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Early hemispherectomy in catastrophic epilepsy A neuro-cognitive and epileptic long-term follow-up

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Summary The authors report their experience about a neuro-cognitive and epileptic long-term follow-up of children with catastrophic epilepsy treated with hemispherectomy in the first 5 years of life.

Nineteen children with resistant epilepsy that significantly interfered with their neuro-cognitive development underwent hemispherectomy within 5 years of life (mean: 2 years, 3 months; range: 5 months to 5 years). All patients were assessed before surgery and after, at least at the end of the follow-up (mean: 6 years and 6 months; range: 2–11 years and 2 months) with a full clinical examination including motor ability and functional status evaluation as well as behaviour observation, neuroimaging and an ictal/interictal prolonged scalp video-EEG.

A seizure-free outcome was obtained in 73.7% of patients. Gross motility generally improved and cognitive competence did not worsen, with an evident progress in two cases.

Consistently with previous reports, evolution was worse in cortical dysplasia than in progressive or acquired vascular cerebropathies. The excellent epileptic outcome and the lack of developmental deterioration in comparison with other more aged series seem to suggest a possible better evolution in earlier surgery treatment. To confirm this suggestion, however, further experience with larger series is needed.

Introduction

Hemispherectomy has been successfully used to treat various types of medically intractable

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hemispheric epileptogenic conditions, mostly in children and adolescents.[1–5] Indeed, the procedure has proved to provide excellent seizure control and improvement in the quality of life in a high percentage of the cases.[2,6–13]

In more recent times, increased interest has been paid towards the possible advantages of an early referral for elective surgery in infants and very young children. Several factors account for the progressively diminishing reluctance for an earlier treatment. First, the cumulated experiences of the deleterious effects of the so-called catastrophic epilepsies. Then, the conviction that a precocious removal or disconnection of the epileptogenic hemisphere may favour the compensatory reorganization of the healthy brain besides avoiding the interference of seizures with the early neurological development.[2,4,14] Further contributing factors should be identified in (1) the earlier recognition of an organic lesion and, consequently, the possibility of an early surgical indication, which is nowadays allowed by the modern diagnostic tools for anatomical and functional neuroimaging, (2) the reduced complication rate of this kind of operation, which results from the introduction of less heavy technical surgical variants, and (3) the progress in intraoperative anesthesiology and postoperative intensive care.

In the absence of randomized studies on early versus late surgery, which can not be proposed for ethical reasons, and in the light of the difficulty to compare relatively small and un-homogeneous clinical series, we considered that the report of our own experience, concerning 19 young children surgically treated in the first five years of life and fully investigated preoperatively and followed postoperatively for a relatively long period of time, could contribute to provide further insight into the outcome of young children undergoing hemispherectomy, with particular regard to the timing of the surgical treatment and the aetiologies of the epilepsy.

Patients and methods

Among the patients treated with hemispherectomy within 5 years of age in the Child Neurosurgery Unit of our Hospital, from 1980 to December 2003, we enrolled in the study only 19 thoroughly studied children, six of which had been reported in a previous paper.[10]

This study was retrospective for the patients who underwent hemispherectomy before December 1996, and prospective for those treated between January 1997 and December 2003.

The patients were examined for the surgical candidature after a non-effective drug treatment that made epilepsy to be considered refractory: epilepsy was considered drug resistant when at least three drugs at the maximal dosage were used without seizure control.

All patients were assessed in the Child Neurology Unit before and after surgery using a standard procedure as follows:

- full clinical examination with a detailed anamnestic history;
- ictal/interictal prolonged scalp video-EEG examination;
- neuroimaging (mainly, MRI);
- evaluation of motor abilities;
- neuropsychological assessment (general intelligence and specific abilities);
- behaviour observation;
- evaluation of functional status.

Generally, after surgery this procedure was performed at outcome; in some cases there was a serial assessment.

EEG and seizure evaluations

The pre-surgery EEG was aimed at evaluating type, localisation, extent, frequency and amplitude of interictal epileptiform discharges in both the affected and healthy hemispheres; the presence of independent, asymmetric or synchronic discharges was also considered. Moreover, ictal patterns were analyzed, with particular attention to the focal location of seizure onset and the type of extension.

Epilepsy was classified according to the International League Against Epilepsy (ILAE) classification (1989).[15]

Seizure outcome was assessed using the Engel's scale. Engel's classification[16] includes four classes of worsening epileptic outcome, ranging from a ''seizure-free'' condition (class I) to a ''not worthwhile improvement'' (class IV). Furthermore, every class is subdivided into sub-categories with different degrees of outcome severity (increasing from a to d).

Neuroimaging

All the patients studied from 1980 to 1992 (# 1, 2, 11, 14 and 15) underwent brain CT scan examination before and after surgery, using uninter-leaved 5 mm thick axial slices.

All the patients evaluated from 1992 to 1998 (# 4, 5, 6, 8, 9, 12, and 13) were examined using a 0.5 T

MR system (Vectra, General Electric, Milwaukee, USA) and those evaluated from 1999 to 2005 (# 3, 7, 10, 16—19) using a 1.5 Tesla MR system (Horizon Echospeed/Excite, General Electric, Milwaukee, USA). When requested, cerebral angiography or, more frequently, angio-MRI or angio-CT scan were performed.

MRI was repeated after surgery at least once and sometimes the neuroimaging control was performed with a CT scan.

Neurological evaluation

Motor function was pre and post-operatively estimated through the neurological evaluation. In addiction, to evaluate general motor skills, we used the Gross Motor Function Classification System (GMFCS).[17] Therapists who performed it received formal training in its use.

GMFCS is a scale conceived for children with cerebral palsy; it focuses on some basic postural or movement function such as truncal control and walking. Children are coded in five levels, from the best to the worse mobility (1—5), scored according to different ranges of age (0—2, 2—4, 4—6, and after 6 years). Since GMFCS deals with an ordinal scale whose graduation is not homogeneous, the measure of motor activity is approximate; yet, it is generally used to have an evaluation of the temporal changes in functional ability of children with cerebral palsy.

