

# Drug-resistant parietal epilepsy: polymorphic ictal semiology does not preclude good post-surgical outcome

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**ABSTRACT** – We investigated the anatomico-electro-clinical features and clinical outcome of surgical resections strictly confined to the parietal lobe in 40 consecutive patients who received surgery for pharmacoresistant seizures. The population was subcategorized into a paediatric (11 subjects; mean age at surgery: 7.2±3.7 years) and an adult group (29 patients; mean age at surgery: 30±10.8 years). The paediatric group more frequently exhibited personal antecedents, neurological impairment, high seizure frequency, and dysplastic lesions. Nonetheless, compared with adults, children had better outcome and more frequently reached definitive drug discontinuation after surgery.

After a mean follow-up of 9.4 years (range: 3.1-16.7), 30 subjects (75%) were classified as Engel Class I. The presence of multiple types of aura in the same patient, as well as a high incidence of secondary generalization, represented a characteristic feature of parietal seizures and did not correlate negatively with surgical outcome. A total resection of the epileptogenic zone and a localizing/regional interictal EEG were statistically significant predictive factors of outcome. Intracerebral investigation, performed in 55% of cases, contributed to complete tailored resections of the epileptogenic area and determination of prognosis. Frequent subjective manifestations of parietal lobe seizures, such as vertiginous, cephalic and visual-moving sensations, underscore their potential misdiagnosis as non-epileptic events.

**Key words:** parietal epilepsy, ictal semiology, epilepsy surgery, extratemporal epilepsy, surgical outcome

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Parietal lobe seizures are reported to account for approximately 5% of all focal seizures (Siegel, 2003; Salanova, 2012), however, their frequency may be underestimated mainly because of their misleading semiology and diagnostic difficulty (Blume *et al.*, 1991; Salanova *et al.*, 1995; Ristic *et al.*, 2012). Parietal lobe resections are the least commonly performed resections of the brain (Williamson *et al.*, 1992; Kim *et al.*, 2004a; Binder *et al.*, 2009; Bartolomei *et al.*, 2011; Salanova, 2012), therefore parietal lobe epilepsy (PLE) surgery has been examined less extensively in the literature with respect to other localization-related epilepsies. Moreover, in surgical series, PLE is usually grouped together with the occipital and occipito-temporal epilepsies as posterior cortex epilepsies (Blume *et al.*, 1991; Boesebeck *et al.*, 2002).

In this study, we aimed to investigate the anatomico-electro-clinical features and the clinical outcome of surgical resections strictly confined to the parietal lobe in patients who received surgery for pharmacoresistant seizures.

## Patients and methods

We retrospectively reviewed 1,024 patients who underwent resective surgery for pharmaco-resistant focal epilepsy at the “Claudio Munari” Epilepsy Surgery Centre, Milan, from May 1996 to December 2010. We identified 40 subjects (3.9%) who benefited from a tailored resection confined to the parietal lobe (PL).

All subjects were submitted to an individualized pre-surgical diagnostic protocol, including:

- detailed history-taking with accurate analysis of the semiological chronology of the habitual seizure pattern;
- interictal and ictal scalp EEG;
- high-resolution MRI with images acquired parallel and perpendicular to the antero-posterior commissure line, with coronal sequences localized over the area of seizure generation, as indicated by the electroclinical data (Colombo *et al.*, 2003), and where necessary, functional imaging;
- neurological and neuropsychological evaluation with standardized tests applied according to the age of the patient (Scarpa *et al.*, 2006; Guerrini *et al.*, 2013).

In cases where these data failed to delineate a precise topography of the epileptogenic zone (EZ: the site of origin and of primary propagation of ictal discharges [Bancaud *et al.*, 1970; Kahane *et al.*, 2006]), a stereo-electro-encephalography (SEEG) evaluation, with stereotactically-placed intracerebral electrodes arranged according to a pre-defined localization hypo-

thesis, was performed (Cossu *et al.*, 2005; Cardinale *et al.*, 2013) in order to explore the areas putatively involved in seizure onset and early propagation. Following electrode implantation, electrical bipolar cortical stimulations of two adjacent contacts were carried out at both low (LF; 1 Hz, pulse width: 2 msec, for 30 sec) and high frequency (HF; 50 Hz, pulse width: 1 msec, for 5 sec) in order to define eloquent cortex of motor, language and visual functions and to reproduce patient ictal symptoms and signs.

