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GIANT SUBCORTICAL HETEROTOPIA INVOLVING THE TEMPORO-PARIETO-OCCIPITAL REGION: A CHALLENGING CAUSE OF DRUG-RESISTANT EPILEPSY

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INTRODUCTION

Gray matter heterotopia is a well recognized cause of intractable epilepsy and cognitive delay related to malformations of cortical development. On the base of the MRI appearance subependymal, subcortical and diffuse or band heterotopia can be recognized. Only few cases of giant unilateral subcortical heterotopia are reported in literature (Barkovich 1996; Preul et al., 1997; [illegible] et al., 1998; [illegible] et al., 2005; Battaglia et al., 2006). The main concern is the association with high frequency of drug-resistant epilepsy which can lead to a progressive clinical deterioration, influencing the quality of life of the patients and their relatives. Surgical treatment has been proposed to achieve the control of seizures and data from the literature suggest that good results can be achieved in unilateral subcortical heterotopia when a complete excision of the lesion is obtained (Thibeaut et al., 1999; Preul et al., 1997; [illegible] et al., 2005). The [illegible] of catastrophic epilepsy urges the surgeon to treat these patients even in very young age [illegible] [illegible] by the purpose of allowing the compensatory development of the apparently healthy cerebral tissue.

PATIENTS AND METHODS

Between October 2002 and November 2005 three patients affected by unilateral giant subcortical heterotopia [illegible] parieto-occipital region were admitted to our Department. Detailed clinical information was collected. Development was assessed using the Griffiths' Mental Development Scales or WISC-R according to the patient age, the Vineland Adaptive Behaviour Scales and the Child Behaviour Checklist.

The brain malformation was investigated with high-resolution magnetic resonance imaging (HR-MRI). All three subjects had extensive ictal and interictal video-EEG monitoring. The patients underwent surgical resection of the malformed tissue. The postoperative epileptic outcome was assessed using the Engel classification.

RESULTS

Mean age at seizure onset was within the first months of life. Seizures consisted of [illegible] infantile spasms in the first and third case and by [illegible] partial seizures in the second one. The patients presented with contralateral hemiparesis [illegible] in cases 1 and 3. Moderate to severe developmental delay was observed in all cases. MRI showed a huge [illegible] mass, [illegible] to gray matter associated with corpus callosum partial agenesis and anomalies of the [illegible] (Fig. 1).

Focal and diffuse paroxysmal activities in the affected hemisphere were detected in all three cases. In cases 1 and 3 [illegible] [illegible] were observed [illegible] (Fig. 2).

The 1st and 3rd cases underwent total excision of the heterotopia [illegible] in the [illegible] of the [illegible] and the [illegible] to produce a severe loss of functions [illegible] a partial excision of the lesion was performed and a subsequent [illegible] shunt was revised [illegible] for mechanical blockage.

The post-operative follow-up was characterized by complete regression of seizures in the 1st and 3rd cases and significant seizure reduction in the 2nd case. All three patients experienced a [illegible] improvement of the neuropsychological impairment [illegible] worsening of the preoperative neurological deficit. Table 1 summarizes the main data of the three patients.

Fig. 1

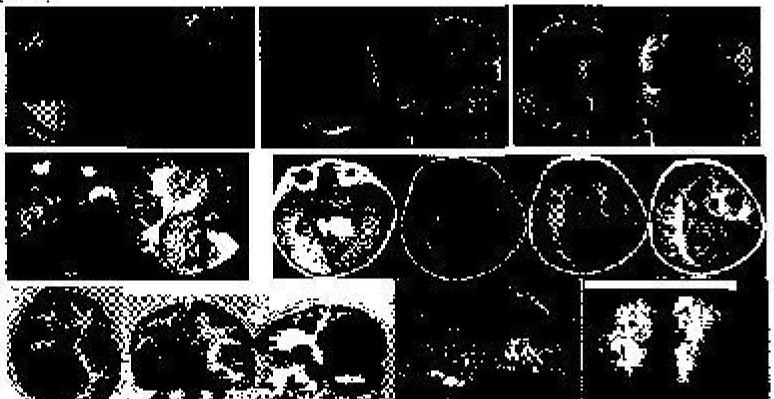
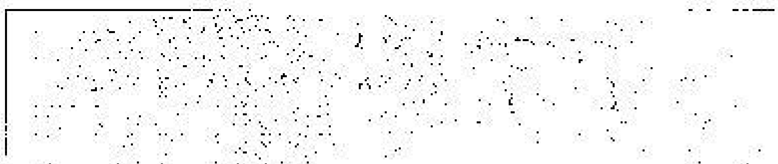


Table 1: [illegible]

	Case 1	Case 2	Case 3
[illegible]	[illegible]	[illegible]	[illegible]

Fig. 2



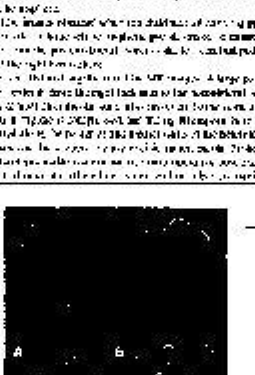


Figure 3

[illegible]

DISCUSSION

[illegible]

CONCLUSIONS

Patients affected by giant subcortical heterotopia [illegible] a favourable prognosis [illegible] surgery [illegible] EEG [illegible].

