

# Temporal lobe epilepsy: neuropathological and clinical correlations in 243 surgically treated patients

Laura Tassi<sup>1</sup>, Alessandra Meroni<sup>2</sup>, Francesco Deleo<sup>2</sup>, Flavio Villani<sup>2</sup>, Roberto Mai<sup>1</sup>, Giorgio Lo Russo<sup>1</sup>, Nadia Colombo<sup>3</sup>, Giuliano Avanzini<sup>2</sup>, Chiara Falcone<sup>4</sup>, Manuela Bramerio<sup>5</sup>, Alberto Citterio<sup>3</sup>, Rita Garbelli<sup>2</sup>, Roberto Spreafico<sup>2</sup>

<sup>1</sup> Epilepsy Surgery Centre "C. Munari"

<sup>2</sup> Division of Epilepsy Clinic and Experimental Neurophysiology, I.R.C.C.S. Foundation Neurological Institute "C. Besta"

<sup>3</sup> Department of Neuroradiology, Niguarda Hospital

<sup>4</sup> Epidemiology Unit, I.R.C.C.S. Foundation Neurological Institute "C. Besta"

<sup>5</sup> Department of Pathology, Niguarda Hospital, Milan, Italy

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**ABSTRACT** – The present study included analysis of data from 243 patients surgically treated for Temporal Lobe Epilepsy (TLE). Resection was confined to the temporal lobe, with at least two years of follow-up, and specimens sufficiently preserved to allow a precise evaluation of both lateral neocortex and hippocampus. The frequency of different types of lesion and hippocampal sclerosis (HS), isolated or associated with neocortical lesions, risk factors and surgical outcomes in relation to neuropathological findings were evaluated. We found tumours in 33% of patients, malformations of cortical development (MCD) in 45%, isolated HS in 14%, no lesion in 5% and less common lesions in 3%. HS was present in 8% of tumour cases and 70% of MCD. Statistical analysis of antecedents was significantly associated only with febrile seizures (FS). In MCD patients with no history of FS, a strong association between HS and duration of epilepsy was revealed. A Class I outcome was identified in 87% of cases with tumours and 79% in cases with MCD. In 93 patients the anti-epileptic drug therapy was withdrawn. Our findings show that MCD, which is significantly associated with HS, is the most common lesion in TLE and support the concept that an optimal outcome is obtained when mesial and neocortical structures are removed. FS are particularly relevant in patients with focal cortical dysplasia and HS.

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. In surgical series of patients with drug-resistant epilepsy, 60-75% of cases are reported to have TLE (Blümcke *et al.*, 2002; Lahl *et al.*, 2003).

Since the work of Falconer *et al.* (1964) and Margerison and Corsellis (1966), hippocampal sclerosis (HS) has been recognized as a common pathological finding in TLE surgical series. More recent MRI techniques,

## Correspondence:

R. Spreafico, MD, PhD  
Division of Epilepsy Clinic and Experimental  
Neurophysiology, Fondazione I.R.C.C.S.  
Istituto Neurologico "C. Besta",  
Via Celoria 11, 20133 Milano, Italy  
<spreafico@istituto-besta.it>

such as hippocampal volumetry and T2 relaxometry, which are able to reliably diagnose HS *in vivo* (Bernasconi et al., 2000) have reinforced the idea that the hippocampus plays a leading role in the genesis of seizures in patients with drug-refractory TLE. However, pathological studies show that lesions correlated with TLE may be found well beyond the hippocampal formation (Margerison and Corsellis, 1966) and conventional MRI often identifies developmental or vascular malformations and tumours within the temporal lobe in TLE patients, which may or may not be associated with HS (Kuzniecky et al., 1999; Raymond et al., 1994; Lee et al., 1998). More recently, post-processing MRI techniques, in particular quantitative volumetric analysis, have identified extrahippocampal abnormalities such as temporal lobe volume loss and entorhinal cortex atrophy in TLE patients (Moran et al., 2001; Bernasconi et al., 2005) suggesting that TLE may depend on either a more widespread temporal lobe disturbance or is the result of so-called dual pathology, *i.e.* HS with alterations in neocortical temporal structures (Falconer et al., 1964; Lèvesque et al., 1991; Li et al., 1999).

Evidence that neocortical structures, particularly the temporal pole, can be involved in the genesis of TLE has been presented by several other studies dating back to the late 1980s (Kuzniecky et al., 1987; Kahane et al., 2002; Coste et al., 2002). Studies that examined the electroclinical features in patients with TLE (Burgerman et al., 1995; Chabardès et al., 2005) suggest a pivotal role of the temporo-polar cortex in many cases, while MRI (Moran et al., 2001), neuropathological (Mitchell et al., 1999) and metabolic (Ryvlin et al., 1998) abnormalities have also been identified in the temporal pole, associated or not with HS. However, there is no consensus regarding the genesis of neocortical abnormalities, although gliosis (Falconer et al., 1964), developmental cortical abnormalities (Hardiman et al., 1988; Thom et al., 2001), loss of myelin (Meiners et al., 1999) and non-specific increase

in temporal lobe water content (Mitchell et al., 1999; Concha et al., 2009) have all been suggested to play a role.

Dual pathology is estimated to occur in 5-30% of TLE cases. The most common second alteration is a malformation of cortical development (MCD), most often focal cortical dysplasia (FCD) (Raymond et al., 1994; Cendes et al., 1995; Lèvesque et al., 1991; Li et al., 1999). Since an optimal outcome is obtained when both the HS and FCD are removed (Li et al., 1999; Salanova et al., 2004; Chabardès et al., 2005) it seems evident that both contribute to seizure genesis.

Retrospective studies have repeatedly found that a large number of patients undergoing surgery for intractable TLE have both HS and a history of febrile seizures (FS) as infants (French et al., 1993), suggesting that FS may cause injury to mesial temporal structures causing HS with subsequent development of TLE (Mathern et al., 1995; VanLandingham et al., 1998). It has also been suggested that congenital neocortical or hippocampal abnormalities may render the temporal lobe particularly vulnerable to prolonged infantile FS and hence TLE (Annegers et al., 1987; VanLandingham et al., 1998; Blümcke et al., 2002). In this regard it is noteworthy that induced neuron migration defects in rat pups result in greater susceptibility to seizures and greater irreversible hippocampal neuron damage following hyperthermia than those controls with no neuron migration defects (Germano et al., 1996). Despite the fact that an association between dysgenesis and subsequent increase of susceptibility to hyperthermic seizures and neuronal injury has been documented in animals, a similar relationship has not been demonstrated in humans (Lewis, 2005). However, recent MRI and neuropathological data also provide evidence of a correlation between HS and duration of epilepsy (Fuerst et al., 2001; Bernasconi et al., 2005).

