysplasia or agyria/pachygyria, so that in some instances the differential diagnosis may be difficult [14, 43, 89].

Pathology

At macroscopic examination, the affected hemisphere appears almost invariably enlarged and exhibits an increased consistency, a malformed surface (agyria, polymicrogyria, pachygyria, lissencephaly), and an increased vascularization [24, 49, 62] (Fig. 6). These alterations can involve the whole hemisphere or some of its lobes or even parts of them; the malformed areas may alternate with apparently normal brain areas [23, 48, 50, 76]. Generally, the posterior regions of the hemisphere (parietal and occipital lobes, posterior aspect of the temporal lobe) appear more involved in the malformative process (severe hypertrophy or atrophy, lissencephaly, agyria) than the anterior temporal (usually mildly

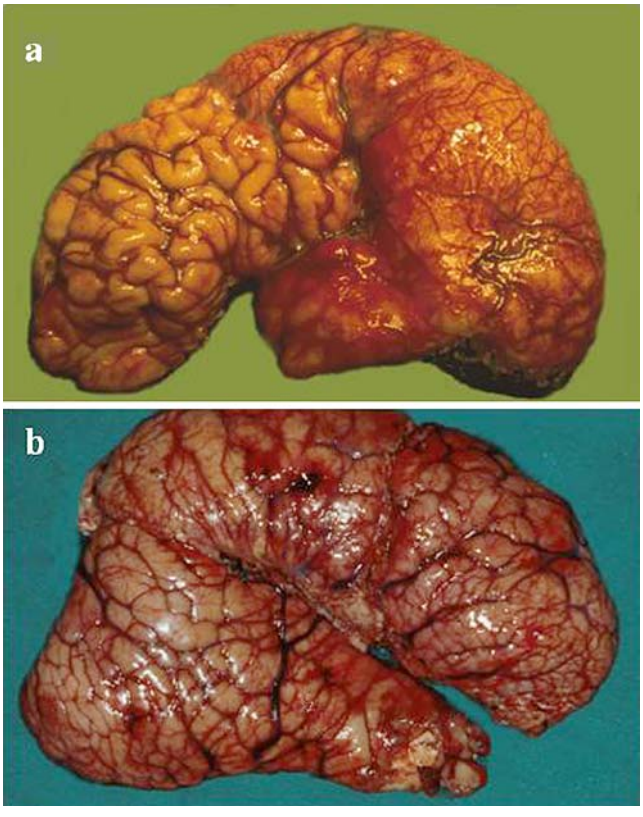

Fig. 6 Two surgical specimens of megalencephalic hemispheres. **a** En bloc removal: note the frontal polymicrogyria, the hypoplasia of the temporal lobe, and lissencephaly/agyria of the parietooccipital lobes. The hemisphere is diffusely hypervascularized. The sylvian vessels are abnormal in shape and position. **b** En pieces removal: the hypertrophy mainly involves the frontal and anterior parietal lobes while the temporal lobe is hypoplastic. Note the diffuse hypervascularization and the microgyria of the occipital lobe and frontal pole

atrophic) or frontal regions (often polymicrogyric or grossly normal) [26, 32] (Fig. 6). The abnormally shaped lateral ventricle, with its distorted configuration and diffuse or focal enlargement, is obvious on the anatomical sections together with the areas of focal neuronal heterotopia within the white matter. In spite of the definition of HME, the affected hemisphere in patients with a long history of catastrophic epilepsy may be widely atrophic as a result of the long-standing seizure disorder [88].

The microscopic analysis of the specimens of malformed cerebral tissue confirms both neuronal and glial anomalies [62, 63]. Such anomalies may exceptionally involve also the contralateral hemisphere [40, 62]. The cerebral cortex lacks its normal stratification and a demarcation from the white matter; moreover, several anomalous giant neurons presenting an increased dendritic proliferation, an abnormal distribution of the Nissl's bodies, and an abnormal orientation are variably scattered in the different cortical layers (Fig. 7). These neurons are also ectopically located within the white matter, especially in the superficial subcortical layer, thus justifying the poor demarcation from the overlying gray matter. While the neuronal alterations are constant, the glial anomalies are evident only in about 50% of the cases [63] and concern astrocytes more than oligodendrocytes [30]. They include the presence of anomalous cells, such as balloon cells (glial elements positive to glial fibrillary acid protein and vimentin) within either the gray or the white matter, multinucleate glial cells involving the molecular layer of the cortex, Rosenthal's fibers and areas of demyelinization. Furthermore, non-differentiated/immature cells were also described [12, 30]. These cells are characteristically hypertrophic and morphologically ambiguous, and show an immunohistochemical response either to glial or to neuronal markers (neurons positive for glial markers and glial cells positive for neuronal markers).

