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Surgical management of Focal cortical dysplasia

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Abstract

Focal cortical dysplasia is a malformation caused by abnormalities of cortical development. It is characterized by no dysmorphic or ballon cells (type I), dysmorphic neurons witout or with ballon cells (type II). It is the main cause of pharmacoresistant epilepsy. The combination of clinical and neurophysiological findings provided by VEEG and MRI had lead to an improvement in the diagnosis and outcome of FCD. This paper describes our experience in the form of a retrospective study conducted on the patients affected by FCD who were treated in the Clinical Neurophysiology Service at University Hospital of Lille in France.

Key words: Focal cortical dysplasia; epilepsy surgery; VEEG; balloon cells; seizure.

Introduction

The development of the cerebral cortex is a complicated process during the process of embryogenesis. Disturbance in this development causes cortex deformity and a variety of neurological manifestations. Malformations of cortical development, in particular FCD, are the main causes of pharmacoresistant epilepsy.

FCD was described for the first time by Taylor *et al*. in 1971 (11). At first, the term was used for all deformities of cortical development. Recent progress in neuropathology, genetics and more particularly neuroimaging led up authors to propose various classifications. Various causes can lead to FCD, for example abnormalities in cell proliferation or apoptosis, cortical architectural abnormality, loss of cortical lamination with the presence of balloon cells, giant neurons and dysmorphic neurones. Several papers suggested the presence of a relationship between FCD and Tuberous Sclerosis.

Palmini *et al.* (8) have proposed a classifiaction which is widely used in the literature and is often refered to as 'palmini system clasification. This classification proposes two types of FCD. Type I: no dysmorphic neurons or ballon cells.

Type IA: isolated architectural abnormalities (dyslmination, accompanied or not by other abnormalities of mild MCD

Type IIA: architectural abnormalities, plus giant or immature, but not dysmorpphic neurons

Type II: Taylor-type FCD (dysmorphic neurons without or with ballon cells)

Type IIA: architectural abnormalities with dysmorphic neurons but without ballon cells

Type IIB: architectural abnormalities with dysmorphic neurons and ballon cells

A revision of this classification in 2011(7) suggests adding the third category-FCD III-in cases in which type I is associated to another epileptogenic lesion.

FCD accounts for about 30% of histological diagnosis as published in series whose topic was the cause of epilepsy after surgery. In the majority of cases, it occurs extratemporal mainly in the frontocentral region. FCD has a high epileptogenicity. The mechanisms of epileptogenicity are multifactorial and are not completely understood. Neuron excitement through N-Méthyl-D-aspartate receptor (NMDA) is responsible for the epileptic activity. $GABA_A$-receptor-mediated inhibition is also altered and abnormal synaptic interconnectivity changes occur in the pattern of catecholaminergic innervation. SISODIYA had suggested that there is a hyperexpression of a Multidrug Resistance-Associated Protein 1 in neurons in FCD (10, 11).

Lawson *et al.* (5) showed that non-balloon cell pathologic subtype causes more severe form of epilepsy.

Clinical features

In a typical case of FCD, the patient presents with a severe partial and high frequency seizure in early childhood. The types of seizures and the

neurological development of the child vary depending on many factors as well as the extent of involvement of the cortex. The child can present with psychomotor and cognitive dysfunctions. Neurological deficit can be also observed according to the location of the abnormality.

Electroencephalography (EEG)

In half of the cases, interictal activity shows continuous and quasicontinuous rhythmic spiking. The most characteristic interictal pattern consists of rhythmic or pseudorhythmic spikes.

Ictal manifestations are characterized by rhythmic spiking in a third or quarter of cases.

Imaging

Diagnosis of FCD began in the era of modern imaging. MRI demonstrates FCD in about 80% of cases, although the small lesions are difficult to detect.