The aims of the present retrospective study, performed through reviewing the neuropathological, MRI and clinical records of 243 patients who received temporal lobe resection for intractable seizures were to determine: (a) the frequency of different types of lesion within the temporal lobe, (b) the frequency of HS isolated or associated with neocortical lesions (dual pathology), (c) the frequency of risk factors and (d) surgical outcomes in relation to neuropathological findings.

## Methods

### Patient selection

Drug resistant epileptic patients were referred to the "C. Munari" Epilepsy Surgery Centre from different epilepsy units all over Italy. Eligibility of patients for epilepsy surgery was made only after a comprehensive discussion among the referring neurologist, the epileptologists,

### Abbreviations

|       |  |
|-------|--|
| AED   | anti-epileptic drugs                     |
| DNT   | dysembryoplastic neuroepithelial tumours |
| EEG   | electroencephalogram                     |
| FS    | febrile seizures                         |
| FCD   | focal cortical dysplasia                 |
| FLAIR | fluid attenuated inversion-recovery      |
| GFAP  | glial fibrillary acid protein            |
| HN    | heterotopic neurons                      |
| HS    | hippocampal sclerosis                    |
| IR    | inversion recovery                       |
| MAP2  | microtubule-associated protein-2         |
| MCD   | malformation of cortical development     |
| MRI   | magnetic resonance imaging               |
| NeuN  | neuron-specific nuclear protein          |
| SE    | spin-echo                                |
| SEEG  | stereo-electroencephalography            |
| TLE   | temporal lobe epilepsy                   |
| TSE   | turbo spin-echo                          |
| VEEG  | video-electroencephalography             |

neurosurgeons and neuroradiologists of the epilepsy surgery centre. Drug resistance was defined according to the criteria proposed by Perucca (1998).

Neuropathological data on 291 patients out of 506 operated on between May 1996 and May 2005, with resection confined to the temporal lobe, were retrospectively reevaluated. Only 243 patients, with surgical specimens sufficiently preserved to allow a precise evaluation of both lateral neocortex (including white matter) and hippocampus, were considered in the present report. The neuropathological data were classified and related to clinical and MRI findings and post-surgical outcome.

All patients underwent extensive pre-surgical evaluation including detailed history with questions about family history of epilepsy, spontaneous abortions, infections, head trauma, FS and risk factors for pre- or perinatal brain damage. For these data the clinical records of each patient were accurately assessed and only precise descriptions of the pathological events were taken into account, particularly for FS; when the source of the information and the description of anamnestic data were not reliable the event was not considered. Age at seizure onset, mode of presentation, seizure characteristics and frequency and antiepileptic treatments up to the time of surgery were also recorded. All patients received neurological examination, complete neuropsychological work up, MRI and comprehensive EEG or video-EEG (VEEG) examinations (or both). When the electroclinical data and MRI findings did not identify the epileptogenic zone with sufficient precision, invasive pre-surgical Stereo-EEG (SEEG) was performed to achieve the required accuracy (Cossu *et al.*, 2005). The description of neuropsychological and electrophysiological data are beyond the scope of the present paper and thus have not been presented.

## MRI

Preoperative MR imaging was obtained using a 1.5 T machine (Philips ACS-III-NT) in all patients. The MR protocol (Colombo *et al.*, 2003) included the following sequences: transverse spin-echo (SE) double echo images of the entire brain (2,000-2,500/20-90) [TR msec/TE msec], 1 avg, 128 x 256 matrix, 230 FOV; 4-5 mm thickness; coronal turbo spin-echo (TSE) TW2 images (2,300/100) [TR msec/TE msec], 4 avgs, 256 x 256 matrix, 230 mm FOV, 3 mm thickness; coronal TSE fluid-attenuated inversion-recovery (FLAIR) T2W sequence (6,000/100/2,000) [TR msec/TE msec/inversion time msec], 3 avgs, 238 x 256 matrix, 230 mm FOV, 3 mm thickness; coronal TSE inversion recovery (IR) T1W images (3,000/20/400) [TR msec/TE msec/inversion time msec], 3 avgs, 256 x 256 matrix, 230 mm FOV, 3 mm thickness.

Images, both parallel (transverse) and perpendicular (coronal) to the major hippocampal axis were acquired. Intravenous contrast was injected when necessary.

Mass lesions, gyration anomalies, focal thickening of the cortex, blurring of the grey-white matter junction, areas of abnormal signal intensity in the cortex and white matter, atrophic changes and vessel anomalies were all assessed. Hippocampal alterations were assessed visually with attention to atrophy, increased signal on TSE-T2W and TSE-FLAIR-T2W images, decreased signal in TSE-IR-T1W images and loss of definition of the internal structures.

## Surgery and follow-up

Resections were performed for strictly therapeutic reasons after informed consent. Both the anatomic lesion (where identified) and the cortical epileptogenic zone, as identified by electroclinical and MRI examinations, were removed. When MRI was unrevealing, the resection was planned using electroclinical data. The extent of resection was planned pre-operatively, in each case considering the severity of epilepsy and risk of post-surgical deficits. In 42 (17%) patients the surgery was performed after invasive SEEG. No patient received selective amigdalohippocampectomy.