Calcifications and gliotic and/or microcystic areas within the white matter complete the pathologic picture of HME [14, 50, 76].

Surgical aspects

Hemispherectomy, applied to a variety of epileptogenic unilateral hemispheric conditions, results in an overall seizure-free rate of 70 to 85% of the cases [18, 60, 90]. Such a result tend to be maintained over time, although with a minor decline leading to a rate of 60% of postoperative seizure control at 5-year follow-up observation [17, 47, 75]. These figures can apply also to the treatment of HME but with some limitations, due to the possibility of dysplastic anomalies in the contralateral hemisphere, which could escape the neuroimaging recognition, and the difficulties in completely disconnecting the malformed hemisphere because of its severe anatomical distortion. Actually, among the heterogeneous group of conditions, which may benefit of hemispherectomy, HME is the less likely to be seizure-free after the operations [15, 47]. However, recent series [42] and our own experience [25] demonstrate that seizure control can be achieved in at least 60% of the cases, that is a rate significantly higher than that previously reported by some authors [86]. Furthermore, these children, although often characterized by the most severe psychomotor development before the operation as compared, for example, to the epileptic children with cerebral infarct/ischemia or Sturge–Weber syndrome, may still show significant improvement in behavior and cognitive functions after surgery [6, 42]. Such an outcome should be kept in mind in establishing the surgical indication by considering the dismal prognosis and

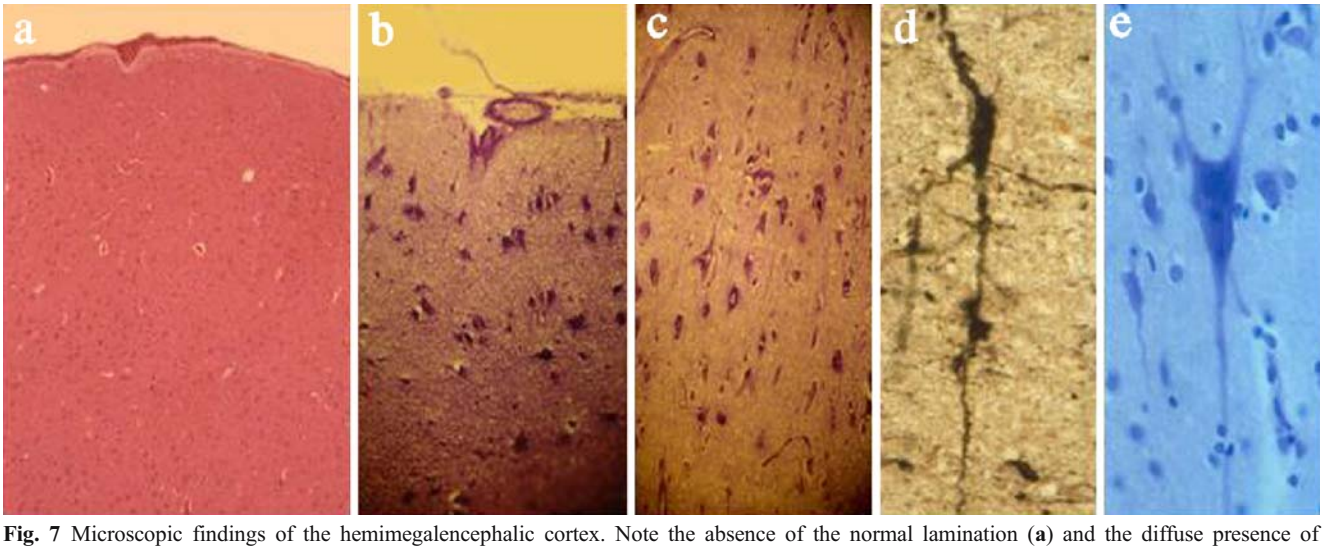

Fig. 7 Microscopic findings of the hemimegalencephalic cortex. Note the absence of the normal lamination (**a**) and the diffuse presence of abnormally shaped giant pyramidal cells scattered throughout the cortical ribbon with an abnormal orientation (**b**–**e**)

the high mortality of unoperated on hemimegalencephalic subjects [13, 45, 69].