FCD has often cortical thickening blurred GM/WM transition; hyperintense cortical lesions on T2 weighted images with radial bands in the white matter and cortical lamination defects. FLAIR sequence shows hypersignal in the white material. This hypersignal corresponds to the balloon cells.

According to Lawson, MRI features of focal cortical thickening with associated cortical T2 signal change show excellent sensitivity (94%) and reasonable specificity (73%). PET and SPECT can help to confirm the diagnosis in some cases.

Materials and methods

This paper involves a retrospective study of patients affected by FCD with severe epilepsy. In the Department of Clinical Neurophysiology of University Hospital of Lille in France, we studied 14 patients treated between 2000 and 2004.

There were 6 males and 8 females. The average age of patients is 33.42 years and of a limit (16-45 years). We excluded the patients with other associated epiletogenic factors such as as tumor or past history of meningitis. All the patients had a rigorous evaluation that included a conventional EEG and EEG in sleep. VEEG during hopsitalisation was done and it lasted for 48 hours in 4 days. One or several MRIs and sometimes PET scan and brain scintigraphy were realized. A prior history of febrile convulsion was obtained only in one patient (case number 12). All the patients had at least one seizure per week. Table 1 summarizes main characteristics of the patients.

All the patients had complex partial seizures and sometimes became generalized secondarily.

Table 2 shows clinical and EEG characteristics of the patients.

Candidate patients for surgery were those who did not answer to the medicinal treatment inspite of an adapted change of treatment and double-agent even triple-agent therapy. The main anti-epileptic agents used by the patients were the following ones: *Lamotrigin, Valproic acid, Topiramate, Carbamazépine, Gabapentin, Oxcarbazépine, phénytoïne, levetiracetam, phenobarbital.....*All the patients used to follow their treatment for many years.

Clinical case 1

A young 16-year-old man with foetal suffering and cranial trauma during his first year of life presented primarily at the age of 2 with complex partial seizures characterized by loss of contact and head rotation to the right.

Medical treatment was ineffective. Psychomotor development and cognitive functions remained normal. MRI showed a limited FCD in left infero-posterior frontal region. The EEG-video monitoring (VEEG) showed clinical syndrome of temporal epilepsy and seizure activity (rhythmic spike) in left temporal. Regarding this discordance, SEEG was proposed but the patient refused surgery. Bi therapy with Levetiracetam and Oxcarbazépine decreased, exponentially, the frequency and the rate of seizures.

Clinical case 2

37-year-old male without medical history but with the family history of epilepsy and normal psychomotor development presented for the first time at the age of 31 with partial seizures that became secondarily generalized with a left internal temporal lesion. Seizures took the form of heart palpitations, sensation of heat and speech disturbances. Stereotaxic biopsy concluded FCD. He underwent temporal polar resection and histologic analysis confirmed cortical dysplasia. He became seizure-free.

Clinical case 3

37-year-old right-hander male with cranial trauma at the age of 2 and psychotic disturbance in 2001 with two failed suicide attempts but with normal psychomotor development presented with seizures since the age of 6. He was on long-term sick leave for one year due to his epilepsy. The seizures manifested with loss of contact, oroalimentary automatisms and spontaneous slamming of tongue. Medical treatment

Table 1

Main characteristics of patients

Patient	Sex	Age	Past history	Epilepsy onset	Localisation	Surgery	follow up
1	M	16	Foetal suffering, cranial trauma	1 y	Left infero posterior frontal	NON (SEEG refused)	36 m
2	M	37	Epileptic father	31 y	Left temporo polar	Yes	39 m
3	M	37	Cranial trauma, psychotic disturbance	2 y	Right temporal	Yes	24 m
4	M	44	None	9 y	Right frontopolar et temporal	Yes	48 m
5	M	22	Nothing	5 y	Right frontal	Non	39 m
6	F	37	Epileptic brother	32 y	Left temporal	Non	48 m
7	F	39	Nothing	14 y	Bilateral parietal	Non (refused)	48 m
8	F	38	Nothing	8 y	Right temporal	Non	37 m
9	F	45	None	13 y	Frontal bilateral	Non	25 m
10	F	30	None	2 y	Right temporal	non	19 m
11	F	23	None	4 y	Right fronto orbital	Yes	28 m
12	M	43	Febrile seizure	6 m	Right Ammon's horn	Yes	48 m
13	F	35	None	13 y	Left Head and Ammon's horn of hippocampus	Yes	48 m
14	F	23	None	14 y	Right internal temporal	Yes	38 m