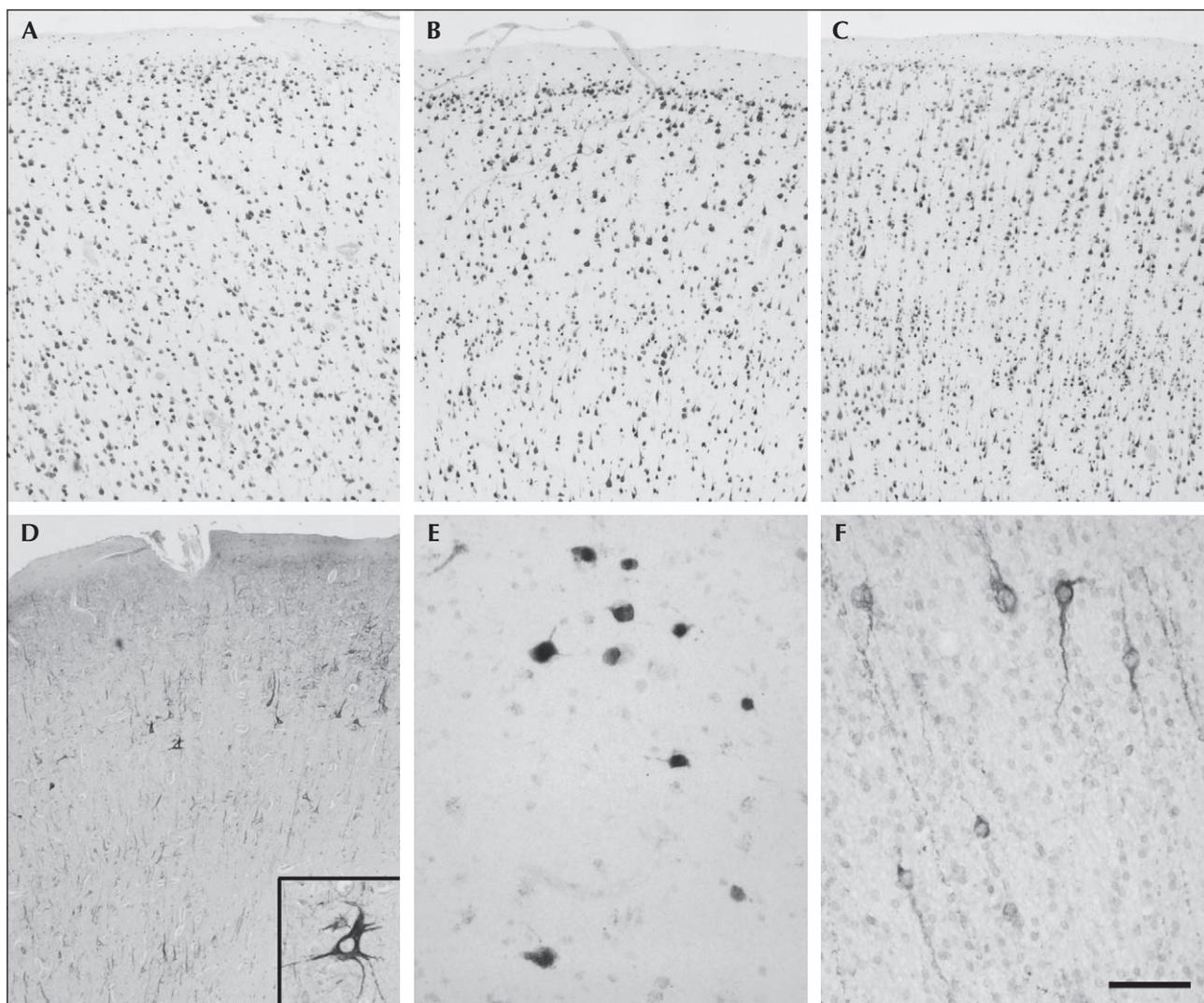
Seizure freedom was monitored periodically and determined according to Engel's classification (Engel *et al.*, 1993), with at least two years of follow-up, in all the recruited patients. Withdrawal of anti-epileptic drugs (AEDs) was performed only after 24 months of seizure freedom in patients in class I. The reported data regarding follow-up and anti-epileptic medication status were compiled through office visits or telephone contact during the first half of 2008.

## Histopathological procedures

Each surgical specimen was fixed in 10% neutral buffered formalin, embedded in paraffin and processed routinely. Serial 7 µm sections were stained with haematoxylin and eosin, thionin, Luxol Fast Blue or Bielschowsky. Other sections were immunostained using antibodies against glial fibrillary acid protein (GFAP, Boehringer Mannheim, Germany), neurofilaments (2F11 monoclonal, DAKO, Germany), microtubule-associated protein-2 (MAP2, Boehringer Mannheim, Germany) and neuron-specific nuclear protein (NeuN, Chemicon International, Temecula, CA). The immunoperoxidase procedure was described elsewhere (Tassi *et al.*, 2001). The slides were reviewed independently by three neuropathologists, one of whom had not been involved in the initial diagnoses and was unaware of the electroclinical data, MRI findings and surgical outcomes. Disagreements were discussed and a consensus diagnosis was achieved. Tumours were assigned to histopathological subtypes following the World Health Organization classification of tumours (Louis *et al.*, 2007). Hippocampal sclerosis (HS) was diagnosed in the presence of diffused gliosis associated with pyramidal cell loss in CA1, CA3 and CA4 (hilus) sectors of the Ammon's horn (CA) (Blümcke *et al.*, 2002). Cases with

tissue fragmentation obscuring hippocampal anatomy were excluded. Focal cortical dysplasia (FCD) was diagnosed according to Tassi *et al.* (2002) as refined by Palmini *et al.* (2004), recognizing two main morphological types: type I and type II (Taylor's type dysplasia). The type II FCD was quite clearly defined by the presence of profound disruption of cortical layering coupled with cytological abnormalities characterized by the occurrence of dysmorphic neurons (FCD type IIA) and the presence of balloon cells (FCD type IIB). Since only 12 patients presented this type of dysplasia in the present cohort, the subdivision into the two subgroups was not considered in the report. Type I FCD was diagnosed on the basis of cor-

tical dyslamination (*figure 1A*), frequently associated with reduction of cortical thickness and with the presence of numerous heterotopic neurons in the white matter. In the majority of the patients, laminar alteration was observed particularly in the supragranular layers (*figure 1B*), however, columnar arrangement was also observed in some specimens (*figure 1C*). In only eight patients, hypertrophic pyramidal-like neurons, as described by Tassi *et al.* (2002), were observed in addition to the laminar disorganization and thus defined as FCD type IB (cytoarchitectural dysplasia) (*figure 1D*). Thus, as was the case for type II FCD, all the patients were similarly grouped within category type I. For heterotopic neurons



**Figure 1.** Examples of neuropathological findings observed in FCD type IA (A-C), FCD type IB (D), and neuronal heterotopy (E-F). A-C NeuN immunocytochemistry showing disruption of cortical architecture (A), abnormal clustering of layer II neurons (B), and prominent microcolumnar arrangements of the cortex (C). D) Giant pyramidal neurons showing excessive neurofilament protein immunoreactivity (see insert) are a typical hallmark of FCD type IB. E-F NeuN (E) and MAP2 immunocytochemistry (F) showing excessive neurons in subcortical white matter. Bars: 240  $\mu\text{m}$  (A-D), 70  $\mu\text{m}$  (insert in D), 40  $\mu\text{m}$  (E-F).