When dealing with HME, anatomical hemispherectomy is the procedure associated with the highest rate of postoperative seizure-free patients [17, 25, 34, 80, 81] (Fig. 8). Cumulated experience indicates that the most feared complication the procedure was blamed on—that is superficial hemosiderosis—is likely the result of a widely accepted theoretical hypothesis, which was propounded before the introduction of CT scan and MRI [28, 35] rather than a really occurring phenomenon [17, 25, 34, 57]. There are, however, some reasons that justify a cautious adoption of such a type of drastic procedure, especially in centers without dedicated pediatric anesthesiologists. Among them, the hemorrhagic risk is the most important one. Generally, hemispherectomy techniques are burdened by a high risk of peroperative bleeding complications, the entire blood volume or more being often lost during the surgical procedure, with subsequent risk of coagulative impairment and need of clotting factor replacement [58]. Significant peroperative blood losses have been reported in more than 10% of the patients undergoing hemispherectomy [16], especially subjects affected by HME or large cortical dysplasia, which can require the replacement of even three to four blood volumes in about one-sixth of the cases [86]. Bleeding complications are the most frequent cause of operative deaths [17, 21]. Indeed, deaths due to catastrophic bleeding after hemispherectomy are reported in about 5% of cases in large series [16, 37, 57, 86].

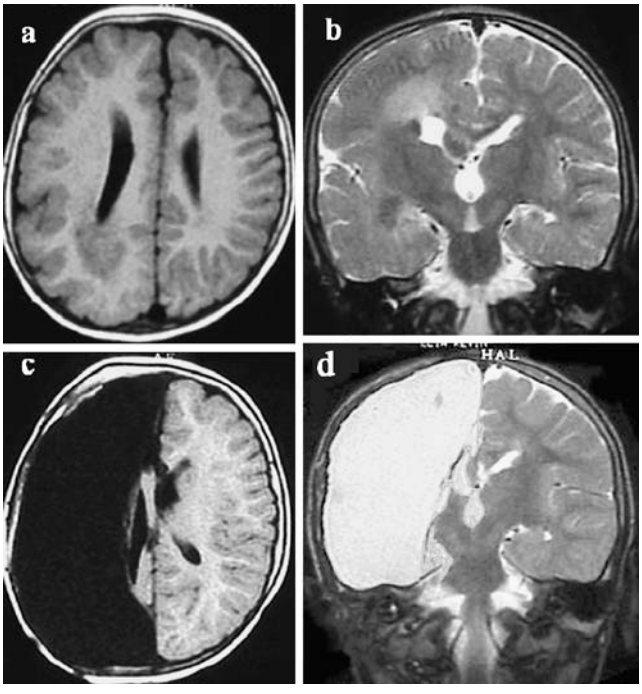

Fig. 8 Preoperative (**a**, **b**) and postoperative (**c**, **d**) axial (T1-weighted) and coronal (T2-weighted) MRI of a 2-year-old boy operated on because of a right hemimegalencephaly. Note the huge residual intracranial cavity after the anatomic hemispherectomy and the absence of secondary hydrocephalus

Comparison of the various hemispherectomy techniques based on the estimated blood loss and the amount of RBC transfusions invariably leads to the conclusion that anatomical hemispherectomy is associated with the highest intraoperative hemorrhages, in relation to the extent of the surgical resection and the major duration of the operation [58, 65, 85]. Data reported by Cook et al. [17] show a mean amount of blood transfusion of 688±90 cm^3 after anatomical hemispherectomy, 547±75 cm^3 after functional hemispherectomy, and 288±32 cm^3 after hemispherotomy. In our series of hemimegalencephalic children that underwent hemispherectomy (Table 2), the mean blood volume transfused was 550 cm^3, with one case of severe peroperative anemia (patient no. 8). As expected, the patients who underwent anatomical hemispherectomy required the highest mean blood transfusion (607 cm^3) compared with those treated by means of hemidecortication (523 cm^3) or functional hemispherectomy/hemispherotomy (367 cm^3).

The hematological concerns are particularly justified in HME in relation to the possibly increased cerebral vascularization, the peculiarly fragile bridging veins, and the anomalies of the vascular anatomy [12].