was unsuccessful. The frequency of the seizure was once per week on average. Assessment showed left exposed intellectual and mnesic disabilities. MRI showed hippocampal sclerosis and right temporal FCD. VEEG objectivized a very active seat in right temporal region. We performed right temporal lobectomy in 2003. Since then and till two years after, he had only one seizure and he got his job back.

Clinical case 4

44-year-old male without medical history had, for the first time, a seizure at the age of nine. He had a normal psychomotor development. Seizures were characterized by loss of contact, fixed gaze, important excitement, inconsistent comment while moving his hands and falling forward. Despite combination therapy, he had seizures several times per day. MRI showed diffuse abnormal signal in favour of CFD in right fronto-temporal and frontopolar lobes. PET demonstrated orbitofrontal cortex hypometabolism.

SEEG demonstrated intercritical period characterized by the presence of the pseudorhythmic spikes in the right external fronto-basal region.

He had a right external and internal anterior frontal cortectomy. Since then and after 4 years of follow-up, he was seizure-free.

Clinical case 5

22-year-old male without medical history presented at the age of 5 with partial seizures that secondarily became generalized. Seizures were stereotypical and in the form of non-speech vocalization and deviation of the head towards the left and short loss of contact. Intercritical EEG showed slow waves in the right frontal region and ictal EEG demonstrated fast discharges. MRI brought to light a very extensive FCD in the right frontal region which was difficult to remove by surgery, because of the large extent of the lesion. Despite combination therapy, he continues to have seizures.

Clinical case 6

37-year-old woman with an epileptic brother presented since her first year of life with partial seizures. Seizures were associated with abdominal pain and sudden sense of unprovoked fear. The first seizure was generalized but other seizures were partial. Medical treatment was not effective. Preoperative assessment confirmed temporal epilepsy. EEG showed an active seat in left temporal region and MRI demonstrated that FCD was in the left para-

Table 2

Clinical and EEG characteristics of patients

Patient	Type of seizure	Main characteristic EEG
1	Loss contact, right rotation head	Rhythmic spikes
2	Heart palpitation, heat sensation,speech disturbance	Pseudorhythmic spikes
3	Loss contact, oroalimentary automatisms, slamming of tongue	Rhythmic spikes
4	Loss contact, fix glance, falling forward	Pseudorhythmic spikes
5	Non speech vocalisation, left rotation head, short loss contact	Polyspike activity
6	Abdominal pain, sudden sense of unprovoked fear	Rhythmic spikes
7	Numbness,tingling, sensation of weird position of arm and leg	Psudorhythmic spikes
8	Heart palpitation, heat sensation, panic and burning sensation	Pseudorhythmic spikes
9	Right rotation of head, tensing of the right hand, break loss of contact	Pseudorhythmic spike
10	Out-of-body feeling, fear, anger, déjà vu	Rhythmic spikes
11	Left jacksonian march, stiffening of the limbs and face	Diffuse high voltage theta, spiked waves
12	Fear, nausea, left hemi-paresthesia	Spike waves
13	Deja vu et deja vecu Olfactive sensation of fresh wind, belly ache and vomit	Rhythmic spikes
14	Quick abrupt ascending epigastric embarrassment, fear, profuse perspiration	Spike waves complexes

hippocampal gyrus. We proposed doing a surgery but the patient refused.