(HN), specimens from 42 patients with suspected neuronal heterotopia in white matter were processed for further semi-quantitative estimation of heterotopic neurons in the white matter from the same anatomical region for all the specimens. Two temporal autopsy brains obtained from patients without known neurological disorder and one surgical specimen of neocortex, adjacent to low-grade glial temporal tumours from a non-epileptic patient, were used as internal normal controls. Briefly, 4  $\mu$ m thick sections were de-waxed in two changes of xylene and hydrated through graded alcohols. Pre-treatment with microwave was performed before incubation in 10% (v/v) normal serum and the following 12 hours incubation in primary antibody (MAP2, 1:300). The grey-white matter boundaries were delineated at 2.5 x objective with a fine ink line using Luxol Fast Blue-stained sections as a reference (Thom *et al.*, 2001) and only neurons in the deep white matter (at least 500  $\mu$ m from the grey matter boundary) were measured using a BX51 microscope (Olympus, Japan) with motorized stage linked to an image-analysis system (Prior Optic Scan II camera and Image Pro-Plus 6 software). Cell counting was performed at 20 x objective in randomly placed visual fields corresponding to a final surface of  $5.54 \pm 2.4$  mm<sup>2</sup>/section, according to the methodological description by Hildebrandt *et al.* (2005). Using this methodology, the number of neurons in the white matter in our control samples was estimated at  $8.2 \pm 1.4$ /mm<sup>2</sup>, thus below the value of  $13.3 \pm 0.6$ /mm<sup>2</sup> estimated by Hildebrandt *et al.* (2005). However, 15 neurons/mm<sup>2</sup> was considered the cut-off for the diagnosis of HN.

### Statistical procedures

The association between HS and familiarity for epilepsy, miscarriage, risk of spontaneous abortion, pre- and perinatal infections, neonatal distress, head trauma, and FS was assessed using Pearson's chi-square or Fisher exact test (when appropriate). Association between HS and FS was also evaluated between the two subgroups with tumours and with MCD.

A logistic regression model was performed to evaluate the association between duration of epilepsy, age at surgery and HS. Associations with  $p \leq 0.05$  were considered significant. All statistical analysis were performed with STATA for Windows software version 9.0.

### Results

Of the 506 consecutive patients who underwent surgery for drug-resistant focal epilepsy, 243 (48%) fulfilled the inclusion criteria and thus were included in the present study (table 1). There were 114 (47%) females and 129 (53%) males. Surgery was performed on the right temporal lobe in 128 (53%) and on the left in 115 (47%) patients. Neurological examination was normal in 219 (90%) patients. Mean age of epilepsy onset was 10 years (SD 9; range 0-53). Mean duration of epilepsy was 20 years (SD 12, range 0-59). Mean age at surgery was 30 years (SD 12, range 1-60). Mean seizure frequency at surgery was 19 per month (SD 26, range 1-150). General data of the population are represented in table 1.

**Table 1.** Main clinical characteristics of 243 patients.

| Neuropathology                            | N. of patients (%) | Males (%)       | Females (%)     | Mean age at epilepsy onset (SD) | Mean duration of epilepsy (SD) | Mean age at surgery (SD) | Mean n. of seizures per month (SD) |
|---|--------------------|-----------------|-----------------|---------------------------------|--------------------------------|--------------------------|------------------------------------|
| Glial and meningeal tumours <sup>a</sup>  | 19 (8)             | 12 (63)         | 7 (37)          | 16 (13)                         | 12 (11)                        | 27 (13)                  | 18 (26)                            |
| Mixed neuronal-glial tumours <sup>b</sup> | 60 (25)            | 31 (52)         | 29 (48)         | 8 (7)                           | 16 (12)                        | 24 (14)                  | 27 (35)                            |
| <b>Tot. tumours</b>                       | <b>79 (33)</b>     | <b>43 (54)</b>  | <b>36 (46)</b>  | <b>10 (9)</b>                   | <b>15 (12)</b>                 | <b>25 (13)</b>           | <b>25 (34)</b>                     |
| FCD I                                     | 60 (25)            | 31 (52)         | 29 (48)         | 10 (10)                         | 22 (11)                        | 32 (12)                  | 13 (15)                            |
| FCD II                                    | 12 (5)             | 7 (58)          | 5 (42)          | 8 (7)                           | 22 (9)                         | 30 (10)                  | 20 (19)                            |
| Heterotopic neurons                       | 23 (9)             | 15 (65)         | 8 (35)          | 8 (8)                           | 23 (11)                        | 31 (9)                   | 18 (23)                            |
| Other MCD <sup>c</sup>                    | 15 (6)             | 9 (60)          | 6 (40)          | 9 (7)                           | 23 (13)                        | 32 (11)                  | 20 (29)                            |
| <b>Tot. malformations</b>                 | <b>110 (45)</b>    | <b>62 (56)</b>  | <b>48 (44)</b>  | <b>9 (9)</b>                    | <b>23 (11)</b>                 | <b>32 (11)</b>           | <b>16 (20)</b>                     |
| HS Only                                   | 34 (14)            | 18 (53)         | 16 (47)         | 7 (6)                           | 26 (10)                        | 34 (11)                  | 12 (13)                            |
| Other <sup>d</sup>                        | 7 (3)              | 2 (29)          | 5 (71)          | 17 (9)                          | 16 (8)                         | 34 (10)                  | 23 (36)                            |
| No pathology found                        | 13 (5)             | 4 (31)          | 9 (69)          | 11 (9)                          | 19 (10)                        | 30 (10)                  | 19 (28)                            |
| <b>Totals</b>                             | <b>243</b>         | <b>129 (53)</b> | <b>114 (47)</b> | <b>10 (9)</b>                   | <b>20 (12)</b>                 | <b>30 (12)</b>           | <b>19 (26)</b>                     |

<sup>a</sup> Meningiomas, astrocytomas, pilocytic astrocytomas, oligodendrogliomas, pleomorphic xanthoastrocytomas.

<sup>b</sup> Gangliogliomas, gangliocytomas, dysembryoplastic neuroepithelial tumours.

<sup>c</sup> Glioneuronal hamartoma, periventricular heterotopia, polymicrogyria.

<sup>d</sup> Cavernous angioma, arachnoid cyst, arterovenous malformations.