The increased size and consistency of the malformed cerebral hemisphere are further features that contribute to the difficulty of the operation (Fig. 9). Actually, such characteristics limit the manipulation of the cerebral parenchyma necessary to expose the main cerebral arteries, which should be preliminarily clipped to reduce the intraoperative blood loss. Furthermore, according to some authors, the increased consistency of the brain parenchyma may result in heavier maneuvers of hemisphere dislocation in cases where the en bloc hemispherical excision is carried out. Such maneuvers could account for the occurrence of postoperative edema phenomena of the brainstem resulting in postoperative decline in consciousness of variable duration [16]. En pieces removal of the malformed hemisphere, that is a series of subsequent lobectomies, may reduce the difficulties related to the dislocation and lifting of the brain as compared to the en bloc removal of the hemisphere. Piecemeal hemispherectomy, however, is weighted by major blood losses as compared with the en bloc surgical excision.

The first step of anatomical hemispherectomy is the reduction of intraoperative blood loss obtained through the surgical occlusion of the major feeding vessels. In most cases, the clipping of the middle cerebral artery is sufficient to control major hemorrhages and the surgical procedure can be carried out with acceptable intraoperative blood loss. The advantage of occluding the anterior cerebral artery should be weighted against the risk of an improper closure

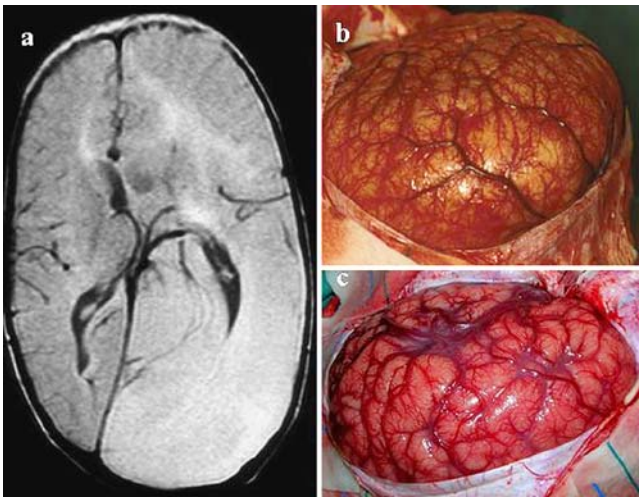

Fig. 9 The axial FLAIR MRI of a hemimegalencephalic hemisphere demonstrates the significant contralateral shift of the midline venous system, which may make difficult the callosotomy procedures required for its deafferentation and/or excision (**a**). The peroperative images emphasize the huge size of the malformed hemisphere, which protrudes from the hemiskull and their abnormally rich vascularization (**b**, **c**)

of the contralateral artery. Indeed, in some children, the two anterior cerebral arteries may run in the same vertical plane, one over the other, along an oblique or nearly vertical interhemispheric commissure, rather than parallel on the horizontal plane offered by the dorsal surface of the normally shaped corpus callosum [23]. The clipping of the posterior cerebral artery may be difficult because of the abnormal size of the hemimegalencephalic hemisphere and the resistance offered by the rigid brain to the lifting of the temporal lobe to reach the lateroposterior surface of the mesencephalon. In our experience, however, the anatomical hemispherectomy can be safely carried out with acceptable blood losses without the preliminary control of the posterior cerebral circulation; a similar observation was made by other authors [16]. Preoperative embolic occlusion of the major intracranial vessels has been propounded on the basis of a single clinical experience to facilitate the surgical excision [50]. Such a procedure, which was apparently well-tolerated by the patient, resulted in a temporary reduction of the seizures, and, according to the authors, probably contributed to diminish intraoperative blood loss. However, we are not aware of any further application of the technique.

Controlling intraoperative hemorrhages from venous source may be also difficult in HME. Usually, the bridging veins are large, but shorter and more fragile than in other pathological conditions. Furthermore, these vessels are more difficult to reach and to coagulate, as they are pushed against the superior sagittal sinus and the falx by the overgrown cerebral hemisphere. Consequently, particular care should be taken to avoid their accidental tearing. These veins should be coagulated when they are still embedded within the cerebral cortex rather than in their course in the almost absent epiarachnoid space. Leaving some amount of cortical tissue around the coagulated veins before actually cutting them may assure an easier and more reliable closure [23].