To measure visual field in the youngest children, we used a standardized method.[18]

Cognitive assessment

The assessment of cognitive development was performed using different scales as appropriate for the child's chronological age and level of functioning: Griffiths' Mental Development Scales or Uzgiris-Hunt Scales in children below four years, Wechsler Preschool and Primary Scale of Intelligence (WIPPSI) between 4 and 6 years, and Wechsler Intelligence Scale for Children-Revised (WISC-R) above six years.

We considered a Developmental Quotient (DQ) or Intellective Quotient (QI) higher than 85 as normal, borderline between 70 and 85, mildly impaired between 50 and 70, moderately between 35 and 50, and severely when lower than 35.

Functional status and behaviour

The functional status was determined by the observation of patients and interviews with parents, and was defined in three categories: (a) dependent, when full assistance was required including living functions (eating, dressing, etc), (b) semi-independent, when almost-adequate daily living functions were present, even though there were needs of special education programs and cares, and (c) independent, when children fully coped physical disabilities.

Behavioural features such as irritability, hyperactivity, aggressive behaviour and autistic traits were evaluated on the basis of family report and through clinical observations. Using the DSM-IV criteria, we defined the behavioural disturbances as (a) severe (+++) when associated with major

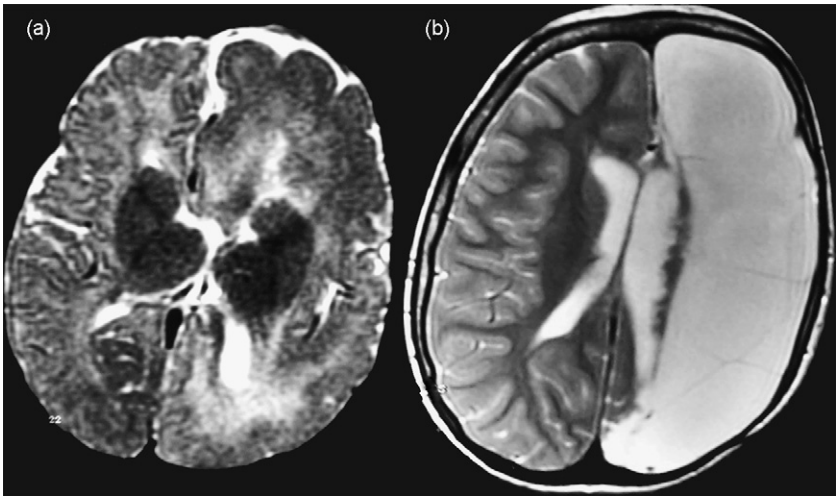

Figure 1 Hemimegalencephaly. (a) Preoperative axial FSE T2w MR image showing hamartomatous overgrowth of the left cerebral hemisphere, mainly due to marked enlargement of hemispheric white matter. The left frontal cortex exhibits an appearance suggestive of polymicrogyria; the lateral ventricle is deformed and distorted. Also note periventricular high signal in the frontal and parietal region resulting from heterotopia and gliosis in the white matter surrounding the enlarged ventricle. (b) Postoperative axial T2w MR image (4 years after anatomical hemispherectomy).

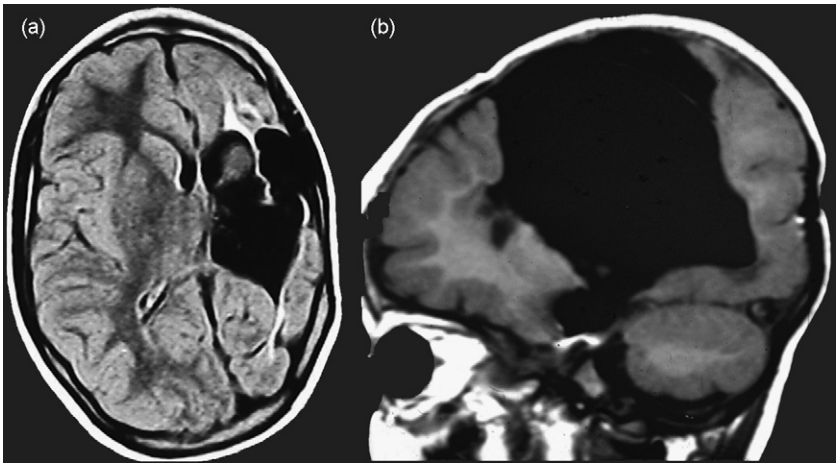

Figure 2 Poroencephalic cyst. (a) Preoperative axial FLAIR RM image showing extensive poro-encephalic left fronto-temporal cyst with involvement of basal ganglia region and thalamus; the left lateral cerebral ventricle and Sylvian fissure are dilated, ex-vacuo, the left hemicranium is clearly reduced in size. (b) Postoperative (functional hemispherectomy) sagittal RM T1w image.

disorders in communication and in social interaction, with autistic traits; (b) moderate (++) when characterized by a lower degree of these major behavioural troubles; and (c) mild (+) when minor social disorders, abnormal adaptive problems or major inhibition were present.

Results

Pre-surgery data

Neuropathology was ascertained by imaging (Figs. 1a, 2a, 3a and 4a) and confirmed after surgery by pathological examination of surgical specimens.

We divided our sample into three aetiological groups: patients with developmental pathology, with perinatal brain vascular injuries, and with progressive diseases. Developmental lesions included 13 hemimegalencephaly (Fig. 1a). Two cases presented with early acquired vascular pathology. They were affected with poroencephaly, one due to a MCA ischemic infarction (Fig. 2a) and one from a grade IV intraventricular hemorrhage (IVH).

