

Progressive hemispheric shrinking in hemimegalencephaly: a possible role for seizure-related neuronal loss

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Hemimegalencephaly (HME) is a developmental brain lesion consisting of a unilateral enlarged, dysplastic, and often highly epileptogenic cerebral hemisphere. Most patients exhibit early onset intractable seizures, status epilepticus, hemiplegia, hemianopsia, and developmental delay. Major surgical procedures are advocated for limiting the devastating consequences of epilepsy. We studied a female with HME, early onset intractable seizures and recurrent status epilepticus, in whom progressive hemiatrophy of the enlarged hemisphere and normal growth of the contralateral hemisphere, exceeding the size of the dysplastic hemisphere, was demonstrated by magnetic resonance imaging.

Histopathology, following functional hemispherectomy at the age of 7 years, demonstrated severe neuronal loss with an elevated number of cells exhibiting the morphological and biochemical features of apoptosis. Eighteen months after surgery the patient was seizure-free (Engel class I) and exhibited improved motor and language skills, alertness and social behaviour. We hypothesize that nearly continuous seizure activity might sustain seizure-induced brain injury in the dysplastic hemisphere but causal heterogeneity and associated anatomical factors may influence differently the individual predisposition to atrophic changes.

Hemimegalencephaly (HME) consists of a unilateral enlarged dysplastic cerebral hemisphere. Most patients exhibit early onset intractable seizures, hemiplegia, hemianopsia, and moderate to severe developmental delay.¹

Through repeat magnetic resonance imaging (MRI) we demonstrated progressive hemiatrophy of the enlarged hemisphere in a female with HME and intractable, nearly continuous seizure activity, and episodes of status epilepticus. Histopathology, following functional hemispherectomy, performed at the age of 7 years, demonstrated severe neuronal loss. We hypothesize that severe and protracted seizure activity might underlie atrophic changes in the dysplastic hemisphere.

Method

CASE REPORT

The patient, an 8-year-old female, had refractory seizures that started on her first day of life. At 2 days of age, MRI of the brain revealed HME of the right hemisphere (Fig. 1). Facial asymmetry, with the right side larger than the left, was noticed after birth. Left hemiparesis became apparent at 3 months of age and severe developmental delay was noticed in the first months of life. The patient could hold up her head at 12 months, sit up at 18 months, shuffle at 3 years, and walk with help at 4 years. Right gaze preference and left homonymous hemianopsia were evident. No language development occurred.

See end of paper for list of abbreviations.

Seizures exhibited different characteristics through age. Early seizures were hypomotor, with pallor and staring and appeared in series or in status from the first day of life. Treatment with multiple drugs brought seizures down to four to five episodes per day. From the age of 10 months, however, asymmetric spasms appeared, which were not improved by drugs and were accompanied, from the age of 18 months, by asymmetric tonic posturing with hypermotor activity, screaming, and an expression of fear, occurring while awake and asleep. Such hypermotor seizures occurred in clusters on several occasions and, from the age of 18 months to 22 months, in status epilepticus on three occasions. Seizure clusters and episodes of status were followed by periods of reduced vigilance and worsening of motor skills, lasting days or weeks. The origin of these was difficult to attribute with certainty to the sedative effect of acute administrations of drugs, status-induced cognitive regression, or both. Several antiepileptic drug trials proved ineffective. Numerous electroencephalogram (EEG) recordings were obtained from the neonatal

period through childhood, showing severe slowing of background activity on the left, with recurrent multifocal seizure activity in the right hemisphere, intermingled with bilateral, right predominant decremental events, followed by low voltage activity of increasing voltage and decreasing frequency. We proposed hemispherectomy after first seeing the patient at age 4 years but her parents were initially reluctant.