Resective microsurgery was aimed at removal of the EZ, taking into account potential functional constraints to avoid new neurological deficits.

Seizure outcome was assessed according to Engel’s classification (Engel *et al.*, 1993).

Six months after surgery, all subjects had a first follow-up visit with EEG, MRI, and neurological and neuropsychological evaluation; further follow-up visits were repeated annually for at least five years.

The following variables were analysed in relation to the postoperative seizure outcome:

- (1) Seizure frequency: low (<8 seizures/month); mid (8-25 seizures/month); high (>26 seizures/month).
- (2) Preoperative MRI: non-informative (negative or unclear); positive multi-lobar (unique lesion extending over the anatomical limits of the PL or multiple lesions); positive lobar/sub-lobar (unique lesion confined to the PL).
- (3) Seizure semiology, considering the dominant subjective and objective signs of the most frequently presented episodes in each patient according to the ILAE glossary (Blume *et al.*, 2001).
- (4) Localization of surgical resection: mesial (parietal cingulum, precuneus); dorso-lateral (superior parietal lobule, angular gyrus, supramarginal gyrus); opercular (parietal operculum); post-central gyrus (Nieuwenhuys *et al.*, 2008).
- (5) Completeness of resection of:
  - the EZ;
  - the MRI-identifiable lesion.
- (6) Histological result: focal cortical dysplasia (Palmini *et al.*, 2004; Blumcke and Spreafico, 2011); tumour lesions; gliosis; various pathologies.

Statistical analysis was performed to investigate the variability of seizure outcome, which was categorized as a dichotomous variable: Engel class I versus non-Engel class I (class II-IV). The Kruskal-Wallis rank-sum test was used to analyze numerical variables and the Fisher two-tailed exact test was applied to analyze categorical (binomial or multinomial) variables. Probability values <0.05 were considered as evidence of findings not attributable to chance. The statistical analysis was performed with R3.03 (R Development Core team, 2014).

For the purpose of the study, ictal and interictal EEG patterns were classified according to the distribution of the paroxysmal activity: localizing (parietal or central-parietal); regional (posterior or central-posterior); falsely-localizing; only-lateralizing; falsely-lateralizing; bi-hemispheric/diffuse; or normal (Kim *et al.*, 2004a; Kim *et al.*, 2004b).

Finally, in order to allow a direct comparison across age groups and for neuropsychological tests applied for different functional domains, the results, according to the guidelines of each test, were classified as :

- impaired: strongly impaired, impaired, borderline;
- normal: average, above average.

Post-operative neuropsychological findings of each patient were compared to the preoperative results obtained in each specific test and classified as:

- declined;
- unchanged;
- improved;
- normal: average, above-average.

## Results

The general characteristics of the studied population are summarised in *table 1*.

The total population of 40 subjects (17 females) was subcategorized into two groups: 11 subjects who received surgery before 16 years of age (paediatric group; mean age at surgery: 7.2+/-3.7 years) and 29 patients who received surgery after 16 years (adult group; mean age at surgery: 30+/-10.8 years).

Mean age at epilepsy onset was 3.2+/-2.7 years for the paediatric and 8+/-3.8 years for the adult group. All patients started having seizures before 14 years of age. The paediatric group has previously been reported as part of a study on paediatric epilepsy surgery in the posterior cortex (Liava *et al.*, 2014).

### Neurological and neuropsychological features

A neurological impairment was found in 63.6% of the paediatric group; three children exhibited a hemiparesis, three presented praxic impairment, and one child presented an inferior quadrantic visual field defect. Concerning the adults, 34.5% of subjects showed a neurological deficit, consisting of a visual field defect in two cases (one hemianopsia and one inferior quadrantanopsia), dyspraxia in four, and a focal sensitive deficit in one, while two subjects exhibited agnosia digitorum, in one case associated with hemineglect, and one subject presented agnosia.