The patients with progressive diseases were affected with Sturge—Weber disease (Fig. 3a) (three

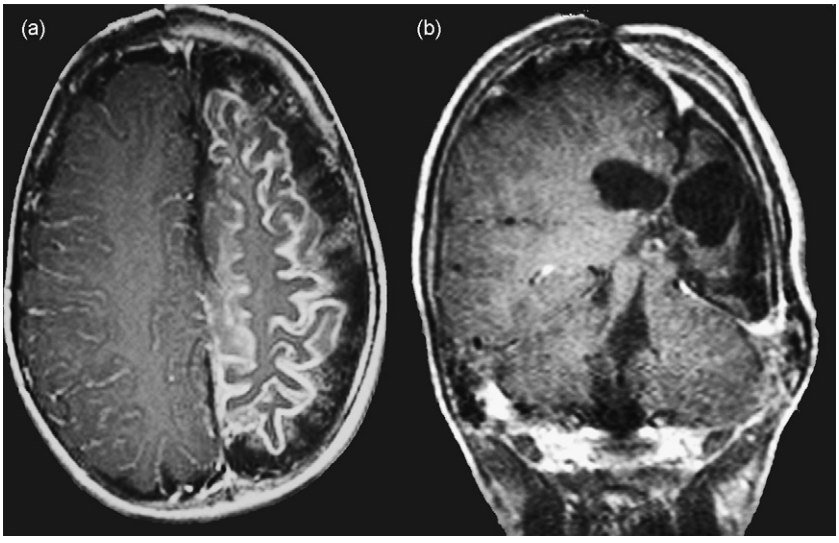

Figure 3 Sturge—Weber disease. (a) Preoperative Gadolinium-enhanced Axial FSE T1w MR image demonstrates enhanced cortical gyri of the atrophic left cerebral hemisphere. (b) Postoperative (hemidecortication) coronal FSE T1w MR image after iv gadolinium injection confirms the removal of the affected cortex and demonstrates the controlateral shift of the preserved normal hemisphere toward.

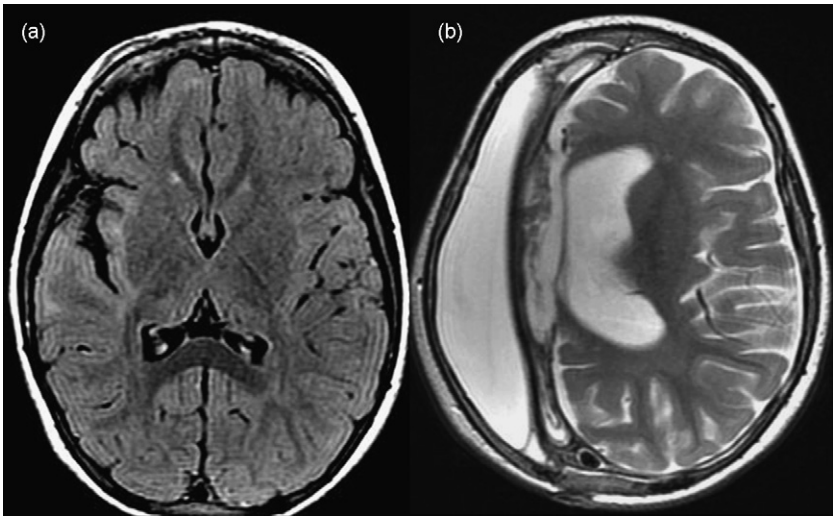

Figure 4 Rasmussen encephalitis. (a) Preoperative axial FLAIR MR images showing multiple areas of increased signal in the sub-cortical white matter of right insula, temporal and frontal lobes due to parenchymal gliosis, associated to a mild hemi-atrophy of the right hemisphere (see the enlarged right Sylvian fissure). (b) Postoperative axial post-surgical T2w MR image (2 years after anatomical hemispherectomy).

cases) or Rasmussen Encephalopathy (Fig. 4a) (one case).

As illustrated in Table 1, the onset of seizures was very early in cases with developmental disorder ranging between one and 60 days (median: one day); in the other groups there was a later onset, even though the median was always within the first months of life (4 months in acquired, 3 months in progressive). The age of surgery was variable according to the different categories, being earlier in disorders of development (median: 7 months), and later in acquired injuries (median: 5 years), while median in progressive diseases was 3 years.

Epileptic findings

Presurgical electroclinical characteristics are illustrated in Table 1.

Seizure semiology. All patients showed a pattern of partial motor seizures, isolated in four of them (three of which affected with Sturge—Weber syndrome and the other one with Hemimegalencephaly); in the remaining patients partial motor seizures were associated with one or more kinds of seizures. Spasms were observed in 12 patients, most of whom affected with hemimegalencephaly (10 cases). Tonic, genaralized tonic—clonic and myoclonic were the other types of seizures.

All patients had daily seizures. Twelve cases presented epileptic status (partial epileptic status in 10 patients and generalized tonic-clonic in 2; electrical epileptic status was observed in two cases.

Epileptic syndromes. According to the ILAE classification, epileptic syndromes consisted of Symptomatic partial epilepsy (SPE) in all cases, one of which was associated with epilepsia partialis continua and one followed by continuous spike waves during slow sleep (CSWS). Eight cases were affected with West syndrome and the remaining six cases with Ohtahara syndrome, both associated with SPE.

EEG features. Background activity in all patients was disorganized and asymmetrical. The disorganization was more severe in the group with developmental pathology (12 cases out of 13); unilateral burst-suppression pattern was observed in 7 of them and hemipsarrhythmia in 5. Prevailing abnormalities in the other etiological groups were focal (four cases) and multifocal (two cases) spikes and spike-waves. Continuous spike-waves appeared in three cases, in one of whom during sleep.

Paroxysmal activity was spreading syncronously on the other side in 16 patients, whereas independent contra-lateral paroxysmal activities were found in 7 cases (cases #. 1, 6, 7, 8, 16, 17 and 19).