Repeat MRI, performed at the age of 5 years, revealed that the right dysplastic hemisphere had become smaller than the contralateral, probably due to a combination of arrested growth and atrophic changes. The right cerebellar hemisphere was mildly atrophic (Fig. 1). Cognitive assessment (Behavior Assessment Battery² [BAB] and Vineland Adaptive Behaviour Scales³) was consistent with severe impairment. Language production was limited to a few words. Visual field assessment, by clinical examination, revealed right hemianopsia. At 7 years of age, functional hemispherectomy was performed, with section of corpus callosum and partial removal of the temporal and parietal lobe. Cognitive

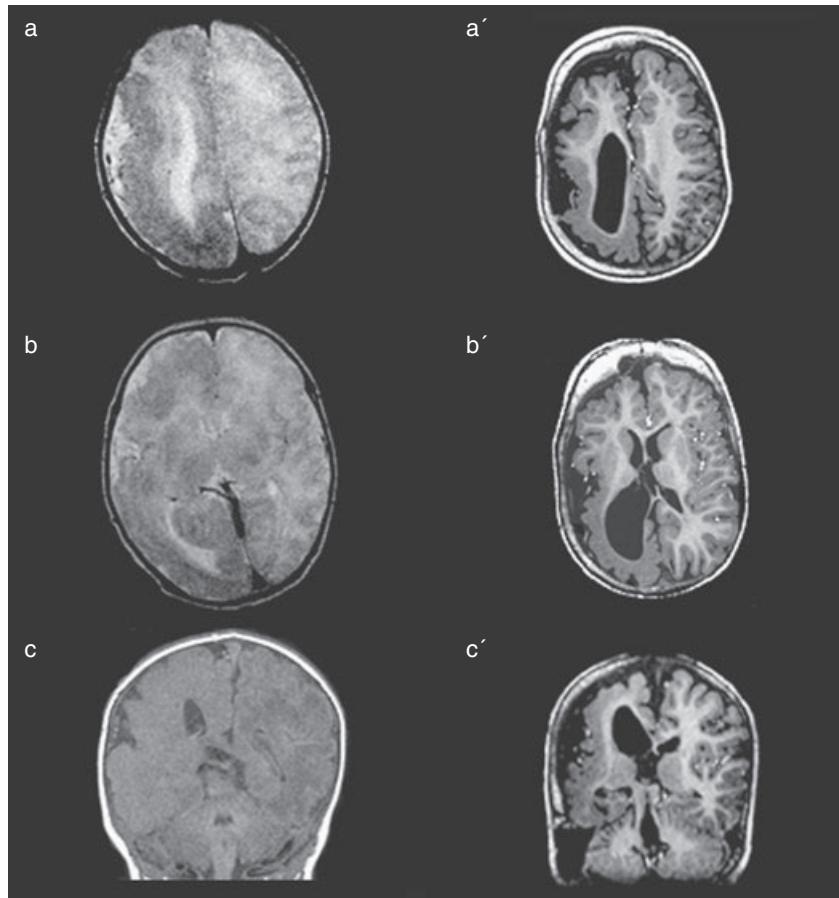


Figure 1: Magnetic resonance imaging of the brain at day 2 (a, b, c: 1T, a and b are T₂-weighted axial section; c is a T₁-weighted coronal section) and at age 5 years (a', b', c': 1.5T, IR images; a' and b' are axial sections and c' is a coronal section). In a, b, and c, the right hemisphere (on the left-hand side) is larger than the left hemisphere and exhibits a simplified gyral pattern, with thickened cortex and dilated ventricular horns. In b and c a dilated calvarium and midline shifting towards the right are also obvious. In a', b', c' the right hemisphere is clearly smaller than the contralateral, the subarachnoid space is much enlarged on the right; increased cortical thickening and an irregular, simplified gyral pattern are also apparent, especially in the posterior quadrant. Some increase in width of cortical sulci is visible in the right cerebellar hemisphere, just beneath the tentorium, possibly due to reduced pressure from the overlying cerebral hemisphere which is now raised.

evaluation 6 months after surgery (BAB² and Griffiths scales⁴) revealed severe to moderate impairment, with verbal skills being better preserved than visuo-perceptual skills. The patient was able to point to several alphabetical letters, to repeat sounds of animals, and to use about 20 words. Eighteen months after surgery the patient was seizure-free (Engel class I), was able to move a few steps without support, no longer neglected her left hand during bilateral movements, had increased her vocabulary to around 30 words, and exhibited improved alertness and social behaviour. Postoperative EEG showed normal activity on the left and residual epileptiform discharges limited to the right occipital region.

Informed consent for anonymous publication of this patient's case was obtained from the parents.

