

Hemimegalencephaly and Epilepsy: An Overview

Vera C. Terra-Bustamante*, Hélio R. Machado**, Américo C. Sakamoto*

Ribeirão Preto School of Medicine, University of São Paulo, Brazil

ABSTRACT

Introduction: Cerebral cortical development is a highly complex process influenced by environmental, genetic and functional abnormalities. Hemimegalencephaly (HME) is a rare brain malformation that involves overgrowth of one hemisphere. Clinically macrocephaly, mental retardation, contralateral hemiparesis, hemianopsia and intractable epilepsy may be present. Diagnosis is mainly done with image and clinical findings. MRI typically reveals an enlarged cerebrum involving at least one lobe, with a thickened cortex; broad gyres; abnormal gray-white matter differentiation with abnormal sign; neuronal heterotopia, ventricle asymmetry, and basal ganglia and internal capsule abnormalities. Electroencephalographic abnormalities usually involve the affected hemisphere, with an asymmetric amplitude of the normal, age-related rhythms; slow, rhythmic or fast activity and multifocal unilateral or bilateral high-amplitude spikes and spike-wave complexes. Histopathologic changes include abnormal gyrification, with loss of cortical lamination, neuronal heterotopia, gliosis, large bizarre neurons and balloon-cells. The presence of highly refractory seizures in patients with HME is an important factor to consider epilepsy surgery in these patients. **Methods:** Multiple surgical techniques are actually being used for hemispheric disconnection. We discuss here the main surgical techniques that are used for hemispheric disconnection. **Conclusions:** Postsurgery outcome for HME may be not as good as that for focal lesions with approximately 40% of patients being seizure free, but the main indication for surgery in these patients may be preventing additional cognitive injury and developmental delay. Surgical complications are observed in most of the series of patients with HME submitted to hemispheric surgery. Minimal resections may contribute to diminish surgical complications.

Key words: hemimegalencephaly, epilepsy, surgery.

RESUMO

Hemimegalencefalia e epilepsia: uma revisão

Introdução: O desenvolvimento cortical cerebral é um processo altamente complexo influenciado por fatores ambientais, genéticos e funcionais. A hemimegalencefalia (HME) é uma malformação cerebral rara que envolve o crescimento anormalmente maior de um hemisfério cerebral. Clinicamente há macrocefalia, retardo mental, hemiparesia contralateral, hemianopsia e epilepsia intratável. O diagnóstico é feito pelos achados clínicos e de imagem. A ressonância magnética revela aumento do encéfalo que envolve ao menos um lobo, com afilamento cortical e alteração da diferenciação da transição branco-cinza, com alteração do sinal. Observa-se ainda heterotopia neuronal, assimetria ventricular e alterações dos gânglios da base e da cápsula interna. As alterações eletrográficas geralmente envolvem o hemisfério afetado, com assimetria da amplitude dos ritmos idade relacionados. São observados ainda paroxismos epileptiformes do tipo pontas, polipontas ou ponta-onda, multifocais unilaterais ou bilaterais, descargas rápidas. As alterações histopatológicas incluem giração anormal, com perda da laminação cortical, heterotopia neuronal, gliose, presença de neurônios bizarros e células em balão. A presença de crises epiléticas intratáveis em pacientes com HME é um fator importante para a indicação do tratamento cirúrgico. **Métodos:** Múltiplas técnicas cirúrgicas são atualmente utilizadas, predominando as técnicas desconectivas. Serão discutidas aqui as principais técnicas cirúrgicas empregadas nas desconexões hemisféricas. **Conclusões:** O prognóstico pós-cirúrgico é pior do que em outras formas de lesões focais, sendo que aproximadamente 40% dos pacientes tornam-se livre de crises,

* Department of Neurology, Psychiatry and Psychology, Ribeirão Preto School of Medicine, University of São Paulo, Brazil.

** Department of Surgery, Ribeirão Preto School of Medicine, University of São Paulo, Brazil.

Received Mar. 30, 2006; accepted May 26, 2006.

mas a principal indicação para o tratamento cirúrgico é, além da redução da frequência de crises a prevenção da instalação de novos déficits neurológicos. Complicações cirúrgicas são observadas na maioria das séries de pacientes com HME submetidos ao tratamento cirúrgico. Ressecções menores podem contribuir na diminuição destas complicações.

Unitermos: hemimegalencefalia, epilepsia, cirurgia.