Preserving the ventricular system was postulated to diminish late hemorrhagic complications, and, consequently, cerebral decortication procedures were suggested in the place of anatomical hemispherectomy [16]. Actually, the main advantage of preserving the ventricular system is believed to be the minor interference with the CSF circulation, which hopefully could result in a diminished rate of postoperative hydrocephalus. In most clinical series, HME is associated with a higher rate of postoperative hydrocephalus as compared to other pathological conditions requiring hemispherectomy [34, 47]. However, in our experience, this complication did not correlate with a specific surgical technique, as postoperative hydrocephalus was associated with anatomical and functional hemispherectomy as well as with decortication procedures [25]. Data from the literature confirm that hydrocephalus, though occurring more frequently after anatomical hemispherectomy [16, 57, 85], is not rarely observed after functional techniques [17, 65, 85], being reported even in 5–15% of the cases [68, 84]. The only relevant finding in our clinical series related to the development of this complication was the young age at operation, as postoperative hydrocephalus developed nearly exclusively in very young children operated on during the first year of life [25] (Table 2).

The necessity or the usefulness to preserve the deep thalamic nuclei is still a subject of debate [17, 21, 68, 86]. We did not observe in our children any different motor outcome when the nuclei were removed and when they were left in place. The presence of abnormal neurons in these structures was postulated to explain the case of children who underwent operation showing seizures characterized by limb hypertonia contralateral to the excised hemisphere some months after the operation [33]. The spontaneous disappearance of such an attack in all the patients exhibiting such clinical manifestations clearly rules out the propounded hypothesis suggesting the nonepileptic nature of the phenomenon.

The herniation of the healthy hemisphere below the falx into the contralateral hemicranial cavity resulting from the hemispherectomy and, generally, the greater potentiality of the residual nervous and vascular structures to be mechanically dislocated with the movement of the head have been advocated as the cause of late intracranial hemorrhage [71]. Actually, the best clinical results in terms of improvement in cognition and dexterity were observed in children whose healthy hemisphere expanded maximally within the contralateral hemiskull postoperatively [6, 7]. In any case, it is possible to limit such potential shifting within the cranial

cavity by confining the basal ganglia left in place against the falx in a kind of nest obtained by suturing strips of dura mater to this structure and to the basal dura [23] (Fig. 10).

Functional hemispherectomy may also be utilized in the treatment of HME. This technique, with its different variants, is essentially based on the disruption of the internal capsula and corona radiata, the resection of the mesial temporal structures, the section of corpus callosum from the lateral ventricle, and the interruption of the frontal horizontal fibers [51] (Fig. 11). Functional hemispherectomy or hemispherotomy provides nearly the same rate of seizure control than anatomical hemispherectomy in the short postoperative period [65, 85]. However, its results may not be stable and, in a variable proportion of the cases, a recurrence of the seizures can be noticed [17, 57] (Table 1). In such an event, a repeated surgical approach with anatomical hemispherectomy may again assure the complete disappearance of epilepsy [34].

The major efficacy of the complete removal of the affected hemisphere vs its disconnection should be seen in the anatomical characteristics of the hemimegalencephalic hemisphere that may preclude its correct and safe disconnection. Furthermore, in particularly severe cases, the excision of the abnormally enlarged hemisphere may, per se, constitute an advantage, as the maneuver could remove the compression, with possible secondary impairment of the normal growth exerted over the contralateral healthy brain. Incomplete disconnection was actually the only variable that can be statistically associated with persistent seizures after surgery in the study of Gonzalez-Martinez et al. [34]. These authors defined the unintentional epileptogenic tissue left behind and still connected to the contralateral hemisphere or to the homolateral basal ganglia and thalamus or to descending fibers as incomplete disconnection, and pointed on the possible adverse anatomical features, which could favor the phenomenon. First of all, the disruption of the horizontal fibers connecting the orbitofrontal cortex and the mesial structures of the temporal lobe may be made difficult by the abnormal shape and distortion resulting in a secondary defective visualization during the surgical operation. According to the authors [34], the frontal basal fibers are the most difficult to access. A second difficulty has to be faced at the posterior aspect of the frontal basal region where no clear differentiation can be obtained between the cortical gray matter of the frontal lobe and the gray matter of the hypothalamus. Practically, the surgeon should consider the anterior margin of the anterior cerebral artery as the only landmark and to place its incision anterior to this structure to