MRI was normal in 13 (5%) patients, isolated hippocampal abnormalities were found in 55 (23%) and dual pathology was diagnosed in 64 (26%) patients; in the remaining 111 (46%) cases a single lesion (tumour, malformation, etc.) was identified. However it should be noticed that MRI data could be biased by the continuous implementation of MRI protocols and progressive improvement in expertise of neuroradiologists during the 10 years of patient recruitment. This aspect is especially relevant for MCD and particularly for FCD, thus the correlation between neuropathological findings and MRI data will not be further considered in the following description.

Neuropathological revision showed tumours in 79 (33%) patients, including 6 (8%) with associated HS. Malformative lesions were found in 110 (45%) patients and in 77 (70%) HS was also present. Thus a dual pathology was present in 83 (34%) cases of the total considered cohort. HS was present with no other lesion in 34 (14%) patients. In 13 (5%) cases no lesion was found. In the remaining seven (3%) patients other types of lesion were found (tables 1, 2).

Post-surgical follow-up was available for all the considered patients; 201 (83%) were in Engel class I (64% in class Ia and Ic), 17 (7%) in class II, 16 (7%) in class III, and nine (4%) in class IV (table 3). Of the 201 patients in class I, 93 (46%) were no longer taking AEDs while 87 (43%) were receiving therapy reduction at last contact (table 4).

No patient died peri-surgically. Unexpected post-surgical neurological deficits such as mild hemiparesis and hemianopsia occurred in one patient.

### Patients with tumours

In 79 (33%) out of the 243 patients considered, 36 (46%) females and 43 (54%) males, the neuropathological diagnosis was determined as tumour (table 1). Mean age of epilepsy onset was 10 years (SD 9, range 0-50), mean duration of epilepsy was 15 years (SD 12, range 0-44), mean age at surgery was 25 years (SD 13, range 1-51) and mean seizure frequency was 25 per month (SD 34, range 1-150). Neuronal and mixed neuronal-glial tumours constituted 76% of all the

**Table 2.** History of febrile seizure and presence/absence of hippocampal sclerosis.

| Neuropathology               | N. of patients | HS (%)         | FS (%)         | FS and HS (%)  |
|------------------------------|----------------|----------------|----------------|----------------|
| Glial and meningeal tumours  | 19             | 2 (11)         | 2 (11)         | 1 (5)          |
| Mixed neuronal-glial tumours | 60             | 4 (7)          | 6 (10)         | 0              |
| Tot. tumours                 | <b>79</b>      | <b>6 (8)</b>   | <b>8 (10)</b>  | <b>1 (1)</b>   |
| FCD I                        | 60             | 50 (83)        | 29 (48)        | 27 (45)        |
| FCD II                       | 12             | 6 (50)         | 3 (25)         | 3 (25)         |
| Heterotopic neurons          | 23             | 16 (70)        | 13 (57)        | 12 (52)        |
| Other MCD                    | 15             | 5 (33)         | 5 (33)         | 3 (20)         |
| Tot. malformations           | <b>110</b>     | <b>77 (70)</b> | <b>50 (45)</b> | <b>45 (41)</b> |
| HS Only                      | 34             | 34 (100)       | 15 (44)        | 15 (44)        |
| Other                        | 7              | 0              | 1 (14)         | 0              |
| No pathology found           | 13             | 0              | 3 (23)         | 0              |
| Totals                       | 243            | 117 (48)       | 77 (32)        | 61 (25)        |

**Table 3.** Surgical outcome according to the histopathological subtypes.

| Neuropathology               | Ia-c (%)       | Ib (%)         | Id (%)       | Tot. I (%)     | II (%)        | III (%)      | IV (%)       |
|------------------------------|----------------|----------------|--------------|----------------|---------------|--------------|--------------|
| Glial and meningeal tumours  | 16 (84)        | 0              | 0            | 16 (84)        | 0             | 1 (5)        | 2 (11)       |
| Mixed neuronal-glial tumours | 43 (72)        | 5 (8)          | 5 (8)        | 53 (88)        | 5 (8)         | 2 (3)        | 0            |
| Tot. tumours                 | <b>59 (75)</b> | <b>5 (6)</b>   | <b>5 (6)</b> | <b>69 (87)</b> | <b>5 (6)</b>  | <b>3 (4)</b> | <b>2 (3)</b> |
| FCD I                        | 37 (62)        | 5 (8)          | 7 (12)       | 49 (82)        | 3 (5)         | 4 (7)        | 4 (7)        |
| FCD II                       | 9 (75)         | 2 (17)         | 0            | 11 (92)        | 0             | 1 (8)        | 0            |
| Heterotopic neurons          | 12 (52)        | 3 (13)         | 1 (4)        | 16 (70)        | 5 (22)        | 2 (9)        | 0            |
| Other MCD                    | 7 (47)         | 4 (27)         | 0            | 11 (73)        | 2 (13)        | 2 (13)       | 0            |
| Tot. malformations           | <b>65 (59)</b> | <b>14 (13)</b> | <b>8 (7)</b> | <b>87 (79)</b> | <b>10 (9)</b> | <b>9 (8)</b> | <b>4 (4)</b> |
| HS Only                      | 22 (65)        | 4 (12)         | 6 (18)       | 32 (94)        | 1 (3)         | 0            | 1 (3)        |
| Other                        | 3 (43)         | 1 (14)         | 0            | 4 (57)         | 0             | 1 (14)       | 2 (29)       |
| No pathology found           | 7 (54)         | 2 (15)         | 0            | 9 (69)         | 1 (8)         | 3 (23)       | 0            |
| Totals                       | 156 (64)       | 26 (11)        | 19 (8)       | 201 (83)       | 17 (7)        | 16 (7)       | 9 (4)        |

**Table 4.** Withdrawal of therapy in patients in Engel class I.

| Neuropathology               | N. patients in class I (%) | Therapy stopped (%) | Therapy in reduction (%) |
|------------------------------|----------------------------|---------------------|--------------------------|
| Glial and meningeal tumours  | 16 (84)                    | 7 (44)              | 9 (56)                   |
| Mixed neuronal-glial tumours | 53 (88)                    | 22 (42)             | 26 (49)                  |
| Tot. tumours                 | <b>69 (87)</b>             | <b>29 (42)</b>      | <b>35 (51)</b>           |
| FCD I                        | 49 (82)                    | 20 (41)             | 21 (43)                  |
| FCD II                       | 11 (92)                    | 6 (55)              | 4 (36)                   |
| Heterotopic neurons          | 16 (70)                    | 11 (69)             | 5 (31)                   |
| Other MCD                    | 11 (73)                    | 5 (45)              | 6 (55)                   |
| Tot. malformations           | <b>87 (79)</b>             | <b>42 (48)</b>      | <b>36 (41)</b>           |
| HS Only                      | 32 (94)                    | 16 (50)             | 12 (38)                  |
| Other                        | 4 (57)                     | 1 (25)              | 3 (75)                   |
| No pathology found           | 9 (69)                     | 5 (56)              | 1 (11)                   |
| Totals                       | 201 (83)                   | 93 (46)             | 87 (43)                  |

tumours and these patients had a mean age of epilepsy onset lower than those with low grade or meningeal tumours (*table 1*).