In all patients ictal-EEG abnormalities were unilateral, ipsilateral to the side of changes highlighted by neuroimaging. Ictal activity usually spread towards the unaffected hemisphere. We never recorded the onset of seizures on the contralateral side.

Neurological features (Table 2)

On neurological examination, all patients presented a hemiparesis; in addiction 16 children showed a homonymous hemianopia and 2 a hemi-inattention;

Table 1 Clinical data at surgery

# Sex	Neuropathology	Age of seizure onset	Type of seizures	Frequency of seizures (drug number)	Epileptic syndrome	EEG patterns (hemisphere)	Age of surgery	Hemispherectomy	Complications
1 M	Dysplastic (grade II HME)	7 days	Partial, spasms, tonic, ges	Daily (6)	Othahara s.; West s.; SPE	BS (R)	4 years, 6 months	R anatomical	Transient dystonia and fever
2 M	Dysplastic (grade II HME)	1 day	Spasms, partial, pes	Daily (5)	West s.; SPE	BS (R)	9 months	R anatomical	Hydrocephalus
3[a] M	Dysplastic (grade I HME)	1 month	Spasms, partial, ees	Daily (3)	West s.; SPE	Hyps; CSW (R)	3 years	R anatomical	Transient dystonia and fever
4 M	Dysplastic (grade II HME)	1 day	Spasms, partial TCS, pes	Daily (2)	Othahara s.; SPE	BS (R)	7 months	R anatomical	Deep infection, hydrocephalus
5 F	Dysplastic (grade I HME)	2 months	Partial, tonic	Daily (2)	West s.; SPE	Hyps (R)	7 months	R anatomical	Subdural fluid collection
6 F	Dysplastic (grade II HME)	1 day	Partial, tonic spasms, myoclonic, pes	Daily (5)	Othahara s.; SPE	BS (R)	5 months	R anatomical	CSF leakage, hydrocephalus
7[a] F	Dysplastic (grade I HME)	1 day	Partial, tonic spasms, myoclonic, pes	Daily (3)	Othahara s.; SPE	BS (R)	6 months; 1 year	R functional, R hemidecortication	No
8 M	Dysplastic (grade II HME)	14 days	Partial, spasms, tonic, ges	Daily (6)	West s.; SPE	Hyps (R)	10 months	R functional	Superficial infection, hydrocephalus
9[a] M	Dysplastic (grade I HME)	1 month	Spasms, partial	Daily (5)	West s.; SPE	Hyps (R)	1 years, 8 months	R hemidecortication	Transient fever
10[a] F	Dysplastic	1 day	Partial	Daily (2)	SPE	Plurif. (L)	1 years, 7 months	L functional	No
11 M	Dysplastic	1 day	Tonic, partial, myoclonias	Daily (2)	Othahara s.; SPE	BS; Hyps (L)	7 months	L anatomical	Superficial infection, transient fever
12 F	Dysplastic	7 days	Partial, spasms, tonic, pes	Daily (6)	West s.; SPE	Hyps (L)	3 years, 2 months	L anatomical	No
13[a] F	Dysplastic (grade II HME)	1 day	Partial, spasms, tonic myoclonic, pes	Daily (6)	Othahara s.; SPE	BS; CSW (L)	4 years, 2 months	L hemidecortication	Deep infection, hydrocephalus
14 M	Progressive (Sturge—Weber)	3 months	Partial, pes	Daily (2)	SPE	Focal PO (L)	11 months	L anatomical	No
15 F	Dysplastic	3 months	Partial, pes	Daily (2)	SPE	Focal PO (L)	3 years	L anatomical	No
16[a] M	Dysplastic	5 months	Partial, pes	Daily (3)	SPE	Focal PO (L)	3 years, 3 months	L hemidecortication	No
17[a] F	Dysplastic (Rasmussen e.)	2 years, 8 months	Partial, myoclonic, pes	Daily (7)	SPE; EPC	Plurif (R)	4 years	R anatomical	CSF leakage
18[a] M	Acquired (MCA stroke)	3 months	Spasms, partial, ees	Daily (7)	SPE	Focal FCT; CSWS (L)	5 years	L functional	Transient fever
19[a] M	Dysplastic (grade IV IVH)	5 months	Spasms, partial, tonic	Daily (7)	West s.; SPE	Hyps; Plurif (L)	5 years	L Functional	No

TCS: tonic—clonic seizures; pes: partial status epilepticus; ges; generalized status epilepticus; ees; electrical epilepticus status; BS: burst-suppression; Hyps; hypsarrhythmia; CSW; continuous spikes and waves; CSWS: continuous spike-waves during sleep; Plurif: plurifocal; EPC: epilepsia partialis continua; SPE:symptomatic partial epilepsia; s: syndrome; PO: parieto-occipital; FT: fronto-temporal; FCT: fronto-centro-temporal; L: left; R: right. CSF: cerebrospinal fluid.

[a] Cases with a prospective study.

in case #17 (Rasmussen encephalitis) buccal dyspraxia and dyslalia were also observed.

GMFS showed a poor level (4/5) in all the dysplastic cases. The gross motility was good in the other patients, except in two, one with Sturge–Weber disease and one with vascular pathology.

Cognitive and adaptive development

The cognitive assessment is shown in Table 2.

A severe DQ or IQ impairment was observed in almost all the patients with developmental disorders (9/13, 69%) and only in one patient out of three with Sturge–Weber syndrome.

The retardation was much less relevant in the other patients with a progressive pathology, and with relatively more severe values (DQ/IQ between 40 and 50) in cases with perinatal brain injury. Among the children where analytical analysis was possible, a discrepancy between performance and verbal items was observed in three patients, with a better verbal competence in two cases (#10 and #19, both left injured children). On the contrary, in the remaining left-hemisphere injured patient (case # 18) performance items were better than verbal items.