Clinical case 7

38-years-old female presented since the age of 14 with partial seizures. Seizures were partial complex with sensations of numbness and tingling and weird position of both arms and legs. Inspite of combination therapy, the patient continued to have seizures. MRI showed bilateral FCD in the parietal regions. Clinical situations were stable. Considering the area (extent) of the lesion, a surgical operation seemed unfair to us.

Clinical case 8

38-years-old female presented with seizure since childhood. Seizures were associated with heart palpitations, sensation of heat, panic attack and burning sensation. MRI demonstrated a FCD in the right hippocampal region. EEG demonstrated pseudorhythmic spikes in interictal and rhythmic spiking in ictal in right temporal region. Surgical discussion was made but following the introduction of the treatment by levetiracetam, frequency of the seizure widely decreased thus the surgery was postponed.

Clinical case 9

45-year-old female had seizure since the age of 13 characterized by drop attack, turning of the head towards the right, tensing of the right hand and a brief break of contact. Inspite of an adapted combination therapy, she had about ten crisis per month. MRI showed a FCD in the frontal region. EEG showed discharges of pseudorhythmic spikes suggestive of an FCD. Due to the bilateralism of the lesion, surgery was not proposed.

Clinical case 10

30-years-old female presented since the age of 2 with complex partial seizures with out-of-body feeling, fear, anger and “déjà vu”. She had a half sister who was also epileptic. EEG showed rhythmic spike in right temporal region. MRI confirmed FCD in right hipocampus. The last modification of medical treatment had led to a total control of the seizure.

Clinical case 11

23-year-old female is affected by a severe epilpsy since the age of 4 with important school difficulties. She had left Jacksonian march, stiffening of the limbs, and face, condition in which the crisis increased until it became generalized secondarily. The MRI showed a right internal fronto-orbital FCD and the front of the cingulate gyrus, the data given by EEG tally with these localizations and showed an ictal diffuse high-voltage theta and diffuse spike and waves, in the right frontal region.

The patient was operated for a frontal cortectomy and since then she is seizure-free.

Clinical case 12

43-year-old male with a feverish convulsion at the age of 6 months during meningitis made his first partial crisis at the age of 23. They were associated with fear, nausea and left hemi-paresthesia. MRI revealed a right Ammon's horn FCD and hippocampal sclerosis; interictal EEG showed spike and waves in right temporal region. He was operated and he was free of crisis during 9 months but seizures reappeared with a frequency that seemed to be much less important.

Clinical case 13

35-year-old female presents since the age of 13 years with seizures. The first crisis was generalized then they become partial in the form of deja vu and deja vecu olfactive sensation of fresh wind in nostrils, belly ache and vomit. MRI presents an FCD of the region of the head and Ammon's horn of hippocampus. EEG demonstrated pseudorhythmic spikes in interictal and rhythmic spiking in ictal period. Epilepsy was resistant to medical therapy. She was operated and for 3 years, was seizure-free. Recently, the less grave crises had reappeared.

Clinical case 14

23-year-old female had seizures since the age of 14 and the medical treatment was ineffective. There was an abrupt appearance of sensation of quick abrupt ascending epigastric embarrassment followed by fear and by a profuse perspiration. MRI shows a right internal temporal FCD. EEG showed a temporal extra zone and limbic seat in form of spike wave complexes. In front of this conflict, an SEEG was made which revealed a focus in internal temporal. She was operated but some weeks after seizures reappeared.

Results

Seven patients included in this study were operated (50% of all the patients). All these patients were epileptic since many years and they took many treatments unsuccessfully or with a relative effect without satisfying seizures control. The decision of surgery was made for the patients after an assesment. 8 patients had FCD located in temporal region (57.14%) and 6 patients (42.85%) had FCD in extra temporal region: 5 in the frontal region (35.71%) and 1 in the parietal region (7.14%). One patient (case 4) had FCD frontal and temporal. We classified him in the extratemporal category because his frontal FCD was active clinically as proved by EEG. Two patients (cases 3 and 12) had associated hippocampal sclerosis.