INTRODUCTION

Cerebral cortical development is a highly complex process and can be divided into three steps that included cell proliferation, neuronal migration and cortical organization⁽¹⁾. The normal development of these three steps may be modified by multiple causes such as environmental or acquired factors, genetic and functional abnormalities. The main environment factors are related to pregnancy and deliver, including any factor that may affect the pre-natal phase, as infections or hypoxia. Genetic factors may include chromosome deletions or duplications, X inactivation or mosaicisms. Genetically, brain development ontogenesis is programmed and controlled by organizers and regulators genes, but the way these genes are up and down regulated is not clear and the same genes may have different functions in different ages⁽²⁾. An abnormal regulation of these genes may contribute to the occurrence of cortical developmental malformations. Functionally, clinical expression of central nervous system malformations may vary widely and the extension of anatomic defects do not predict clinical manifestation.

Hemimegalencephaly (HME) is a rare, sporadic and nonfamilial congenital brain malformation with a low recurrence rate, even when associated with neuro-

cutaneous syndromes. HME involves overgrowth of a part of one hemisphere, an entire hemisphere or a hemisphere and part of the other side. Hypertrophy of the ipsilateral cerebellum and brainstem may be seen, with enlargement of skull. HME was originally described by Sims⁽³⁾ and is classified as a malformation of cortical development due to non-neoplastic abnormal cell proliferation or apoptosis⁽¹⁾, having characteristic image findings. Although HME causes are unknown it is correlated to insults during the first month to the second trimester of pregnancy⁽⁴⁾.

HME may be an isolated finding or be associated with a genetic syndrome. The real proportion of isolated and syndromic cases is not clear in the literature, since most of the papers do not describe sufficient clinical data to support diagnosis of the different syndromes. Tinkle et al.⁽⁵⁾ reported a series of 29 patients with HME, with 47% of them were syndromic. The most common syndromes associated with HME are epidermal nevus syndrome, Proteus syndrome, Encephalocraniocutaneous lipomatosis, hypomelanosis of Ito, Klippel-Trenaunay syndrome and tuberous sclerosis complex (Figure 1)^(1,3,5,6,7). The association of HME and tuberous sclerosis complex is extremely rare, with few reports in the literature^(8,9).

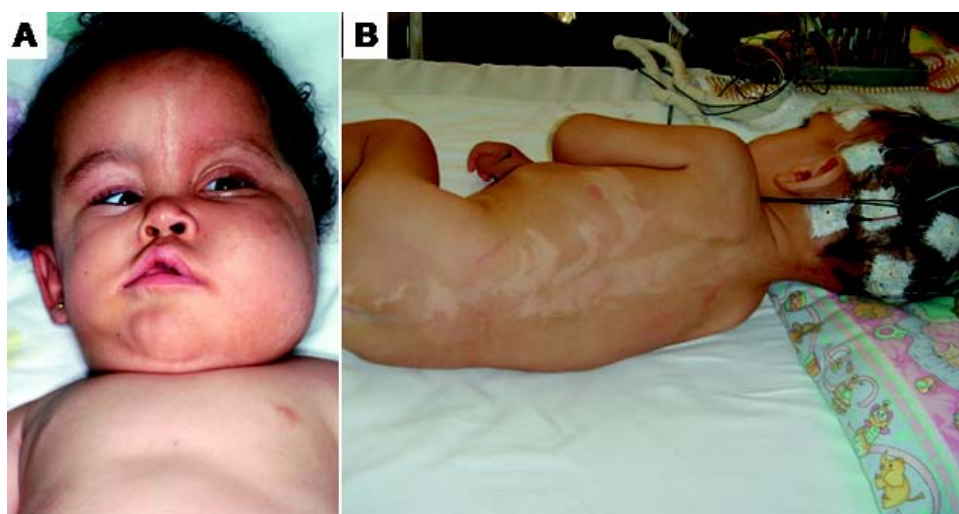


Figure 1. Syndromes associated with HME. **A.** A patient with epidermal nevus syndrome. **B.** A patient with hypomelanosis of Ito.