Behaviour abnormalities (irritability, hyperactivity, aggressive and autistic behaviours) were present in eight cases (moderate in five cases, severe in 2, mild in 1). In the most of children (8 cases) behaviour was not valuable due to the young age.

Functional status

The functional status is illustrated in Table 2. Ten patients belonged to the category a (dependent); one to the category b (semi-independent) and eight cases were not valuable because of the young age.

Surgery procedures (Table 1)

The choice of the surgical technique was based on the results of preoperative neuroimaging studies. Actually, MRI and/or CT scan supplied useful dimensional and morphological information about the affected hemisphere, the ventricular system and the corpus callosum. In addition, cerebral angiography or, more frequently, angio-MRI or angio-CT scan, allowed to complete the surgical planning by showing the vascularization of the malformed side and the possible venous anomalies in the case of hemimegalencephaly. Such anomalies as the contralateral deviation of the median sinuses, hypoplasia of the deep venous system and hyperplasia of the superficial veins draining into the sagittal sinus were observable. On these grounds, anatomical hemispherectomy was adopted when the affected hemisphere was abnormally enlarged and vascularized, or presented a small and/or highly malformed lateral ventricle, or major anomalies of the venous structures, namely in patients with hemimegalencephaly. Functional hemispherectomy, on the other hand, was carried out mainly in children harbouring poroencephalic cysts, since the atrophic brain tissue and large lateral ventricle made transventricular disconnection safer and easier.

Anatomic hemispherectomy (Figs. 1 and 4b) was performed with piecemeal or, seldom, "en bloc" removal of the affected hemisphere. The basal ganglia were spared in the majority of the cases. In some instances, a more conservative surgical excision, namely hemidecortication, was performed (Fig. 3). In any case, a deep liodural patch was utilized to shelter the basal ganglia and reduce the homo-lateral shift of the midline due to cranio-cerebral disproportion. Functional hemispherectomy (Fig. 2) was performed according to the standard technique proposed by Rasmussen[6] or, more recently, as suggested by Villemure (peri-insular hemispherotomy).[19]

Fifteen out of 19 patients underwent anatomic hemispherectomy (four hemidecortications). Eleven of them (68.7%) were affected by hemimegalencephaly, while three presented Sturge–Weber syndrome. Another child suffered from Rasmussen's encephalitis. The remaining four children of the series (two with poroencephalic cysts and two with hemimegalencephaly) underwent functional hemispherectomy (two hemispherotomies). Only one child (case # 7), who had undergone functional hemispherectomy for hemimegalencephaly, required a further surgical procedure (hemidecortication) because of the initially poor results. In total, 20 surgical operations, including the second intervention in case # 7 (15 anatomic and 5 functional hemispherectomies) were performed (Table 1).

The mean age at operation of the whole series was nearly 2 years 3 months, ranging from 5 months to 5 years. With regard to the surgical technique, the mean age of the group treated by anatomic hemispherectomy was lower than that of those treated by a functional procedure (2 years versus 3 years 10 months). This data results from the preferential use of the anatomic technique for children affected by hemimegalencephaly who usually manifest early intractable seizures. In the present series, actually, these patients had a mean age of 21 months at operation which is notably shorter than that of the "non-hemimegalencephalic" children (3 years, 5 months). The low age and the unfavourable characteristics related to the hemimegalencephalic brain tissue such as the increased consistence and vascularization and severity of malformation, may

Table 2 Neurological, cognitive and adaptive development

Pre-surgical data							Outcome					
#	Side	Assessment age	Neurological deficits	DQ/IQ (VIQ; PIQ)	Functional status	Behaviour disorders	Assessment age	Neurological outcome	GMFCS (pre, post)	DQ/IQ (VIQ; PIQ)	Functional status	Behaviour disorders
1	R	4 years	HP, HA	29[b]	Dependent	+++	13.6 years	Unchanged	5, 5	25 (21; 23)	Dependent	+++
2	R	7 months	HP, HA	29[b]	NV	NV	15.8 years	Unchanged	5, 3	30 (18; 22)	Dependent	+++
3	R	2,8 years	HP, HA, strabismus	38 (43; 38)	Dependent	++	6.1 years	Improved	4, 1	50(50; 44)	Semi-independent	Absent
4	R	6 months	HP, HA	29[b]	NV	NV	12.4 years	Unchanged	5, 4	30 (27; 21)	Dependent	+++
5	R	6 months	HP, HA	89	NV	NV	9.11 years	Improved	4, 1	64 (69; 64)[a]	Independent	Absent
6	R	4 months	HP, HA	29[b]	NV	NV	8.11 years	Improved	5, 1	29 (34; 28)	Dependent	++
7	R	6 months	HP, HA	25 (29; 29)	NV	NV	3.10 years	Improved	5, 3	31 (32; 28)	Dependent	++
8	R	9 months	HP, HA	29[b]	NV	NV	8.5 years	Unchanged	5, 5	29 (23; 18)	Dependent	++
9	R	1.7 years	HP, HA	29 (31; 28)	Dependent	++	9.3 years	Improved	5, 1	12 (15; 11)	Semi-independent	++
10	L	1.6 years	HP, HA	42 (61; 41)	Dependent	Absent	4.4 years	Improved	4, 2	39 (47; 42)	Semi-dependent	Absent
11	L	6 months	HP, HA	29[b]	NV	NV	7.7 years	Unchanged	5, 2	29 (24; 23)	Dependent	+++
12	L	3.2 years	HP, HA	45	Dependent	Absent	12.9 years	Improved	5, 1	45 (59; 45)[a]	Independent	Absent
13	L	4.6 years	HP, HA, strabismus	29	Dependent	++	10.10 years	Unchanged	5, 4	21	Dependent	+++
14	L	10 months	HP, HA	29	NV	NV	9.10 years	Improved	5, 1	30 (32; 28)	Semi-dependent	++
15	L	2.10 years	HP, HA	69 (73; 69)	Semi-dependent	Absent	12.6 years	Improved	1, 1	85 (91; 80)[a]	Independent	Absent
16	L	3 years	HP, HA	64 (59; 52)	Dependent	+	5 years	Improved	4, 1	58 (67; 56)	Independent	Absent
17	R	4 years	HP, oral dyspraxia, dislalia	68 (69; 65)	Dependent	++	6 years	Deteriorated	1, 2	62 (82; 45)[a]	Independent	Absent
18	L	4.10 years	HP, HI	47 (35; 50)	Dependent	++	9.10 years	Improved	2, 1	40 (45; 36)	Semi-independent	+
19	L	4.6 years	HP, HI, strabismus	47 (64; 41)	Dependent	+++	6.6 years	Improved	4, 2	47 (60; 33)	Semi-independent	+