Neurological examination was normal in 71 (90%) patients. In six (8%) patients preoperative SEEG was performed to determine the precise localization of the epileptogenic zone to ablate.

In accordance with the WHO classification (Louis *et al.*, 2007), 23 (29%) patients with dysembryoplastic neuroepithelial tumours (DNT), 35 (44%) with ganglioglioma and two with gangliocytoma were included, even though in seven an FCD was found surrounding these lesions (five with ganglioglioma and two with DNT).

The outcome in patients with tumours was particularly favourable; 69 (87%) in Engel class I (75% class Ia-c), 5 (6%) in class II, 3 (4%) in class III and only two (3%) in class IV (*table 3*). Pharmacological therapy was completely withdrawn in 29 (42%) patients and reduced in 35 (51%) of the patients in class I (*table 4*).

#### Malformation of cortical development (MCD)

MCD was found in 110 (45%) of patients, 48 (44%) females and 62 (56%) males (*table 1*). Mean age of epilepsy onset in this group was nine years (SD 9, range 0-53), mean duration of epilepsy was 23 years (SD 11, range 1-59), mean age at surgery was 32 years (SD 11, range 4-60) and mean seizure frequency was 16 per month (SD 20, range 1-120). No significant differences were observed among the categories of MCD with respect to the mean age at epilepsy onset, mean duration of epilepsy mean age at surgery and number of seizures per month (*table 1*). The outcome in this group of patients are shown in *table 3*; 87 (79%) patients were in class I with 65 (59%) in class Ia-c. In this group of patients, AEDs were withdrawn in 42 (48%) and reduced in 36 (41%).

Focal Cortical Dysplasias (FCD) were the most common malformations, recognized in 72 (65%) patients representing the 30% of the total population. Among the 72 patients with FCD, type I was most frequently observed at the

neuropathological investigation accounting for the 55% (60/110) of all malformative lesions and the 83% (60/72) of FCD (*table 1*). Of the FCD patients, 60 (83%) were in class I with 46 (64%) in class Ia-c (*table 3*). No statistical difference in outcome was present between patients with isolated FCD I and those with FCD I plus HS. Of the entire cohort of FCD patients, AEDs were withdrawn in 26 (43%) and reduced in 25 (42%) (*table 4*).

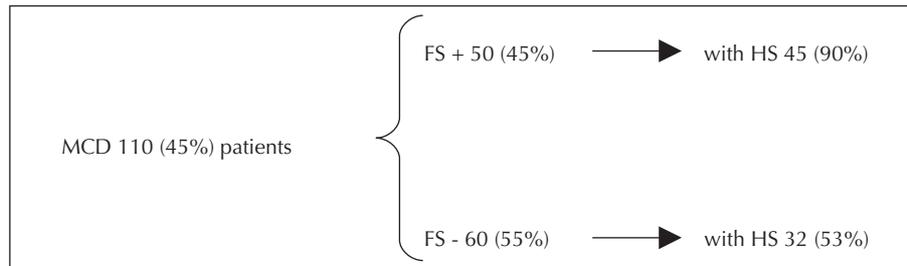
A total of 23 (9%) cases (15 males, 8 females) were judged to have only heterotopic neurons (HN) in the deep white matter of the temporal lobe (*table 1*). Histological and immunocytochemical findings demonstrated numerous medium-size neurons, often arranged in small clusters, most of them showing pyramidal morphology (*figure 1E, F*). Within this group, 16 (70%) patients were in class I with 12 (52%) in class Ia-c (*table 3*). AEDs were completely withdrawn in 11 (69%) patients and were in a phase of reduction for 5 (31%) (*table 4*).

#### Hippocampal sclerosis (HS)

Of the entire cohort of 243 patients, HS was neuropathologically ascertained in 117 (48%). HS was the only pathology found in 34 (29%) patients while in the remaining 83 (71%) it was associated with another pathology (dual pathology).

In the group with HS only, represented by 18 (53%) males and 16 (47%) females, mean age at epilepsy onset was seven years (SD 6, range 1-23), mean duration of epilepsy was 26 years (SD 10, range 6-43), mean age at surgery was 34 years (SD 11, range 7-55) and mean seizure frequency was 12 per month (SD 13, range 1-60) (*table 1*). Follow-up revealed that 32 (94%) were in class I with 22 (65%) in class Ia-c (*table 3*). For 16 (50%) patients, the AEDs were completely withdrawn and were in a phase of reduction for 12 (38%) (*table 4*).

Among the 83 (71%) patients with dual pathology, HS was associated with tumours in only 6 (7%). Of the 110 patients with MCD, HS was found in 77 (70%). The



**Figure 2.** In the MCD group almost all the patients (90%) with a history of FS (FS+) presented HS. In contrast, in those without history of FS (FS-) HS was present in 53% of the patients. Only in this group of patients did a logistic regression model show a significant association between HS and duration of epilepsy ( $p = 0.019$ ; OR: 1.086; CI 95%: 1.013-1.163), but not with age at surgery ( $p = 0.62$ ).

highest incidence of dual pathology was present in association with type I FCD with 50 cases out of 60 (83%) and in 16 out of 23 (70%) patients with HN (table 2).

### Absence of neuropathology (cryptogenic)

In 13 (5%) cases, four males and nine females, no neuropathological abnormalities were found (table 1). Mean age of epilepsy onset was 11 years (SD 9, range 0-28), mean duration of epilepsy was 19 years (SD 10, range 7-43), mean age at surgery was 30 years (SD 10, range 12-46) and mean seizure frequency was 19 per month (SD 28, range 1-90). Nine patients (69%) had an Engel class I outcome, with seven (54%) in class Ia-c (table 3). For five (56%) patients the AED were withdrawn and were in a phase of reduction for one (table 4).