Clinical features include usually macrocephaly without signs of clinical intracranial hypertension at birth. Latter symptoms are some degree of mental retardation, intractable epilepsy, contralateral hemiparesis and hemianopsia, although some cases of near normal neurological development occur^(10,11). Language and motor impairment are usually worst than in patients with focal cortical dysplasia⁽¹²⁾. Hemifacial or hemicorporal hypertrophy of the body and macrodontia may be present, and in rare cases facial lipomatosis is observed and some authors had related contralateral micrencephaly^(3,5,13,14,15,16). Seizures are a common symptom, related in up to 100% of cases¹⁷ and usually start within the first six months of life. They may be of partial onset, infantile spasms, *epilepsia partialis continua* or drop attacks^(7,11). Non-convulsive *status epilepticus* and atypical seizure types are related in the literature and some authors had reported epileptic negative myoclonus^(18,19).

CLINICAL DIAGNOSIS AND INVESTIGATION

Diagnosis is mainly done with image and clinical findings. Clinical diagnosis may be done in syndromic cases but brain image is essential in isolated cases. Prenatal ultrasound examination may reveal hydrocephalus and macrocrania⁽²⁰⁾. Prenatal Magnetic resonance image (MRI) may reveal the ventricular enlargement and restricted diffusion suggesting increased cellularity and advanced myelination in the affected hemisphere⁽²¹⁾. In neonates, cranial sonographic findings include hemisphere enlargement, thickening of the lateral ventricle, periventricular white matter thickened with increased echogenicity and displacement of midline structures⁽²⁰⁾.

Post-natal MRI usually allows the correct diagnosis and typically reveals an enlarged cerebrum involving at least one lobe, with a thickened cortex; broad gyres; abnormal gray-white matter differentiation with abnormal sign; neuronal heterotopia, ventricle asymmetry, and basal ganglia and internal capsule abnormalities. The occipital lobe enlargement usually leaves it to shift across de midline^(7,22,23). Posterior quadrant dysplasia, involving the occipital, parietal and temporal lobes of one hemisphere may represent a less severe variation or a partial HME, with similar clinical and pathological findings⁽⁶⁾.

In patients with association of HME and tuberous sclerosis complex one hemisphere may present with pachygyria, high intensity white matter images, subependymal glial nodules and diffuse mineralization (Figure 2). The affected hemisphere may become smaller with disease progression and might not be larger than the opposite normal hemisphere at the time of imaging. The non HME hemisphere may be normal or have cortical tubers^(8,9).

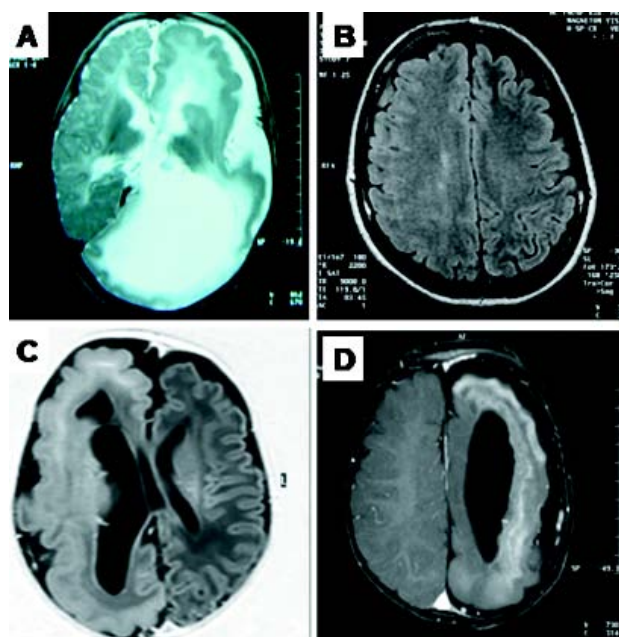


Figure 2. Magnetic resonance image in patients with HME. **A.** Same patient showed in Figure 1A with epidermal nevus syndrome. Note the occipital lobe enlargement with shift across de midline. **B.** HME with abnormal gray-white matter differentiation and sign. **C.** HME in a 2 months boy with continuous focal motor seizures. **D.** Association of HME and tuberous sclerosis complex, with an almost normal contralateral hemisphere.

Magnetic resonance spectroscopy in the affected hemisphere showed a decrease in white matter glutamate, N-acetylaspartate and creatine, with less severe changes or no changes in cortical gray matter, with mild metabolic affection of contralateral normal white matter. These findings generally reflect irreversible loss or damage of neuroaxonal tissue⁽²⁴⁾.