7 patients were operated (50% of all the patients). 3 patients became seizure-free (cases 2, 4, 11) two patients (cases 12 and 13) were seizure free for 9 months and 4 years until seizures reappeared. One patient (case 3) improved exponentially and one patient (case 14) had no change.

Table 3 shows outcomes of the operated patients following Engel classification system.

Operated patients had a middle follow of 39.6 months with a minimum of 24 months and maximum of 48 months. Among the 7 patients not operated, in only one case (case 10) medical treatment controlled seizures totally within 25 months of follow up. In other 6 cases, the patients continued to have seizures. In two cases (cases 1 and 8) frequency of seizures decreased widely. In 4 patients we did not observe significant improvement inspite of combination therapy. Patient 10 had no seizure for 25 months. Patients 1 had less than 3 seizures per month. Patients 6, 8 and 9 had 3 seizures per month and patients 5 and 7 had several seizures per day. Seizure frequency was from 3 to 30 per month. In one patient, he had several seizures per day.

MRI is the paraclinical wide spread imaging which allowed us to pose the diagnosis in 100% of the cases. In 8 patients (57.14%) the first MRI was positive. In 6 other cases; two or several MRI were suspected for the diagnosis. In these 6 patients, the first MRI realized before 2000 was negative and the lesion done before that time did not show up, this makes think that machines were not adequately adjusted and did not have adequate sequences to visualize the cortical abnormalities.

Intercritical Electroenchephalogramme showed:

1. Abnormality in rhythm of base in 11 patients (78.57%)

Table 3

Outcome of operated patients following Engel classification

Patient	ECS
P.2	I
P.3	I
P.4	I
P.11	I
P.12	II
P.13	I
P.14	IV

Table 4

Seizures frequency in non-operated patients

Seizure frequency	SF < 3/m	3 < SF < 30/m	SF > 30/m
Patients	2p.	3p.	2p.

2. Slow waves in 9 patients (64.28%) with the following distribution:

   in one case hemispherical = 7.1%
   in 3 cases frontal = 21.4%
   in 3 cases temporal = 21.4%
   in one case bilateral = 7.1%
   in 2 cases multilobar = 14.2%

3. The spikes and spikes-and-waves: in 10 patients with

   in 1 case hemispherical
   in 6 cases temporal
   in 1 case frontal
   in 1 case central
   in 1 case multilobar

Critical EEC was performed in all the patients with the following results:

Rhythmic spike in 5 cases (35.71%). Pseudo-rhythmic spike in 5 cases (35.71%).

Among these ten patients, 7 patients (70%) localizations were corresponding with the localization of the dysplasia discovered on MRI. One patient (case 2) underwent stereotaxic biopsy.

Among 2 patients of the 7 operated, SEEG was performed In 2 cases it was about a conflict between the data of the classic EEG and those of MRI and thus the result of the SEEG pleaded in favour of the localization visualized on MRI (case 14) and in the other case (no° 4) SEEG helped in finding the active site for surgery.

Discussion

As it was told previously, FCD is responsible of resistant epilepsy. According to our experience, In spite of the small number of our patients, we think that the results are conclusive. 5 patients out of 7 (71.42%) are in category I of the classification Engle. 3 cases (42.9) became seizure-free and in two cases they were seizure-free during certain time(weather) but even after the seizure recurrence, they were less important. In any case only a patient remained unchanged (14.7%) and we noticed in 6 cases out of 7 (85.6%) an improvement in number and frequency of seizures.

IRM is the most successful examination in particular the sequence.VEEG Intuition is also indispensable to understand better the clinical form of seizures and the relation with the data of the EEG. The pattern most visualized in patients was rhythmic spikes and pseudorhythmic spike.