PATHOLOGY

After gross examination, the available portions of the temporal lobe and parietal lobe showed firm brain parenchyma, with enriched meningeal vascularization and simplified gyral pattern. The cortex was thickened and the cortical white matter boundaries were ill-defined. Formalin-fixed and paraffin-embedded samples were obtained for light microscope assessment and sections were cut for hematoxylin-eosin, and luxol fast-blue staining techniques. Immunohistochemistry (IHC) was performed using neurofilament (NF; 1:400), glial fibrillary acidic protein (GFAP; 1:1000), synaptophysin (1:500; Ventana Medical System Inc., Tucson, AZ, USA).

Microscopically, the brain tissue showed areas of agyria, polymicrogyria, leptomeningeal, and periventricular heterotopia (Figs. 2a, 2b). At low-power magnification, widespread

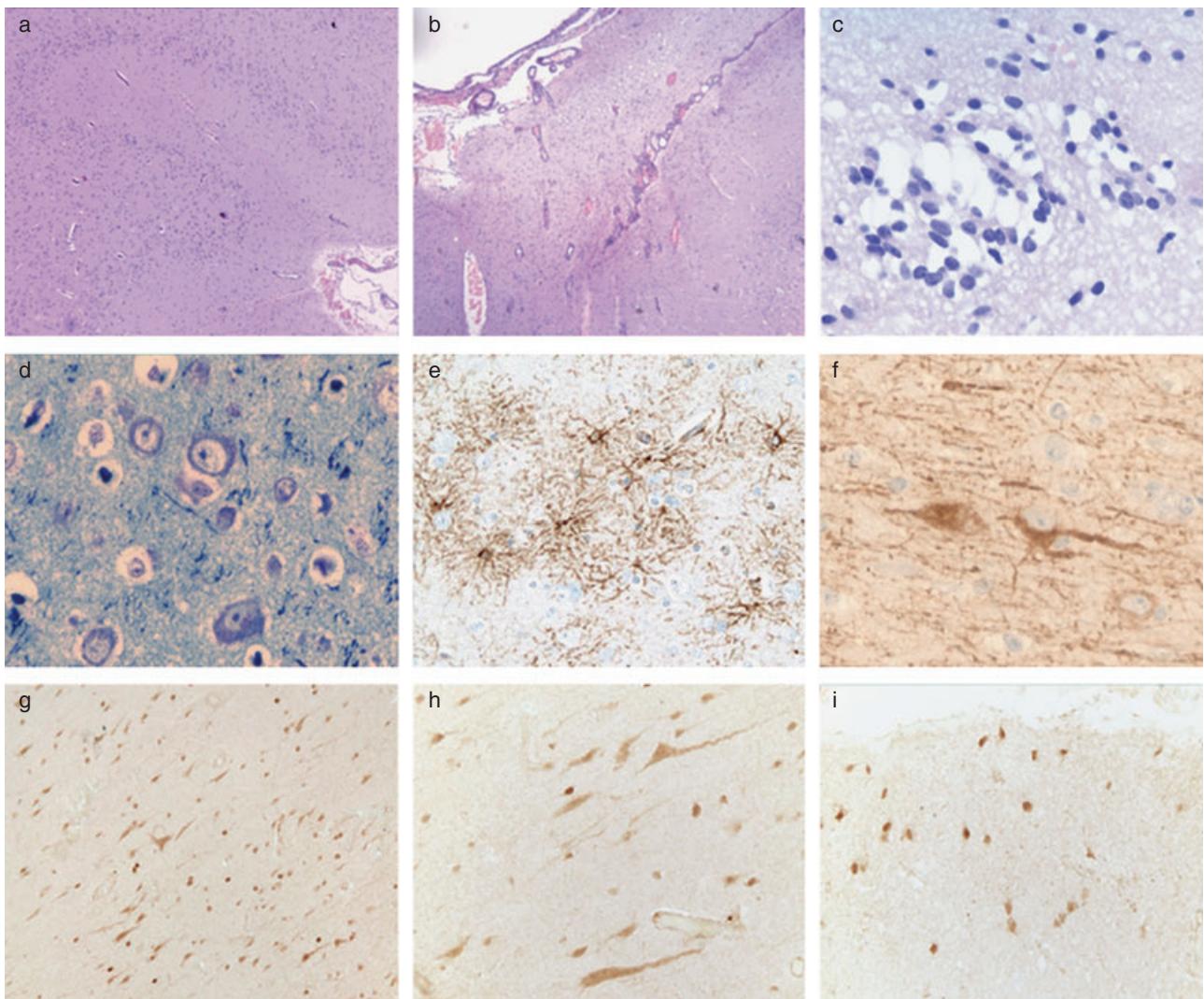


Figure 2: Histological features of dysplastic cortex: (a) polymicrogyric cortex with fused molecular layers (Hematoxilin & Eosin [H&E], magnification 2.5x); (b) leptomeningeal heterotopia (H&E, 2.5x); (c) heterotopic glial-neuronal clusters in the deep white matter (Luxol fast blu, 20x); (d) cyto-architectural dysplasia with ill-oriented, dysmorphic, giant neurons (Luxol fast blue, 40x); (e) gliosis (glial fibrillary acidic protein, 20x); (f) anomalous dendritic processes and neurofilament accumulation in the cellular body of dysmorphic neurons (NF, 40x); (g) immunohistochemistry (IHC) with caspase-3 in neurons and in glial cells in the deep cortical layers, with a nuclear and cytoplasmic staining pattern (caspase-3, 10x); (h) same as in (g) but at higher magnification (20x); (i) IHC with caspase-3 in the most superficial cortical layers, including the molecular layer (20x).

cyto-architectural dysplasia was apparent: the horizontal lamination of the cortex had disappeared and heterotopic glioneuronal clusters were observed on the pial surface and in the deep white matter (Fig. 2c). At high-power magnification, ill-oriented, dysmorphic, giant neurons were scattered throughout the cortex and intermingled with myelinated fibres. Most neurons were pyramidal in shape, with the larger elements lying in the deeper part of the cortex. Anomalous dendritic processes or neurofilament accumulation were evident in the cellular body of dysmorphic neurons (Fig. 2d, 2e, 2f). Morphological signs of hypoxic-ischemic (HI) neuronal damage were also present. In the cortex, gliosis and