HP: hemiparesis; HA: hemi-anopsia; HI: hemi-inattention; GMFCS: Gross Motor Function Classification Scale; NV: not valuable.

[a] Weschler scales.

[b] Uzgiris Hunt scale.

explain the higher risk of complications and the longer duration of surgery for this group of patients. Indeed, the incidence of complications — mostly mild — among the hemimegalencephalic patients was 76.9% (10 out of 13 cases), whilst it was only 33.3% among the remaining children (2 out of 6 cases).

Surgical morbidity

In the present series, classical anatomic hemispherectomy was associated with a complication rate of 72.7% (8/11 procedures), which included however mild complications such as transient fever (four cases), transient cerebrospinal fluid (CSF) leakage from the surgical wound (two cases), transient dystonia (two cases) superficial infection of the surgical wound (one case). Two children had CSF postoperative infections. All the patients operated were transfused intraoperatively and the mean blood volume replaced was 550 ml. The incidence of long term complications, namely hydrocephalus (four cases) or subdural fluid collection (one case), was 33.3% (5/15 procedures). All these last five patients required a permanent CSF shunt device. The mean duration of surgery was 6.2 h.

Although the overall rate of complications for functional hemispherectomy was high (50%; 2/4 procedures), it was still less than that for anatomic hemispherectomy. Actually, one child with postoperative sequelae experienced a short term complication (transient fever), while the remaining child required a permanent shunt for a subdural hygroma. Blood transfusion was necessary in all but one patients (mean volume: 320 ml). This kind of operation required 3.3 h on average to be completed.

Post-surgical data

The mean period of the follow-up was 6 years, 6 months (range: 2—11 years and 2 months).

The *seizure outcome* is illustrated in Table 3, where different follow-up periods were considered: 6 months, 1, 2, 5 and >5 years. In the final seizure outcome, according to Engel's classification, 73.7% (14/19) of children were seizure free (class I), 10.5% (2/19) were in class IIa, and 15.8% (3/19) in class IIIa.

The seizure outcome seemed dependent on aetiology and on surgical procedure. There was an optimal (Ia or Ib) outcome in all cases with vascular brain injuries and in those with progressive diseases. In developmental pathology, six out eight (75%) children who underwent classic anatomic hemispherectomy were in Engel's class I throughout all the follow-up. On the contrary, the percentage of children with good epileptic outcome after other kinds of hemispherectomy (functional and hemidecortication) decreased progressively to only 40% on final evaluation (Table 3).

The patients with persistent seizures (Table 4) belong all to the dysplastic group. The first MRI did not show in all the cases any contra-lateral change, but control MRIs after surgery when the age of infants allowed more precise image definition presented in two patients (#1 and 8) a focal cortical dysplasia contralaterally, consistently with persistent EEG contra-lateral abnormalities, even preexistent to surgery. In other two patients (#4 and 9), contra-lateral EEG abnormalities appeared several years after surgery and there was no evident structural change at neuroimaging. In the last one case (# 7) showing ipsilateral EEG abnormalities seizures are possibly the result of an incompletely disconnected cortical region. Trying to achieve a complete disconnection, case # 7 was the only patient re-operated; the result was an improvement of seizures that changed from Engel's class IV to class II.

Other four seizure-free patients showed EEG abnormalities after surgery: two of them belong to the same dysplastic group (# 10 and 13) and two to the vascular group (#18 and 19).

If we consider now the surgical technique used in the nine cases with persistent EEG abnormalities after surgery (five of which with seizures), we find seven children operated on with hemidecortication or functional hemispherectomy. In three patients EEG abnormalities were located ipsilaterally, showing a residual epileptiform activity in the pathologic hemisphere, that is spreading contralaterally in one case suggesting a possibly incomplete disconnection.

Five patients were no longer taking anti-epileptic therapy at the end of the follow-up. Weaning of aed had begun after two years of complete control of seizures, only in cases without significant EEG abnormalities; discontinuation was very slow and progressive (about six months for each drug). The median of the medication number in the remaining 14 children was only one (range 1—3).

On *neurological follow-up* (Table 1). Hemiparesis seemed to be improved in 12 cases. No change was observed in 6 other patients, whereas in the case of Rasmussen syndrome there was only a moderate worsening. GMFS showed a definite improvement in the majority of dysplastic patients (7 out of 13) and in two patients of the remaining groups that had presented poor gross motility before surgery.