### Febrile seizures and HS

The frequency of familiarity for epilepsy, miscarriage, risk of spontaneous abortion, pre- and perinatal infections, neonatal distress and head trauma were not significantly associated with the different neuropathological entities observed in the present cohort.

History of febrile seizures was present in 77 (32%) patients (table 2) and the presence of HS in patients with FS was revealed in 61 (25% of the whole population and 52% of the patients with HS). A chi-square analysis between the presence of FS and HS was performed and a strong association ( $p < 0.01$ ) was found. A history of FS was present particularly in patients with either a neuropathological diagnosis of MCD (50 out of 110; 45%) or HS only (15 out of 34; 44%). The highest prevalence of FS was found in 29/60 (48%) patients with FCD type I and 13/23 (57%) patients with HN.

In patients not presenting either MCD or HS, FS were less common; in particular among the 79 patients with tumour, only eight (10%) had FS and only one with meningioma had HS. The association in the whole cohort of 243 patients between HS and FS remains significant in the subgroup of MCD (Pearson's chi-square  $p < 0.01$ ) but not in the subgroup of tumours ( $p = 0.48$ , Fisher exact test).

Within the MCD group (110 patients) two subgroups can be recognized: I) patients with a history of FS (FS+ = 50; 45%) that also showed HS in 45 (90%) of the patients; II) patients without documented FS (FS- = 60; 55%) with HS present in 32 (53%). A logistic regression model was performed on these subgroups to evaluate the association of HS and two other parameters: duration of epilepsy and age at surgery. A significant association between HS and duration of epilepsy ( $p = 0.019$ ; OR: 1.086; CI 95%: 1.013-1.163), but not with age at surgery ( $p = 0.62$ ), was found only in the subgroup of patients without a history of FS (figure 2).

## Discussion

Of the 243 patients, with at least two years of follow-up, 83% were classified in Engel class I and only nine (4%) did not benefit from surgery (class IV). A class I outcome was obtained in 87% in patients with tumours and 79% of patients with malformative lesions (92% and 82% in type II and I FCD respectively), irrespective of the presence of HS. These data support the findings of the only randomized trial of surgery for refractory TLE so far published (Wiebe *et al.*, 2001) and highlight the low frequency of post-surgical morbidity and the absence of mortality.

In many studies associated with TLE, HS is primarily investigated, giving the misleading impression that the two entities are the same (Zhang *et al.*, 2002). However HS cannot be regarded as the unique cause of TLE since in recent neuropathological data, HS was found in about 65% of patients that underwent surgery for intractable TLE (Blümcke *et al.*, 2002). In our cohort the presence of HS was observed in 48% of the patients, and in most of these, in association with other pathologies; mainly MCD. Despite the role of HS in TLE, dual pathology is increasingly recognized in these patients and recent electroclinical and imaging findings indicate that extra-hippocampal structures may play an important role (Chabardès *et al.*, 2005).

## Tumours and TLE

The reported frequency of tumours that are believed to be a cause of intractable TLE ranges widely (11-56%), in part due to difficulties in assessing different histopathological subtypes, mainly due to the fragmented nature of tissue available for neuropathological diagnosis (Pasquier *et al.*, 2002). In our series, 33% of the patients had tumours that were believed to be a cause of TLE. This number is unlikely to be representative of refractory TLE in general, because patients were only referred to our centre with a long history of epilepsy.

Although HS is present with other major neuropathological findings in around 30% of TLE surgical cases, the association of HS with tumours is variable (Wolf *et al.*, 1993; Lee *et al.*, 1998; Blümcke *et al.*, 1999; Li *et al.*, 1999; Pasquier *et al.*, 2002). In our series, HS was coupled with a tumour in only 8% of cases showing that the association is rare. Wolf *et al.* (1993) and Blümcke *et al.* (1999) have noticed that tumours, particularly ganglioglioma and DNT, in patients with HS are also associated with the presence of malformative lesions in the temporal lobe, suggesting a maldevelopmental origin of these neuropathological entities. In our series, four of the six tumour plus HS cases had gangliogliomas, and two of them were associated with cortical dysplasia. A history of FS was present in eight (10%) patients and only one with HS.

## Malformations of cortical development and TLE

MCDs were identified in 110 (45%) patients most of which (29% of total population) were FCDs. Reported frequencies of FCD in TLE range from 9% to 16% (Raymond *et al.*, 1994; Lee *et al.*, 1998; Pasquier *et al.*, 2002; Salanova *et al.*, 2004). The high frequency of FCD in our series, in accordance with proportions in other recent studies (Srikijvilaiikul *et al.*, 2003; Fauser *et al.*, 2004), is almost certainly due to refinement of diagnostic neuropathological observations and to the common classification system (Palmini *et al.*, 2004).

Among the patients with malformative lesions, 21% appeared to have an excess number of scattered neurons (HN) in the white matter. Isolated white matter neurons are a feature of normal brains and may be remnants of subplate neurons or an anatomical extension of layer VI (Hardiman *et al.*, 1988; McConnell *et al.*, 1989; Rojiani *et al.*, 1996). It has also been suggested that heterotopic white matter neurons are those that failed to reach their cortical target due to migrational arrest during development and that this disruption can result in altered cortical circuitry (Sarnat, 1991). However the cut-off between normal and excessive white matter neurons is ill-defined. Using a stereological cell counting technique, Thom *et al.* (2001, 2005) demonstrated significantly greater neuronal density in surgical epilepsy cases than in controls, although an overlap between the two groups was noted.

These authors also found, in agreement with Kasper *et al.* (1999), that white matter neuronal density was independent of the extent of secondary gliosis. These data have been confirmed by Hildebrandt *et al.* (2005) showing that the number of solitary neurons within white matter sites was significantly increased in the epilepsy patient cohort, compared to age-matched controls, and these authors suggest that "this anatomical feature associates with chronic epileptic activity, *i.e.* seizure-induced neurogenesis, or point to early disturbances in the architectural development of the cortex and white matter".

In patients with pathologically proven HS, Choi *et al.* (1999) found that white matter neuronal density was greater in patients with MRI white matter changes in the anterior temporal lobe than in those without white matter changes. These findings indicate that HN is a characteristic feature of malformations of cortical development included in the recent classification by Palmini *et al.* (2004).