microcalcifications were associated with shrunken neurons with cytoplasmic hypereosinophilia, nuclear pyknosis, and microglial satellitosis. Several oligodendrocytes with pyknotic nuclei and some axonal spheroids were encountered in the underlying white matter. To investigate further the nature of HI damage, IHC was performed using a monoclonal antibody against cleaved caspase-3 (1:200) (#9661- Cell Signaling Technologies Inc., Danvers, MA, USA), as previously described,⁵ and compared with non-epileptic autopic brain tissue. IHC with caspase-3 showed a high number of positive cells in the patient's brain with respect to control tissue, with a mean of 60 positive cells per 20x magnification power field. The immunoreactivity was conspicuous in the dysplastic cortex, both in neurons and in glial cells. The staining pattern was mostly cytoplasmic, but also involved dentritic branches and glial fibres around capillaries (Fig. 2g, 2h, 2i).

Discussion

In this report we identified imaging and pathological findings indicating that the dysplastic epileptogenic tissue of the hemimegalencephalic hemisphere can undergo atrophic changes and lose its highly characteristic enlarged size and shape. Brain MRI performed at birth revealed HME but a repeated brain imaging at 5 years of age demonstrated remarkable shrinking of the dysplastic hemisphere. No further shrinking was detected on repeating MRI at 7 years of age. Episodes of seizures in clusters and status epilepticus had occurred in the first 2 years of life, between the first and second scan, but not between the second and third.

It is difficult to establish whether hemispheric shrinkage had any detectable clinical consequence in our patient. It was not possible to determine when it had occurred exactly and over how long it developed. In addition, the patient had severe developmental delay, which would have made it difficult to detect mild clinical changes. We do not expect shrinkage of the dysplastic and dysfunctional hemisphere to generate patent clinical changes, although one might argue that cessation of episodes of status epilepticus after 3 years of age might have been correlated to reduced intrinsic epileptogenicity, secondary to reduced 'critical mass'. Yet, the deleterious consequences of 'transmitted' epileptic activity on the healthy hemisphere were still operating after shrinking had occurred, as can be inferred from the clinical benefits observed after hemispherectomy.