Electroencephalographic abnormalities usually involve the affected hemisphere, with an asymmetric amplitude of the normal, age-related rhythms; slow, rhythmic or fast activity and multifocal unilateral or bilateral high-amplitude spikes and spike-wave complexes. Interictal bilateral discharges may be generalized or independent. In the first months of life, unilateral suppression burst pattern or hypsarrhythmia may be present. An age-dependent epileptic encephalopathy corresponding to each particular development stage may be observed, and include Ohtahara's Syndrome, West's Syndrome and Lennox-Gastaut Syndrome. *Epilepsia partialis continua* may be observed and usually aggravate motor function and development^(7,11,25). When abnormalities are unilateral, they usually are observed in the structurally abnormal side. Ictal abnormalities may be composed of unilateral or diffuse fast rhythmic activity that's build-up or bilateral independent activity⁽²⁵⁾.

Functional examinations as PET (positron emission tomography) and SPECT (single-photon emission computed tomography) study cerebral blood flow and glucose metabolism, classic markers of neuronal function. In patients with HME, cerebral blood flow is usually increased in the affected side. Some studies had shown that an increase in blood flow is also observed at the normal hemisphere, suggesting it may be involved in the epileptogenesis by the presence of diffuse spikes. These findings are reversible with the disconnection of the malformed cortex and the disappearance of bilateral spikes. The delay of the surgical treatment may contribute to the development of bilateral independent Interictal spikes and the definitely epileptogenesis organization in the non-HME side, supporting the indication of operating patients with HME as soon as possible⁽²⁶⁾.

PATHOPHYSIOLOGY

Histopathologic changes include abnormal gyrification, with loss of cortical lamination, neuronal heterotopia, marked gliosis, large bizarre neurons and non-neuronal large cells, called balloon-cells^(5,27). Neurons are characterized by expanded dendritic trees and prominent somatic processes. Balloon cells are usually multinucleated and have a fibrillary gliosis. The origin of balloon cells is uncertain and they may be cells that failed to differentiate at very early stages⁽¹⁾. Some of the observed alterations are similar to those observed in tuberous sclerosis syndrome, although ultrastructural cell examination showed differences between balloon cells of HME and tuberous sclerosis patients⁽²⁷⁾.

Cellular and molecular abnormal neurotransmitter expression are being related in patients with HME. Reduced expression of NMDA mRNA and enhanced expression of the GLT-1 glutamate-uptake site mRNA was observed by Baybis et al.⁽²⁸⁾, suggesting a change in cellular excitability. The effects of recurrent seizures in this process

is difficult to analyze, but the presence of different expression in some pathologies such as tuberous sclerosis and a similar expression in others like linear sebaceous nevus suggests that a common mechanism may be present, leading to a high epileptogenicity in HME. Also, increased expression of nerve growth factor (NGF) was observed in HME patients. NGF play a role in neuroblast maturation and its elevation may be associated with HME pathogenesis⁽²⁸⁾.

The presence of clinical and image signs of HME and dysembryoplastic neuroepithelial tumor (DNT) was described by Specchio et al.⁽²⁹⁾. The authors related a patient with an enlarged right hemisphere with a more localized high signal in MRI. The neuropathology of the removed tissue was compatible with DNT and focal cortical dysplasia. This association in focal lesions was already described and suggests that this tumor may have a similar origin or developmental mechanism as cortical dysplasia⁽³⁰⁾.

SURGICAL TREATMENT

The presence of highly refractory seizures in patients with HME is an important factor to consider epilepsy surgery in these patients. Pre-existing hemiplegia or a dense deficit with non functional hand, with visual field deficit are arguments favoring an hemispheric approach, although the absence of previous deficits do not exclude the surgery, specially in circumstances of progressive diseases, such as Rasmussen Syndrome.

Multiple surgical techniques are actually being used for hemispheric disconnection^(31,32). The surgical approach depends of the extension of the lesion and the experience of the neurosurgeon. Large ventricles certainly helps allowing more space for surgeon to work. In HME the great difficulty is related to distortion of the brain and in this circumstance even large ventricles can sometimes be misleading (Figure 3).