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Giant subcortical heterotopia involving the temporo-parieto-occipital region: a challenging cause of drug-resistant epilepsy.

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Abstract

Gray matter heterotopia is a cortical malformation which may cause intractable epilepsy and cognitive delay. Giant subcortical heterotopias have only occasionally been described. Surgical removal has been proposed for the management of seizures. Good results are reported after complete excision, but one concern comes from a possible functional role of the heterotopic tissue.

Three patients affected by giant temporo-parieto-occipital subcortical heterotopia underwent surgical treatment. Two subjects got rid of seizures after complete excision. The third patient underwent a subtotal excision, in order to space the motor cortex possibly involved in the malformation, achieving only a reduction of seizures. An improvement of development and behaviour without neurological worsening was observed in all three patients.

Patients affected by giant subcortical heterotopias seem to present a favourable prognosis after the surgical removal, even in cases of long-lasting epilepsy, in comparison with other extensive cortical malformations for which adjunctive disconnective procedures are often advocated.

Key-words: subcortical heterotopia, infancy, surgery, drug-resistant epilepsy, cognitive delay

Introduction

Gray matter heterotopia is a well-recognized cause of intractable epilepsy and cognitive delay related to malformations of cortical development. On the base of the MRI appearance subependymal, subcortical and diffuse or band heterotopia forms can be recognized. Only few cases of giant form of subcortical heterotopia are reported in literature (Barkovich, 1996; Preul et al., 1997; Ares et al, 1998; Tassi et al, 2005; Battaglia et al., 2006).

The main concern is the association with high-frequency drug-resistant epilepsy which can lead to a progressive clinical deterioration, influencing the quality of life of the patients and their relatives. Surgical treatment has been proposed to achieve the control of seizures and data from the literature suggest that good results can be achieved for unilateral subcortical heterotopia when a complete excision of the lesion is obtained (Dubeau et al., 1995; Preul et al., 1997; Tassi et al., 2005).

The coexistence of catastrophic epilepsy urges the surgeon to treat these patients even in very young age, with increased surgical risks justified by the purpose of allowing the compensatory development of the apparently healthy cerebral tissue.

We present a retrospective evaluation of three patients affected by unilateral giant subcortical heterotopia involving the temporo-parieto-occipital region, who underwent surgical treatment to relieve the associated drug-resistant epilepsy.

Patients and methods

Between October 2002 and November 2007, three patients affected by unilateral giant subcortical heterotopia involving the temporo-parieto-occipital region were admitted to our Department.

Detailed clinical information was recorded. Development was assessed using the Griffiths' Mental Development Scales or WISC-R according to the patient age the Vineland Adaptive Behaviour Scales and the Child Behaviour Check list .

The brain malformation was investigated with high-resolution magnetic resonance imaging (HR-MRI). All three subjects had extensive ictal and interictal video-EEG evaluations. The patients underwent surgical resection of the malformed tissue. The postoperative epileptic outcomes were assessed using the Engel classification.

Results

Mean age at seizure onset was within the first months of life. Seizures consisted of asymmetric infantile spasms in the first and third case, and by complex partial seizures in the second one. The patients presented with contralateral hemiparesis, associated with axial hypotonia in cases 1 and 3. Moderate to severe developmental delay was observed in all cases. MRI showed a huge pseudo-mass, isointense to gray matter associated with corpus callosum partial agenesia and anomalies of the overlying cortex as well as basal ganglia (Fig.1).

Focal and diffuse paroxysmal activities in the affected hemisphere were detected in all three cases; in cases 1 and 3, contralateral independent paroxysmal activity was observed (supplementary Fig.2).

The 1st and 3rd cases underwent total excision of the heterotopic tissue; in the 2nd due to the extension of the heterotopia and the risk to produce a severe loss of functions (???) a partial excision of the lesion was performed and a subsequent cysto-peritoneal shunt was revised two times for mechanical blockage.

The postoperative follow-up was characterized by complete regression of seizures in the 1st and 3rd case, and significant seizure reduction in the 2nd case. All three patients experienced a considerable improvement of the neuropsycological impairment without worsening of the preoperative neurological deficit. Table 1 summarizes the main data of the three patients.

Discussion

Neuroimaging of our cases showed a subcortical hemispheric pseudo-mass, isointense to gray matter, with overlying dysplastic cortex associated with a homolateral small hemisphere, dysplastic basal ganglia and partial agenesis of corpus callosum. Hystopathology confirmed the heterotopic nodular pattern of the lesion.