Although there is always a challenge for the surgery for FCD, we think that this surgery can be useful when the choice of the patients is rigorous and done according to the tallying data of meadow surgical examination. In the series appeared to the literature although little numerous, the results are satisfactory. As regards to the area of the excision, a total lesionectomy is naturally desirable. In the serie of Cohen-Gadol *et al.*, 75% of 22 operated patients were seizure-free after an average follow-up of 6, 3 years.

REFERENCES

1. Chassoux F. Stereo-EEG: the Sainte-Anne experience in focal cortical dysplasias. Epileptic disorders. 2003;Sep;5Suppl 2:S95-103.
2. Chassoux F, Devaux B, Landré E, Turak B, Nataf F, Varlet P, Chodkiewicz JP, Dumas-Duport C. Stereo-electroencephalography in focal cortical dysplasia: A 3D approach to delineating the dysplastic cortex. Brain. 2000;123(8):1733-1751.
3. Cohen-Gadol Ozduman K, Bronen RA, Kim JH, Spencer DD. Long-term outcome after epilepsy surgery for focal cortical dysplasia. J Neurosurgery. 2004;101(1):55-65.
4. Eltze CM, Chong WK, Bhate S, Harding B, Neville BG, Cross JH. Taylor-type focal cortical dysplasia in infants: some MRI lesions almost disappear with maturation of myelination. Epilepsia. 2005; 46(12):1988-92.
5. Lawson JA, Birshansky S, Pacheco E, Jayakar P, Resnick TJ, Dean P, Duchowny MS. Distinct clinico-pathologic subtypes of cortical dysplasia of Taylor. Neurology. 2005;11;64(1):55-61.
6. Noachtar S, Bilgin O, Rémi J, Chang N, Midi I, Vollmar C, Feddersen B. Interictal regional poly-spikes in noninvasive EEG suggest cortical dysplasia as etiology of focal epilepsies. Epilepsia. 2008; 49(6):1011-7.
7. Palmini A. Revising the classification of focal cortical dysplasias. Epilepsia. 2011;52(1):188-190.
8. Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, Jackson J, Lüders HO, Prayson R, Spereafico R, Vintes HV. Terminology and classification of the cortical dysplasia Neurology. 2004;23;62(6suppl3)S2-8.
9. Salamon N, Kung J, Shaw J, Koo SJ, Wu JY, Lerner R, Sanker WD, Sheilds J, Engel JR. FDG-PET/MRIcoregistration improves detection of cortical dysplasia in patient with epilepsy. Neurology. 2008;11,71(20):1954-1601.
10. Sisodiya SM. Malformations of cortical development: burdens and insights from important causes of human. Epilepsy Lancet Neurol. 2004;3(1):29-38.

11. Sisodiya SM. Surgery for malformations of cortical development causing Brain. 2000;123(Pt 6):1075-91.
12. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry. 1971;34(4):369-87.
13. Taylor DC, Lochery M. Temporal lobe epilepsy: origin and significance of simple and complex auras Neurol Neurosurg Psychiatry. 1987;50(6):673-681 .
14. Takenaka J, Aso K, Watanabe K, Okumura A, Negoro T. Transient seizure remission in intractable localization-related epilepsy Pediatre Neurol. 2000; 23(4):328-31.
15. Wang V, Chang E, Barbaro N. Focal cortical dysplasia: a review of pathological features, genetics, and surgical outcome Neurosurgery Focus. 2006;20(1): 15;20(1):E7.
16. Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, Sperling MR, Lüders H, Pedley TA; Commission on Neurosurgery of the International League Against Epilepsy (ILAE): ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia. 2001:42(2):282-6.
17. Widdess-Walsh P, Jeha L, Nair D, Kotagal P, Bingaman W, Najm I. Subdural electrode analysis in focal cortical dysplasia: predictors of surgical outcome. Neurology. 2007;14,69(7):660-667.

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