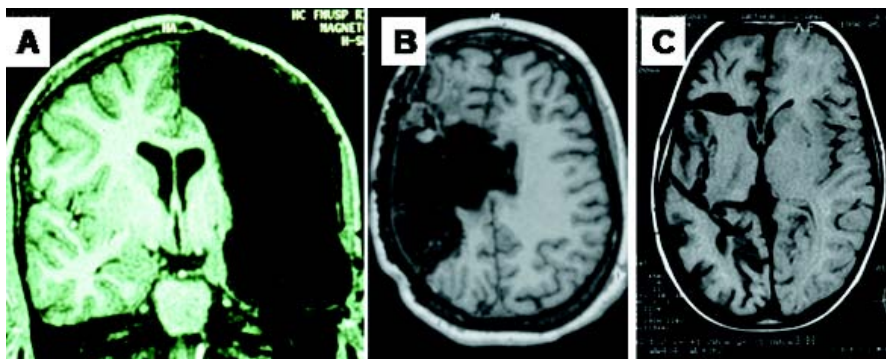


Figure 3. Surgical techniques used for hemispheric disconnection. **A.** Anatomic hemispherectomy. **B.** Functional hemispherectomy. **C.** Hemispherotomy.

Anatomic hemispherectomy was the first technique employed in patients with hemispheric lesions and involved removal of all cerebral cortex, the insula and sometimes portions of the basal nuclei⁽³³⁾. It has been almost abandoned because of the delayed complications of the procedure, which included obstructive hydrocephalus, superficial haemosiderosis, intracranial haematomata and death^(33,34), but nowadays it has been revived, mainly in such difficult cases as HME⁽³⁵⁾.

Hemidecortication or hemicorticectomy includes the removal of cortical grey matter with preservation of the ventricle and a layer of white matter. Here a great amount of cerebral tissue is removed and late complications as haemosiderosis and intracranial haematomata may be observed 4 to 5 years after surgery⁽³⁶⁾.

Less aggressive surgeries, with smaller amounts of cerebral tissue resection are being used nowadays. Aiming at reduction of the complications Rasmussen proposed functional hemispherectomy. Original description of the technique included temporal lobectomy, resection of the central supra-Sylvian cortex with disconnection of the frontal and occipital lobes and complete callosotomy⁽³³⁾. Yoshioka et al.⁽³⁷⁾ reported a patient submitted to a modified functional hemispherectomy in which the authors limited the temporal resection to superior temporal gyros, with removal of the hippocampus and amygdala. Delalande in 1992 coined the term hemispherotomy after describing his technique in which access to the ventricle is superiorly through a corticectomy followed by complete disconnection around the thalamus and basal ganglia, resection of the hippocampus and amygdala and callosotomy⁽³⁸⁾. Villemure and Mascott⁽³⁹⁾ and Schramm et al.⁽⁴⁰⁾ described a similar technique for disconnection through a sylvian "window", posteriorly refined by Shimizu and Maehara⁽⁴¹⁾ using a fronto-parietal resection of the operculum to gain access to the ventricle and then performing the complete disconnection from inside the ventricular cavity. Danielpour et al.⁽⁴²⁾ reported an interhemispheric approach as a variant of the technique of Delalande, followed by internal capsule transection, opening of the roof of the temporal horn and amygdala and hippocampus resection. The original technique described and its modifications are good options in patients with large or normal hemispheres, such as patients with HME.

Hemispherotomy is mainly a disconnective surgery, with less resection of the central cortex and preservation of the temporal lobe. Although initially proposed for patients with large middle cerebral artery lesions and large ventricles⁽³³⁾ in reality with experience surgery can be performed even with small ventricles. Modifications are frequently proposed by surgeons but the main objective of surgery is seizure control and reduce medications allowing

the child to regain neurological milestones. In our Hospital we first used a peri-insular linear corticectomy (preserving the operculum) until the lateral ventricle is opened, from the frontal to the temporal horn, followed by section of the frontal horizontal fibers, complete callosotomy, section of the fornix, temporal lobectomy (not in all cases) and amygdalo-hippocampotomy. More recently resection of the frontal and parietal operculum, as proposed by Shimizu and Maehara⁽⁴¹⁾ really facilitates approach to the ventricle, and subsequent surgery steps as described above.

Some authors had tried more conservative surgeries with a partial resection and little disconnection. Russo et al.⁽⁴³⁾ performed a fronto-centro-parietal resection, with preservation of visual cortex and connections in one patient with HME. Unfortunately the patient did not achieve good surgical control and this raises the question if more conservative approach had benefits in patients with HME. Specchio et al.⁽²⁹⁾ had a good seizure outcome in one patient with DNT and HME submitted to a focal temporal resection, but this patient may not represent the classical features of HME, since DNT patients usually have a more favorable post-surgical outcome.

In patients with diffuse MRI abnormalities and multifocal spikes on EEG, focal resection may not lead to a good seizure outcome, since the definitions of only one epileptogenic region is not easy. Multifocal resection may have the same functional prognosis when considering neurological deficits with a worst seizure control, suggesting that hemispheric approach should be the best options in most of the cases and focal resections should be considered in individual cases.