Cognitive outcome (Table 2). The majority of patients with developmental pathology presented an unchanged cognitive assessment, 9 in the severe

Table 3 Epileptic outcome (Engel classification '87)

No.	6 months	1 years	2 years	5 years	> 5 years	EEG abnormalities.	AED	Follow-up (years)
1	IIIb	IIIb	IIIa	IIIa	IIIa	Yes (diffuse continuous awake and sleep contralateral)	Two drugs	9.6
2	Ia	Ia	Ic	Ic	Ic	No	One drug	11.1
3	Ia	Ia	Ia			No	One drug	3.5
4	Ib	Ib	Ib	Ib	IIa	No	No	11.2
5	Ia	Ia	Ia	Ia	Ia	No	No	9.5
6	Ia	Ia	Ia	Ia	Ia	Yes (focal subcontinuous sleep contralateral)	One drug	8.7
7	IVa, Ia	IIa	IIa			Yes (focal ipsilateral)	Two drugs	3.4
8	IIb	IIIa	IIa	IIIa	IIIa	Yes (focal contralateral)	Three drugs	7.8
9	Ib	Ib	IIb	IIIa	IIIa	Yes (focal sleep contralateral)	Three drugs	7.8
10	Ia	Ib				Yes (focal ipsilateral spreading contralaterally)	Two drugs	2.10
11	Ia	Ia	Ia	Ia	Ia	No	No	7.1
12	Ia	Ia	Ia	Ia	Ia	No	No	9.7
13	Ia	Ia	Ia	Ia	Ia	Yes (focal contralateral)	One drug	6.4
14	Ia	Ia	Ia	Ia	Ia	No	No	9
15	Ia	Ia	Ia	Ia	Ia	No	No	9.8
16	Ia	Ia				No	Two drugs	2
17	Ia	Ia	Ia			No	Three drugs	2
18	Ib	Ib	Ib	Ib		Yes (multifocal ipsilateral)	One drug	5
19	Ib	Ib	Ib			Yes (sporadic focal contralateral)	Two drugs	2

Table 4 Patients with persistent seizures after surgery

Case #	Neuropathology	Epileptic syndrome	Seizure onset	EEG patterns (hemisphere)	Contralateral EEG abnormalities Synchron. Indep.	Neuroimaging before surgery	Surgical technique	Neuroimaging after surgery	Engel's class. (outcome)	EEG abnormalities after surgery	
1	Dysplastic (grade II HME)	Othahara s.; West s.; SPE	7 days	BS (R)	Yes	Yes	Right hemimegalencephaly, no apparent contralateral changes	R anatomical	Focal contralateral dysplasia	IIIa	Yes (diffuse continuous awake and sleep contralateral)
4	Dysplastic (grade II HME)	Othahara s.; SPE	1 day	BS (R)	Yes	No	Right hemimegalencephaly, no apparent contralateral changes	R anatomical		IIa	Yes (focal contralateral)
7[a]	Dysplastic (grade I HME)	Othahara s.; SPE	1 day	BS (R)	Yes	Yes	Right hemimegalencephaly, no apparent contralateral changes	R hemidecortication		IIa	Yes (focal ipsilateral)
8	Dysplastic (grade II HME)	West s.; SPE	14 days	Hyps (R)	Yes	Yes	Right hemimegalencephaly, no apparent contralateral changes	R functional	Focal contralateral dysplasia	IIIa	Yes (focal contralateral)
9[a]	Dysplastic (grade I HME)	West s.; SPE	1 month	Hyps (R)	Yes	No	Right hemimegalencephaly, no apparent contralateral changes	R hemidecortication		IIIa	Yes (focal sleep contralateral)

BS: burst-suppression; Hyps: hypsarrhythmia; SPE:symptomatic partial epilepsy. s: syndrome R: right.
[a] Cases with a prospective study.

and two in the moderate range. Only case #3 presented a significant improvement of IQ. The only case with a normal cognitive competence before surgery (case #5), subsequently presented a mild retardation; she was, oddly, seizure free from soon after surgery.

In the group with progressive pathology, cognitive development was permanently in the range of mild retardation in two cases, whereas there was more than a 10 point improvement in IQ following surgery in case # 15, who moved from the mildly impaired to the borderline category. Only in one child with Sturge–Weber syndrome mental retardation was always severe.

In the two cases belonging to the group with acquired pathology, cognitive outcome was unchanged in the range of moderate retardation.

In all the cases where detailed cognitive data are available at outcome, verbal items were better that performance ones regardless of the side of hemispherectomy.

Functional status and behaviour. Among the cases of developmental pathology, pre-surgery functional status had been valuable only in six infants; at outcome, four improved and two remained permanently dependent. Out of seven cases not valuable before surgery, six presented dependent functional status and one independent.

All the patients of the other etiological groups but one, not valuable before surgery, showed an improvement of functional status.

All cases but one not valuable before surgery presented behavioural disorders after surgery. Of the four children with developmental pathology that presented with pre-operative *behavioural disorder*, one significantly improved after surgery; two were unchanged and one deteriorated. All the patients of the other groups but one showed a definite improvement.

Interestingly, the five cases with improved behaviour were also seizure free.

Discussion

Surgery is performed evermore to treat drug-resistant epileptic children, not only for life-threatening diseases or progressive neurological disorders. Hemispherectomy is a surgical technique largely used in epileptic children with brain hemispheric dysfunction. Several reports concerning children cohorts including infancy with drug-resistant epilepsy, whose hemispherectomy produced favourable results, are now available.[2,4,9,11–13,20–27]

Surgical complications such as hydrocephalus, subdural fluid collections, CSF leakage, deep and superficial infections, are usually reported to be frequent. In our series, complication rate is similar to that reported in recent series, and no death was observed. An excellent seizure control was obtained in 74% of patients (Engel's class I). Even though other cohorts are hardly comparable, especially because of differing neuropathological composition, surgical techniques and variable follow-up duration, our results are particularly rewarding in comparison with other series, including those like ours with young children of the first years of life.[9,13] Our results seem particularly relevant if we consider the generally long follow-up and the etiological composition of the sample, mostly consisting of developmental pathology. Indeed, our data confirm the results of the Great Ormond series[11] regarding the seizure outcome of aetiological groups; developmental pathology presents the worst outcome whereas acquired and progressive pathology is associated with a better epileptic outcome. In fact, the only cases with persistent seizures after surgery were affected with hemimegalencephaly. The analysis of these cases shows in two patients the presence of a contra-lateral focal dysplasia not evident at pre-surgery neuroimaging due to early age. This late detection has been reported in literature.[28] Even though in the other cases of our series unapparent cortical dysplasia can not be excluded on the mere base of MRI, as reported in literature,[29,30] in two patients treated with an hemidecortication a pathogenic role of a possible incomplete disconnection of the megalencephalic hemisphere seems to be more probable, as Gonzalez-Martinez et al.[13] have correctly emphasized in their children. Post-operative MRIs may easily fail to reveal incomplete disconnection.[13]

The general good epileptic outcome of our series is also confirmed by the weaning from antiepileptic drugs at outcome in six cases. In another three seizure-free patients (# 10, 16 and 17), even though in absence of EEG epileptic abnormalities, the weaning was not allowed due to the short follow-up.