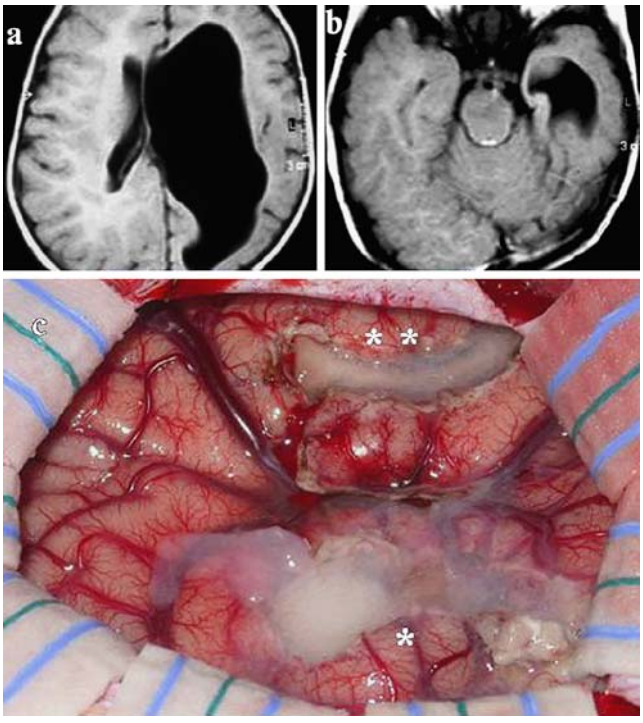

Fig. 11 Preoperative axial T1-weighted MR images of a left hemimegalencephaly with severely dilated lateral ventricle (**a**, **b**) favoring the operation of periinsular hemispherotomy. The suprainsular window (*asterisk*) and the infrainsular window (*double asterisk*) are evident in the peroperative view taken at the end of the surgical procedure (**c**)

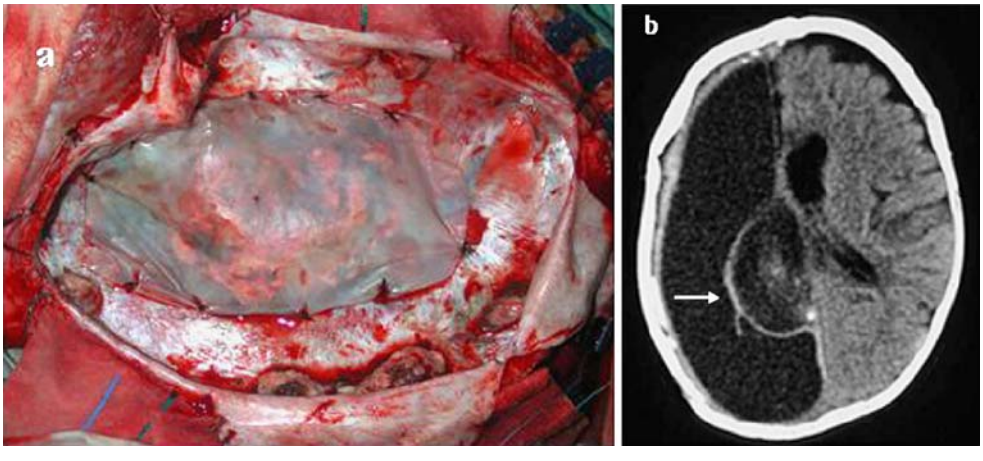

Fig. 10 Intraoperative view after a right anatomic hemispherectomy (**a**). Note the application of a dural patch on the tentorium and cerebral falx to limit the mechanical displacement of the residual basal nuclei and contralateral hemisphere. The dural patch and its containing actions are clearly visible on the postoperative CT scan (**b**, *arrow*)