SURGICAL RESULTS

Postsurgery outcome for HME may be not as good as that for focal lesions or other hemispheric abnormalities. Some authors report approximately 40% of patients being seizure free for hemispheric surgeries due to HME and 38% of patients no longer taking antiepileptic drugs, while patients with Rasmussen Syndrome and vascular injury may achieve 67 to 88% of seizure free^(32,45). Surgical outcome in patients with others forms of focal cortical dysplasia is variable and are between 50-70% of patients seizure-free, results favorably than in HME⁽⁴⁵⁾. This suggests that, even in the context of complete hemisphere disconnection, HME may represent a worst spectrum of developmental abnormalities lesions.

The age at surgery and the integrity of the non-HME hemisphere are important factors in prognosis⁽²⁶⁾ and for children with life-threatening catastrophic epilepsy a reduction in seizure frequency may have great impact in quality of life⁽⁴⁶⁾. One possible reason for surgical failure may be an incomplete hemisphere disconnection or a

greater extent of the lesion, with involvement of the contralateral hemisphere^(46,47). Although seizure free situation may not be observed, some authors suggest that in patients with HME and catastrophic epilepsies, even if the contralateral hemisphere is affected, surgery may be done and the child may achieve an improvement of quality of life⁴⁴. This is an important observation since the main indication for surgery in these patients may be preventing additional cognitive injury and developmental delay.

Surgical complications are observed in most of the series of patients with HME submitted to hemispheric surgery. Mortality is reported in the literature and the most common cause is acute surgical complications that may be related to excessive blood loss^(32,44,48). Others acute complications in hemispheric surgery are infarcts or ischemia, epidural or subdural collections, bone or ventricular infections, inappropriate antidiuretic hormone syndrome, need of acute ventricular-peritoneal shunts, fever with no identifiable source and worsening in motor function. Late complications include hydrocephaly with need of ventricular-peritoneal shunts although in our personal observation in patients submitted to hemispherotomy this complication was not observed^(49,50).

The presence of pos-operative seizures has a controversial implication and may suggest an incomplete disconnection or epileptogenicity of the remaining hemisphere. Koh et al.⁽⁵¹⁾ in a cohort of patients submitted to hemispherectomy found that the occurrence of more than five seizures in the acute post-operative days correlated with poor seizure outcome.

CONCLUSIONS

HME is a complex disease with polymorphic presentation. Epilepsy is one of its worst symptoms and seizure relief is essential to neurological development. Multiple surgical techniques had been proposed and hemispheric disconnection may represent an option with less surgical complications with similar post-operative seizure control. A case by case analysis should be done to find out the best surgical option to be used in each patient considering the lesion extension and the neurosurgeon experience.

ACKNOWLEDGEMENT

The authors wish to thank the fellows, residents, paramedical and medical staff of the Epilepsy Outpatient Clinics and Video-EEG Monitoring Unit of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto/USP. Financial support FAEPA.