Similarly to the epileptic evolution, also the *neurological evolution* presented in our series a general improvement of motor skills, particularly of gross motility. The lack of motor improvement is not always related to seizure post-surgery persistence. The improvement in motor abilities is however unique if compared to other series.[11,31] The relatively longer follow-up of our patients may account for a better final motor outcome. Indeed, in Gonzalez-Martinez et al. series[13] a general partial recovery of the proximal motor function was described. A general improvement of gross motor function is also reported in a more detailed study on the functional consequences of hemispherectomy.[30]

The suggestion that children with better cognitive development before hemispherectomy present a better improvement in motor function after surgery[11,32] was not confirmed by our cohort like by van Empelen's series;[30] larger samples are needed however to draw any conclusion. The worsening outcome in our sample concerned only the case with Rasmussen encephalopathy, and this is consistent with other observations.[11]

The cognitive outcome of our cases, as in other larger cohorts,[11,33] does not seem as positive as epileptic outcome. Yet, it is noteworthy that surgery mostly did not impose a further developmental worsening. Rather, we found an improvement in IQ of more than 10 points in two cases possibly due to a cortical reorganization after surgery and seizure control, about the same percentage found in patients from John Hopkins study.[33] As in other studies[11,33] the dysplastic group had the least favourable presurgery cognitive development and outcome. Persistent post-surgery seizures do not seem evidently related to lower IQ at outcome, as reported by Pulsifer et al.[33] Yet, in spite of some behavioural disorder, functional status of the 4 children out of the six that it was possible to evaluate before surgery improved at outcome, possibly suggesting a better adaptive behaviour.

Among the three patients affected with **Sturge—Weber disease in our sample, two were the cases with presurgery IQ relatively preserved; one of them even improved reaching the normal range at outcome. This post-operative improvement had been emphasized in Sturge—Weber patients.[34,35]

The patient with Rasmussen encephalopathy showed only a mild deterioration, consistently with what happened to the numerous cases reported by Pulsifer et al.[33]

Differently from Pulsifer's[33] and Korkman's[36] experience, right-side injury seems to be associated with worse development.

Interestingly, consistently with previous experience concerning unilateral brain injured children,[37,38] hemispherectomised patients had always better verbal skills than performance and visuo-motor competence independent of the side of hemispherectomy.

Behavioural disturbance were unevenly distributed, being nearly generalised in dysplastic patients and almost absent in the other groups.

Adaptive functioning was generally low. Even if motor abilities improved in a large percentage of patents, visual-motor impairment applicable to everyday life was significant. Yet, the improvement of social skills and the parents' better involvement and acceptance of the child's condition possibly made the disease more acceptable.

The general post-surgical better outcome compared with other series including those with younger children provides further support to the hypothesis of a better effectiveness of early surgery. Possible underlying mechanisms are neuroplasicity in early life and the control of seizures whose detrimental effects on neurodevelopment is well known.[39]

Conclusions

(1) First of all, the predictive value of some presurgery factors such as neuropathology,[40] and better presurgery cognitive development[32] is confirmed.
(2) Even though there is a study on resective surgery of children with infantile spasms that seems to assert a better developmental outcome in earlier surgery[41] stressing the better evolution of earlier treated cases, this conclusion still remains a convincing but speculative suggestion. The general higher percentage of seizure control in our series so as in cohorts of young children treated in the first years of life[9,11] in comparison with large series of children and adolescents could support such a suggestion, which should be proven by larger controlled studies.
(3) In our series the majority of patients, especially in hemimegalencephalic group, were treated with classical anatomical hemispherectomy. Their comparison with cases with a different type of hemispherectomy, especially functional hemispherectomy, puts in evidence a possible greater risk in those cases of leaving active epileptogenic tissues, as reported by others, who observed in functional hemispherectomy the highest rate for recurrent seizures.[42] Moreover, one should consider that in the prolonged follow-up of our cases in which non classical anatomical hemispherectomy was performed, the persistence of EEG abnormalities, particularly bilateral, has discouraged drug weaning, with possible negative consequences on development. On the other hand, surgery complications in classical anatomical hemispherectomy seem less relevant in selected patients,[43] in particular in hemimegalencephalic patients according to the indications previously proposed[2,5,10] and more recently emphasized,[13] stressing the specific technical difficulties in such cases.
(4) Our experience with young children seems to confirm that the success of surgery for epilepsy is not reflected by the control of seizures alone.[21] Developmental improvement, as well

as the recovery of motor abilities and better behaviour, are more adequate measures of the efficacy of surgery outcome.

(5) The limited experience so far collected in few specialized centres makes this cost/benefit evaluation difficult. More data are needed to chart the improvement of cognitive competence in individual cases, the role played by seizures per se, their type, duration, frequency, and relationship to critical brain plasticity periods, the drugs, the age of surgery, and the role of different aetiologies, location and extension of lesions. Finally, the connections between biological factors and social outcome should be studied. Only larger paediatric prospective collaborative studies can give answers to these questions.

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