Although no systematic follow-up imaging studies of HME are available, we found reports of three cases in which either atrophic changes or arrested growth of the hemimegalencephalic hemisphere were documented by repeated MRI. Wolpert et al.⁶ observed a child in whom the hemimegalencephalic hemisphere, first seen in the fifth day of life, had

become atrophic upon repeated brain MRI at 10 months of age. Sakuma et al.⁷ documented HME in the second day of life in a child with tuberous sclerosis, with subsequent progressive atrophy of a portion of the malformed hemisphere on repeated imaging at age 6 months and 3 years 2 months. In both patients the malformed hemisphere had become smaller than the contralateral. An additional observation of HME in a patient with tuberous sclerosis was reported by Parmar et al.⁸ These authors documented, between age 6 month and 2 years 9 months, progressive loss in volume of the malformed hemisphere, which remained larger than the contralateral, and interpreted it as arrested growth, rather than atrophy. Description of seizure characteristics and EEG correlates in these three cases differ in accuracy but, in general, they indicate that the typical picture with severe seizures starting from the first days or months of life, accompanied by episodes of status, was present in all three patients and had been fully expressed between the first and subsequent scan(s). In none of these three patients could clinical or imaging evidence of hypoxic, ischemic, vasculitic, infective, or exogenous toxic factors be demonstrated. In all three patients, poorly controlled seizures were hypothesized to have contributed to progressive atrophic changes, and arrested growth of the malformed hemisphere, although pathology was not available for study.

In the patient reported here, neuropathological study of the resected tissue, in addition to the classical cyto-architectural abnormalities of HME,^{9,10} uncovered morphological signs of HI damage, possibly suggesting a role for a chronic continuous insult in the pathogenesis of hypotrophy. A role in seizure-induced neuronal damage in the human epileptic brain, has been hypothesized for cell death regulatory genes, such as B-cell leukaemia/lymphoma 2 (Bcl-2) and caspase, as suggested by increased immunoreactivities for their products.¹¹ Caspase-3 mediates neuronal apoptosis, which follows trophic factor withdrawal, exposures to inhibitors of protein kinases or phosphatases, or HI brain injury.¹² Using cleaved caspase-3 IHC, we demonstrated an elevated number of cells exhibiting the morphological and biochemical features of apoptosis. Excitotoxic cell death, caused by excessive stimulation of excitatory amino acid receptors is considered to be the fundamental process underlying HI neuronal damage and has been demonstrated in different models of seizures induced brain injury.^{13,14} Seizure-induced acute energy deprivation leads to a cascade which leads to irreversible neuronal injury and death through excessive release of extracellular glutamate, uncontrolled activation of the ionotropic glutamate receptors N-methyl-D-aspartic acid (NMDA), Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid (AMPA), and kainate, impaired energy-dependent re-uptake of glutamate, and rise in intracellular Ca^{2+} concentration.⁹

Considering that HME is often accompanied by intractable epilepsy with recurrent status epilepticus, the number of reported cases of progressive hemispheric shrinking might appear to be exiguous, should intrinsic epileptogenicity of the malformed hemisphere be the sole causative factor. Different reasons may account for the rarity of this association. First, most children with HME and intractable seizures do not undergo repeat imaging studies because they are either operated on early in life or no anatomical changes are expected to occur over time. Therefore, the phenomenon may be underreported. Second, HME is causally

heterogeneous as suggested by its association with different disorders including epidermal nevus syndrome, Proteus syndrome, hypomelanosis of Ito, type 1 neurofibromatosis, and tuberous sclerosis,¹⁵ making it possible that only some patients are anatomically predisposed to seizure-induced brain damage. Third, different patients carry different degrees of structural abnormality in the brain parenchyma and outside it. For example, vascular dysplasia, with vascular dilatations are observed in the affected hemisphere in about 40% of patients and can involve either deep or superficial cerebral vessels, or both.¹⁶ Such associated vascular abnormalities might differently influence the susceptibility to, and consequences of, seizure-induced brain injury.

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List of abbreviations

HI	Hypoxic–ischemic
HME	Hemimegalencephaly
IHC	Immunohistochemistry