REFERENCES

1. Barkovich AJ, Kuzniecky RI, Dobyns WB. Radiologic classification of malformations of cortical development. *Current Opinion in Neurology* 2001; 14(2):145-9.
2. Sarnat HB, Flores-Sarnat. Human nervous system development and malformations. In: *The treatment of epilepsy*. Ed. Wyllie; 2006. p. 12-36.
3. Salamon N, et al. Contralateral hemimicroencephaly and clinical-pathological correlations in children with hemimegalencephaly. *Brain* 2006; 129:352-65.
4. Broumandi DD, et al. Hemimegalencephaly. *Radiographics* 2004; 24(3): 843-8.
5. Tinkle BT, et al. Epidemiology of hemimegalencephaly: A case series and review. *Am J Med Genet* 2005; 139(Part A.3):204-11.
6. D'Agostino MD, et al. Posterior quadrantic dysplasia or hemimegalencephaly – A characteristic brain malformation. *Neurology* 2004; 62(12):2214-20.
7. Dobyns WB, Kuzniecky R. Malformation of cortical development and epilepsy. In: *The treatment of epilepsy*. Ed. Wyllie; 2006. p. 37-53.
8. Sakuma H, Iwata O, Sasaki M. Longitudinal MR findings in a patient with hemimegalencephaly associated with tuberous sclerosis. *Brain & Development* 2005; 27(6):458-61.
9. Parmar H, Patkar D, Shah J, Patankar T. Hemimegalencephaly with tuberous sclerosis: a longitudinal imaging study. *Australasian Radiology* 2003; 47:438-42.
10. Fusco L, et al. Hemimegalencephaly and Normal Intellectual-Development. *J Neurol Neurosurg Psychiatry* 1992; 55(8):720-2.
11. Ohtsuka Y, Ohno S, Oka E. Electroclinical characteristics of hemimegalencephaly. *Pediatric Neurology* 1999; 20(5):390-3.
12. Luders H, Schuele SU. Epilepsy surgery in patients with malformations of cortical development. *Current Opinion in Neurology* 2006; 19(2):169-74.
13. Pavone L, Curatolo P, Rizzo R, Micali G, Incorpora G, Garg BP, Dunn DW, Dobyns WB. Epidermal nevus syndrome: a neurologic variant with hemimegalencephaly, gyral malformation, mental retardation, seizures, and facial hemihypertrophy. *Neurology* 1991; 41:266-71.
14. Aydingoz U, Emir S, Karli-Oguz K, Kose G, Buyukpamukcu M. Congenital infiltrating lipomatosis of the face with ipsilateral hemimegalencephaly. *Pediatr Radiol* 2002; 32(2):106-9.
15. Fonseca LF, Melo RP, Cukiert A, Burattini JA, Mariani PP, Brandao R, Ceda L, Baldauf CM, Argenton M, Forster C, Baise C. Early functional hemispherectomy in hemimegalencephaly associated to refractory epilepsy. *Arq Neuropsiquiatr* 2004; 62(4):1063-7.
16. Flores-Sarnat. Hemimegalencephaly: part 1. Genetic, clinical and imaging aspects. *J Child Neurol* 2002; 17:373-84.
17. Sasaki M, et al. Clinical aspects of hemimegalencephaly by means of a nationwide survey. *J Child Neurol* 2005; 20(4):337-41.
18. Guzzetta F, et al. Epileptic negative myoclonus in a newborn with hemimegalencephaly. *Epilepsia* 2002; 43(9):1106-9.
19. Duane DC, Ng YT, Rekate HL, Chung S, Bodensteiner JB, Kerrigan JF. Treatment of refractory status epilepticus with hemispherectomy. *Epilepsia* 2004; 45(8):1001-4.
20. Hung PC, Wang HS. Hemimegalencephaly: cranial sonographic findings in neonates. *J Clin Ultrasound* 2005; 33(5):243-7.
21. Agid R, et al. Prenatal MR diffusion-weighted imaging in a fetus with hemimegalencephaly. *Pediatric Radiology* 2006; 36(2):138-40.
22. Yagishita A, et al. Hemimegalencephaly: signal changes suggesting abnormal myelination on MRI. *Neuroradiology* 1998; 40(11):734-8.
23. Woo CLF, et al. Radiologic-pathologic correlation in focal cortical dysplasia and hemimegalencephaly in 18 children. *Pediatric Neurology* 2001; 25(4):295-303.
24. Hanefeld F, et al. Hemimegalencephaly – Localized proton magnetic – Resonance spectroscopy in vivo. *Epilepsia* 1995; 36(12):1215-24.
25. Doring S, et al. The significance of bilateral EEG abnormalities before and after hemispherectomy in children with unilateral major hemisphere lesions. *Epilepsy Research* 1999; 34(1):65-73.
26. Soufflet C, et al. The nonmalformed hemisphere is secondarily impaired in young children with hemimegalencephaly: A pre- and postsurgery study with SPECT and EEG. *Epilepsia* 2004; 45(11):1375-82.