Barkovich (Barkovich, 1996), describing subcortical heterotopia (SH) as "a distinct clinico-radiologic entity", reported some cases of unilateral diffuse and extensive heterotopia involving more lobes and the overlying cortex. The frequent association with hypogenesia or agenesia of the corpus callosum and dysplastic basal nuclei besides the hypoplasia of involved hemispheres accounted for a relevant failure of migration. More recently (Barkovich, 2000), Barkovich defined the neuroimaging appearance of SH in two main categories: nodular and curvilinear, although there would be no clinical difference between patients with various structural patterns. In the present series the nodular aspect prevailed in all patients, but contributing areas of the mixed (nodular and curvilinear) giant heterotopia type were identifiable around the main nodular lesion, at least in cases 1 and 3.

Thereafter, in the classification system proposed in 2001 (Barkovich et al, 2001) a subdivision of subcortical heterotopia included "large heterotopia with abnormal cortex and hypogenetic corpus callosum.".

In all our cases the heterotopia was associated with a CSF filled cystic collection located along the medial and posterior margins of the lesion, in two cases as interhemispheric cyst; in one case the cyst was in communication with the homolateral ventricle, while in the other 2 cases it was communicating with the ambiens cistern. One similar case with an interhemispheric cyst had been described by Barkovich (1996).

Other anecdotic cases of massive (giant) SH have been reported in literature (case 11, series of Ares et al, 1998; Preul et al, 1997: four cases, series of Tassi et al, 2005). Interestingly, these cases of "giant" heterotopia were unilateral. Thereafter, Battaglia et al (2006) proposed among nodular heterotopias a group (the 5[th] of their classification) of unilateral periventricular nodular heterotopia, generally very large and extending from the periventricular zone up to the adjacent neocortical or archicortical areas. Rather than a pure genetic origin, an acquired aetiology in the first half of gestation was thus suggested (Barkovich, 1996; Battaglia et al, 2006). Supporting this hypothesis, in two of our cases a miscarriage threat at the second-third month of pregnancy (critical period of the migration beginning) was reported.

Mental retardation is generally related to bilateral large and massive SH. However, in spite of the unilateral location of the malformation, cognitive development was definitely impaired before surgery in two out of our three patients. It is explained by the severe form of epilepsy (infantile spasms) in two cases: infantile spasms, already reported in giant SH (Kuwahara et al, 1996), belong to a well known epileptic encephalopathy with age-dependent clinical expression. For the other case the long-lasting drug-resistant seizures as well as the persistent polytherapy with antiepileptic drugs could have played a mayor role in determining the developmental impairment.

There is no exhaustive data concerning EEG patterns associated with subcortical heterotopia (Barkovich, 1996). It is noteworthy that multifocal EEG abnormalities were often found in patients with SH so that even the unilateral subcortical nodular heterotopia, whatever the origin of epileptic discharges whether cortical or coming from the heterotope nodules, should be considered potentially associated with multifocal epilepsy (Battaglia et al, 2006). IctIG patterns in all our patients were characterized by focal and diffuse paroxysmal activity in the affected hemisphere, but controlateral independent paroxysmal activity was detected in 2 of them. We are not able to establish whether this controlateral independent activity raised from controlateral microdisplastic areas or from the medial surface of the lesion detected by controlateral electrodes, or were caused by a "kindling" mechanism, provoking a secondary epileptogenic focus. Patient 3, with long lasting pre-surgical epilepsy, showed bilateral synchronous tonic discharges.

Incomplete excision of SH seems to be associated with a poor outcome, whereas complete removal of the involved cerebral region may lead to seizure-freedom (Francione et al , 1994). However, the experience in cases of giant forms is limited (Preul et al., 1997; Tassi et al., 2005).

Functional activity may persist in the areas of cortical anomaly (Preul et al., 1997; Villani et al., 2004). On these grounds an individualized surgical planning should be considered and even partial excisions of the involved cerebral areas can be considered as first step. In fact, though relapse of seizures occur more frequently after partial resection, transient control of seizures remains beneficial during a period of rapid brain maturation, and

later on, a second surgery can be planned. This was the policy adopted for our patients who all underwent removal of the subcortical heterotopia alone as first surgical step.

The surgical procedure was performed in the first year of life in cases 1 and 2, who underwent respectively total and partial excision of the SH, obtaining a good brief term seizure control in the first patient and a less favourable epileptic outcome in the second one; the latter had several postsurgical complications which might have interfered negatively on the postsurgical clinical evolution. Patient 3 underwent a total excision of the giant heterotopia, reaching a good control of epilepsy, in spite of long-lasting pre-surgical epilepsy.

The clinical post-surgical evolution showed in all cases some developmental improvement, namely motor in case 1 and of neuropsychological features (especially of language) in the others. Moreover, there was at least partial regression of behavioural disturbances. It is worth noting that the functional recovery was observed also in the patient who underwent surgery later than the other two, supporting the hypothesis of a possible persistent ability of functional re-organization up to adolescence (Chiricozzi et al, 2005).

Patients affected by giant subcortical heterotopias seem thus to present a favourable prognosis after the surgical removal of the lesion, even in cases of long-lasting epilepsy, in comparison with other extensive cortical malformations for which adjunctive disconnective procedures are often advocated. Surgery may be effective with a study for surgical candidature with only scalp video-EEG monitoring.

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