Table 1 Synopsis of the contemporary literature concerning HME cohorts

Authors	No. of cases	Mean age at surgery	Type of hemispherectomy	Epileptic outcome	Complications	Mean follow-up
Bittar et al. (2002) [11]	1	5 months	Functional	>75% of seizure reduction	Reoperation, hydrocephalus, intraoperative hemorrhage, pneumonia	3 years
Carreño et al. (2001) [15]	6	<2 years	Functional	Persistent seizures in 5/6 patients	Reoperation (2) [hydrocephalus (2), infection (1)]	19.3 months
Danielpour et al. (2001) [19]	1	27 months	Disconnective hemispherectomy	Engel's I	Epidural hematoma, cerebral edema	20 months
Di Rocco and Iannelli (2000) [25]	15	2.5 years	13 anatomic, 2 functional	Engel's I (10), II (4: 2 anatomic + 2 functional), IV (1)	Fever (6), hydrocephalus (5), transient neurologic deficit (5), infection (4), subdural hematoma (1), anemia (1)	5 years
Fonseca et al. (2004) [31]	2	<6 months	Functional	Both improved	Transient hemiparesis (1)	Not available
González-Martínez et al. (2005) [34]	7	<2 years	3 anatomic, 3 functional, 1 anatomic + functional	Engel's I (5), II (2, both functional)	[16.7%: hydrocephalus, infection, incomplete disconnection]	34.8 months
Jonas et al. (2004) [42]	16	1.5±1.2 years	5 anatomic, 5 functional, 6 hemispherotomy	33.3% seizure-free	Death (1); 37.5% of complications (4 reoperations + others minor); 27% of shunt	5 years
Kossoff et al. (2003) [47]	11	1.6 years	Hemidecortication	Seizure-free (4), minor seizures (3), major seizures (3)	Death (1); reoperation (2)	4.5 years
Shimizu (2005) [67]	16	Not available	Hemispherotomy	Engel's I (5), II (3), III (5), IV (3)	39% (hydrocephalus, infection, CSF collection, brain swelling)	Not available
Taha et al. (1994) [74]	3	10 months	Anatomic (in two steps)	Regression (2), rare seizures (1)	Hydrocephalus (2)	4 years
Yoshioka et al. (1999) [91]	1	13 months	Modified functional	Engel's I	Subdural hemorrhage	42 months

The papers not providing enough data on hemimegalencephalic patients were not considered
Data enclosed in brackets under the sixth column are deduced from the whole series reported by the authors (not exclusive of the patients with HME)

avoid damaging the vital structures of the most anterior portion of the basal ganglia and the anterior perforated substance crossed by the lenticulostriate arteries. In several subjects with HME, the anterior cerebral artery is undergoing important variations, often being more anteriorly placed than usually, so that in some cases, a disconnection at its level may leave a variable amount of epileptogenic frontal tissue still connected to the basal ganglia and thalamus in place. The irregular and sometimes small lateral ventricle and the hypoplastic temporal horn may provide in some patients an approach insufficient to perform an adequate and complete disconnective procedure. Even the section of the corpus callosum, a maneuver that usually does not represent any obstacle in functional hemispherectomy, may be quite difficult in HME because of its irregular size, shape, and abnormal inclination. The variable anatomy of the neighboring vessels, especially the deep veins, and the frequent presence of interdigitations of the mesial cortical surfaces of the two hemispheres represent a further cause of surgical risk and an adjunctive limit to the application of functional hemispherectomy to HME.

Surgical outcome

The analysis of the literature shows that hemispherectomy, whatever the surgical technique, is an effective procedure for the control of epileptic seizures, with high success rates being reported either after anatomical hemispherectomy [1, 20] or hemidecortication/hemicorticectomy [16, 87] or functional techniques [11, 15, 65, 85, 91]. There is, however, a difference in the length of the follow-up related to these various surgical procedures, being generally longer for the patients treated by the anatomical or "classical" functional hemispherectomy than that of the children who

underwent the more recent hemispherotomy [20, 65]. As to the motor and visual performances, they often remain stable after hemispherectomy [20, 90] or may have an improved result [19, 57]. When the worsening of a preoperative deficit is detected, it usually recovers within a few months [1, 44]. The cognitive performances finally undergo a progressive postoperative improvement, as confirmed by the high rate (up to 70%) of patients with improved IQ and psychomotor development [87], even though more than a half of the hemispherectomized patients show cognitive deficits at long term follow-up [11].

In spite of the quite homogeneous results of the different types of hemispherectomy, the etiology of epilepsy might affect the epileptic outcome after surgery, and hemimegalencephalic patients are usually thought to show worse results when compared to those affected by other hemispheric diseases (e.g., Sturge–Weber syndrome, Rasmussen encephalitis, proencephalic cysts) [15, 42, 47]. The reasons for this difference, as previously discussed, could depend on the possible involvement of the "healthy" hemisphere and on the abnormal anatomy of the affected one that can make the surgical procedure difficult and/or incomplete. However, a statistically significant difference in seizure outcome between HME and other pathologies has not been ever confirmed [17, 23, 80, 81]. Data from the current literature about epileptic outcome in HME are summarized on Table 1.

Although a significant postoperative improvement can be usually observed, there is a general agreement about the usually worse motor and cognitive outcome among the hemimegalencephalic children as compared with different subgroups of hemispherectomized patients [6, 15, 42]. The causes of these worse prognoses should be found in the (long) history of catastrophic epilepsy, the often-poor preoperative psychomotor development, the possible involvement of contralateral hemisphere, and the possible unfavorable epileptic outcome.