27. Arai Y, Edwards V, Becker LE. A comparison of cell phenotypes in hemimegalencephaly and tuberous sclerosis. *Acta Neuropathologica* 1999; 98(4):407-13.
28. Baybis M, et al. Altered expression of neurotransmitter-receptor subunit and uptake site mRNAs in hemimegalencephaly. *Epilepsia* 2004; 45(12):1517-24.
29. Specchio N, et al. Resective surgery for epileptogenic dysembryoplastic neuroepithelial tumor in hemimegalencephaly. *Neurology* 2005; 65(5):777-8.
30. Dumas-Duport C. Dysembryoplastic Neuroepithelial Tumors. *Brain Pathology* 1993; 3(3):283-95.
31. Gonzalez-Martinez JA et al. Hemispherectomy for catastrophic epilepsy in infants. *Epilepsia* 2005; 46(9):1518-25.
32. Jonas R, et al. Cerebral hemispherectomy – Hospital course, seizure, developmental, language, and motor outcomes. *Neurology* (2004); 62(10):1712-21.
33. Smith JR, Fountas KN, Lee MR. Hemispherotomy: description of surgical technique. *Childs Nervous System* 2005; 21(6):466-72.
34. Devlin AM, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain* 2003; 126:556-66.
35. O'Brien DF, Basu S, Williams DH, May PL: Anatomical hemispherectomy for intractable seizures: excellent seizure control, low morbidity and no superficial haemosiderosis. *Child's Nervous system* 2006; 22:489-98.
36. Carson BS, Javedan SP, Freeman JM, Vining EP, Zuckerberg AL, Lauer JA, Guarnieri M. Hemispherectomy: a hemidecortication approach and review of 52 cases. *J Neurosurg* 1996; 84(6):903-11.
37. Yoshioka H, et al. Modified functional hemispherectomy in hemimegalencephaly. *Brain & Development* 1999; 21(2):125-8.
38. Montes JL, Farmer JP, Andermann F, Poulin C. Hemispherectomy: medications, technical approaches, and results. In *The treatment of epilepsy*. Ed. Wyllie; 2006. p. 1111-24.
39. Villemure JG, Rasmussen T. Functional hemispherectomy in children. *Neuropediatrics* 1993; 24(1):53-5.
40. Schramm J, Behrens E, Entzian W. Hemispherical deafferentation: an alternative to functional hemispherectomy. *Neurosurgery* 1995; 36(3):509-15.
41. Shimizu H, and Maehara T. Modification of peri-insular hemispherotomy and surgical results. *Neurosurgery* 2000; 47(2):367-72.
42. Danielpour M, et al. Disconnective hemispherectomy. *Pediatric Neurosurgery* 2001; 35(4):169-72.
43. Russo GL, Tassi L, Cossu M, Cardinale F, Mai R, Castana L, Colombo N, Bramerio M. Focal cortical resection in malformations of cortical development. *Epileptic Disord* 2003; 5 Suppl 2: S115-23.
44. Kossoff EH, et al. Hemispherectomy for intractable unihemispheric epilepsy – Etiology vs outcome. *Neurology* 2003; 61(7):887-90.
45. Alexandre Jr V, Walz R, Bianchin MM, Velasco TR, Terra-Bustamante VC, Wichert-Ana L, Araujo Jr D, Machado HR, Assirati Jr JA, Carlotti Jr CG, Santos AC, Serafini LN, Sakamoto AC. Seizure outcome after surgery for epilepsy due to focal cortical dysplastic lesions. *Seizure*, in press.
46. Edwards JC, et al. Seizure outcome after surgery for epilepsy due to malformation of cortical development. *Neurology* 2000; 55(8): 1110-4.
47. Sisodiya SM. Surgery for malformations of cortical development causing epilepsy. *Brain* 2000;123(Pt 6):1075-91.
48. Carreno M, et al. Seizure outcome after functional hemispherectomy for malformations of cortical development. *Neurology* 2001; 57(2):331-3.
49. Terra-Bustamante VC, et al. Surgically amenable epilepsies in children and adolescents: clinical, imaging, electrophysiological, and post-surgical outcome data. *Childs Nervous System* 2005; 21(7):546-51.
50. Terra-Bustamante VC, Inuzuka LM, Fernandes RMF, Escorsi-Rosset S, Wichert-Ana L, Alexandre Jr V, Bianchin MM, Araújo D, Santos AC, Santos RO, Machado HR, Sakamoto AC. Outcome of hemispheric surgeries for refractory epilepsy in pediatric patients. *Childs Nervous System*, in press.
51. Koh S, Nguyen S, Asarnow RF, LoPresti C, Yudovin S, Shields WD, Vinters HV, Mathern GW. Five or more acute postoperative seizures predict hospital course and long-term seizure control after hemispherectomy. *Epilepsia*. 2004; 45(5):527-33.

Address for correspondence:

Vera C. Terra-Bustamante
 CIREF – Department of Neurology – University of São Paulo
 School of Medicine at Ribeirão Preto – Campus Universitário
 CEP 14049-900, Ribeirão Preto, SP, Brazil
 Phone: (55-16) 602-2613 – Fax: (55-16) 6330760
 E-mail: vctbusta@rnp.fmrp.usp.br