We also found that the heterotopic neurons were arranged abnormally, with numerous incorrectly oriented pyramidal cells and frequent clusters of 5-10 cells. These morphological abnormalities, not evident on thionin-stained sections, were clearly revealed on MAP2-, neurofilaments- and NeuN-immunostained sections. We have included these patients within the group of malformative lesions, in agreement with the data present in the current literature (Fauser *et al.*, 2004).

## Isolated HS and dual pathology

Only 34 (14%) of our cases had isolated HS, 32 (94%) of which had a class I outcome and 16 (50%) were no longer receiving AEDs.

Dual pathology is generally referred to as the presence of HS associated with an additional extra-hippocampal lesion. In the literature, the frequency of dual pathology in cases of refractory TLE ranges from 5% to 30%, the commonest extra-hippocampal lesion being developmental abnormality (Lèvesque *et al.*, 1991; Raymond *et al.*, 1994; Cendes *et al.*, 1995; Li *et al.*, 1999). This wide range is largely due to variations in patient selection. However, it should be considered that routine neuropathological and MRI examinations are unlikely to detect subtle extra-hippocampal abnormalities (Sloviter and Pedley, 1998). Quantitative MRI studies generally report a dual pathology frequency at around 15% (Raymond *et al.*, 1994; Cendes *et al.*, 1995); however many developmental abnormalities, particularly minor malformations of cortical development (Palmini *et al.*, 2004) and type I FCD, cannot be detected even with high resolution MRI (Colombo *et al.*, 2003).

In the present series, dual pathology was present in 34% of the patients. While the number of cases of HS associated with tumours was negligible (8%), the number of patients presenting HS associated with FCD increased from 70% to 83% in those with type I FCD. These data

are in agreement with those reported by Eriksson *et al.* (2005) and further support the concept by Mathern *et al.* (1995) that tumours are less likely than malformations to produce HS. The high proportion of malformative lesion cases with HS has led to speculation that there may be a common pathway for the development of the two lesions. In a recent paper, Thom *et al.* (2009) identified 11% of their cohort of surgically treated patients, presenting temporal lobe sclerosis. On the basis of neuropathological findings, they suggested that the hallmark features were represented by areas of neuronal loss in supragranular layers (layers II-III), indicating that this aspect may represent an acquired non-developmental process. These neuropathological features have been also identified in some of our patients but have been incorporated into FCD type I and justify the large number of FCD in our population. Whether these specific neuropathological findings, restricted to the temporal lobe and almost exclusively associated with HS, should be separated by the other type of FCD would require further data and a reevaluation of the present classification of FCD.

### Febrile seizures and HS

The presence of FS in our cohort is biased, like any other report on adult patients, by the reliability of anamnestic data. Taking into account this aspect that could not be ruled out in retrospective studies, our data show that FS were present in 32% of the entire cohort but significantly increased ( $p < 0.001$ ) when the MCD group was considered (45%). These data suggest that patients with MCD and particularly with FCD are more prone to FS than the other patients.

In patients with MCD there is a significant association with FS and HS. In patients with MCD without FS a strong association between HS and duration of epilepsy is revealed. Thus we can speculate that in MCD patients, HS is the result of either FS or duration of the epilepsy. In this respect it should be noticed that Fuerst *et al.* (2001) demonstrated in their neuropathologic study, a correlation between the degree of HS and duration of epilepsy.

As noted by Raymond *et al.* (1994) and Fisher and Blum (1999), three explanations to correlate malformative lesions, HS and FS can be formulated: (a) malformations of cortical development predispose to prolonged FS in childhood leading to HS, (b) malformations of cortical development are responsible for repeated seizures that cause secondary hippocampal damage and (c) malformations of cortical development and HS share a common embryonic damage.

Statistical analysis of antecedents in our patients leads to the conclusion that only FS are relevant in epilepsy history, and that FS are statistically relevant only in patients with malformative lesions (not tumours) plus HS.

A relationship between developmental malformations FS and HS has been suggested through experimental animals (Germano *et al.*, 1996) and clinical studies (Wolf *et al.*, 1993; Raymond *et al.*, 1994; Kuzniecky *et al.*, 1999; Fauser *et al.*, 2004). The nature of this relationship has been reviewed by Sloviter and Pedley (1998), and Velisek and Moshé (2003).

Our data showing a strong association between extrahippocampal malformative lesions, FS and HS suggest that malformative lesions predisposes to FS and seizures leading to HS. However the hypothesis that malformative lesions and HS share a common embryonic damage (Vernet *et al.*, 2000; Blümcke *et al.*, 2002) cannot be ruled out, since sophisticated methodologies such as those used by these authors were not performed.

With regard to surgery it is controversial whether the lateral temporal neocortex should be removed or selective surgery on mesial regions should be performed on patients whose MRI reveals only HS. However, in patients with dual pathology diagnosed pre-operatively, both the lesion and the sclerotic hippocampus should be removed whenever possible, since hippocampectomy alone and lesionectomy alone give unsatisfactory results (Li *et al.*, 1999; Wieser, 2004).

### Seizure outcome

Although methods to report seizure outcome are quite heterogeneous among different papers, the most well defined, widely accepted and clinically useful scale is that proposed by Engel *et al.* (1993). According to this scale, 83% of the 243 patients were in class I and optimal results were obtained in patients with HS only (94%) and with type II FCD (92%). A very favourable outcome was also obtained in patients with tumour (87%) and with Type I FCD (82%). It should be noted also that in this later group, no statistical difference with respect to the outcome was observed between isolated FCD I and FCD I associated with HS.

Despite the wide use of the Engel scale, antiepileptic medication status is not considered. Thus, although systematic reviews suggest that 66-70% of patients are seizure-free at short term, most papers report difficulties in separating patients that are either taking or not taking AEDs (Spencer and Huh, 2008). This aspect should be taken into consideration in order to evaluate whether the surgical procedure, particularly in temporal lobe epilepsies, is effective in the cure or care of seizures. In the present report, we considered only patients with at least two years of follow-up and, in addition to the usual classification scale, we also reported those patients who did not receive medication and were thus considered to be cured by epilepsy surgery. In the total population of 243 patients, 201 (83%) patients were in class I and of those 93 (46%) were, at last contact, medication free while another 43% were in a phase of therapy reduction. □

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**Disclosure.**

None of the authors has any conflict of interest to disclose.

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