Our series shows a good long-term control of seizures (Table 2), the results matching even those reported in the literature about non-hemimegalencephalic patients. Indeed, after 10-years mean follow-up period, 17 out of 20 patients (85%) belong to the I/II Engel's class and 75% to class I (class Ia: 55% of the whole series). In 60% of the patients (12 cases), no more abnormal EEG activity is present on the contralateral side. The three patients with nonoptimal seizure control (class IIIa) were operated on by means of three different techniques and still show abnormal EEG activity. Only one patient (5%) required an adjunctive surgical procedure because of an initially poor epileptic

Table 2 Personal series: results after a 10.5-year mean follow-up

Cases	Age at surgery	Type of hemispherectomy	Complications	Shunt	Blood transfusion (cm^3)	Epileptic outcome	Follow-up (years)
1	3 months	Functional	–	–	380	Ia	7
2	3 months	Anatomic	Strabismus	–	280	Ia	1
3	5 months	Anatomic	Hydrocephalus, osteomyelitis, transient hemiparesis	VPS	750	Ia	8
4	6 months/ 2.5 years	Hemidecortication/ functional	–	–	500 / 300	IIa	2
5	7 months	Anatomic	Wound infection, fever	–	400	Ia	13
6	7 months	Anatomic	Hydrocephalus, deep infection	VPS	650	IIa	11
7	7 months	Anatomic	Subdural fluid collection	SPS	800	Ia	10
8	8 months	Anatomic	Hydrocephalus, anemia	VPS	550	Ia	12
9	9 months	Anatomic	Hydrocephalus	VPS	400	Ic	16
10	10 months	Hemispherotomy	Subdural fluid collection	SPS	370	IIIa	8
11	1.7 years	Functional	Wound infection	–	420	Ib	1
12	1.8 years	Hemidecortication	Fever	–	380	IIIa	7
13	2 years	Anatomic	Fever	–	410	Ia	17
14	2 years	Anatomic	–	–	1200	Ic	16
15	3 years	Anatomic	Transient dystonia, fever	–	350	Ia	3
16	3 years	Anatomic	Transient third cranial nerve palsy, fever	–	400	Ia	17
17	3.2 years	Anatomic	–	–	520	Ia	16
18	4.6 years	Anatomic	Transient dystonia, fever	–	900	IIIa	17
19	4.8 years	Hemidecortication	Hydrocephalus, deep infection	VPS	690	Ia	6
20	11 years	Anatomic	Subdural hematoma, fever	–	900	Ib	12

VPS Ventriculoperitoneal shunt, *SPS* subduroperitoneal shunt

outcome (class IVa) and now belongs to the class IIa. These results allowed to suspend the AEDs in nine patients (45%) and to reduce them in six other cases (30%).

Motor performances improved in nine children and remained stable in the other 11; no postoperative worsening were detected. To date, two patients present a grossly normal motor outcome and 12 are able to walk (with or without help). All the testable patients show a visual campimetric alteration; nevertheless, the real course of this deficit can not be established because of the lack of cooperation of the large majority of the children at the admission. As to the cognitive outcome, no patients reached a mental development adequate to their age, even though the postoperative performances improved in about a half of the cases and, nowadays, only six patients (30%) show a mild retardation. In one case, an initial worsening of the psychomotor development was found, despite the immediate good epileptic outcome (case no. 7). Six patients present a good social integration (30%) and seven (35%) a partial social integration; four patients are not integrated and the remaining three still present a very young age.

These results were obtained by using the anatomical hemispherectomy in 17 cases (including the three hemidecortications) and the functional techniques in the remaining three (four procedures, including one reoperation) (Table 2). Functional hemispherectomy/hemispherotomy was carried out in case of favorable anatomical conditions, such as large lateral ventricular system and /or atrophic affected hemisphere. As to the surgical timing, we tried to perform an early surgical treatment whenever possible. Actually, although the length of the seizures history and the age at surgery do not seem to play a statistically significant role on the epileptic outcome [47, 90], early surgery is advocated to save the psychomotor development as much as possible [7, 57, 80]. The age at surgery of the present series ranged from 3 months to 11 years (average of 25 months); 14 out of 20 patients were operated on within the second year of age (70%), and 10 of them where less than 10-month-old when they underwent the surgical treatment.

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