Specific neuropsychological deficits concerned 87.5% of patients, with a slight prevalence among the adult

group (*table 1 and supplementary table 1<sup>1</sup>*). In the latter, right PLE cases had mostly visuo-spatial memory (62.5%), verbal memory (43.7%) and visual-motor planning (31.2%) deficits, while among left PLE subjects, impairments concerned different cognitive domains almost to the same extent. Afasia prevailed among the left PLE patients and problem-solving difficulties among the right. In the paediatric group, deficits in attention and verbal fluency were found more frequently among right, with respect to left, PLE patients, while no significant differences were seen among the remaining specific cognitive domains with regard to the side of the resection. There were no behavioural disorders in the paediatric population.

### Electroclinical features

Complex and simple partial seizures presented a similar distribution among the two subgroups, while spasms were exhibited exclusively by the two youngest children. At least one secondary generalized seizure (SGS), more commonly within the first year following epilepsy onset, occurred in 70% of the entire population.

A higher seizure frequency was observed in children with respect to adults ( $p=0.4692$ ).

Eighty percent of patients reported the presence of aura, of whom 72% (all adults; 16 with right and seven with left PLE) reported more than one kind of aura; 10 patients reported two types of aura, six reported three types, four reported four types, and three patients reported five types.

Subjective and objective ictal manifestations are shown in *table 2a and b*. Somatosensory symptoms were reported to be contralateral to the epileptogenic side in 15 subjects (75%), ipsilateral in one, and diffuse in four subjects. The most frequent visual aura consisted of visual illusions (9 of 10 patients). Vertiginous sensations were described mainly as rotatory vertigo (5 of 9 cases), while cephalic symptoms were described as a “weird” sensation in the head with centrifugal direction in two cases, a sensation of “slowing-down” in three cases, and a “head-pulsing” sensation in one case. Fear was frequently reported by children.

There was no substantial intergroup difference in the lateralizing and localizing value of surface EEG features (*table 1*). Interictal scalp EEG revealed a well-localizing pattern in 25%, whereas it was misleading in 35% of subjects. A temporal or fronto-temporal distribution of interictal discharges was observed in 11 cases (27.5%). Ictal scalp EEG, available in 32 cases, was correctly localizing in 25%, but misleading in 10% of cases.

<sup>1</sup> Available on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)

**Table 1.** General characteristics of the patients included in the study as a whole (total pts: patients) and subdivided into patients who received surgery before 16 years of age (children) and after 16 years of age (adults).

	<b>Total pts (40 pts)</b>	<b>Adults (29 pts)</b>	<b>Children (11 pts)</b>
Age at onset (yrs)	5.9 +/- 3.9	8.1 +/- 3.8	3.2 +/- 2.7
Age at surgery (yrs)	22.8 +/- 13.4	30 +/- 10.8	7.27 +/- 3.7
Duration of epilepsy (yrs)	15.8 +/- 12.8	21.5 +/- 12.4	4.1 +/- 3.3
Family antecedents	12 (30%)	8 (27.6%)	4 (36.3%)
Personal antecedents	12 (30%)	7 (24%)	5 (45.4%)
Neurological imp.	17 (42.5%)	10 (34.5%)	7 (63.6%)
Neuropsychological imp.	35 (87.5%)	26(89.6%)	9 (81.8%)
Seizure frequency:			
high	14 (35%)	9 (31%)	5 (45.4%)
mid	8 (20%)	7 (24%)	1 (9%)
low	18 (45%)	13 (44.8%)	5 (45.4%)
Type of seizures:			
SPS	10 (25%)	8 (27.6%)	2 (18.2%)
CPS	33 (82.5%)	25 (86.2%)	8 (72.7%)
SGS	28(70%)	22 (75.8%)	6 (54.5%)
spasms	2 (5%)	0	2 (18.2%)
Aura	32 (80%)	28 (96.5%)	4 (36.4%)
MRI:			
negative	1 (2.5%)	0	1 (9.1%)
unclear	3 (7.5%)	1 (3.4%)	2 (18.2%)
lobar/sub-lobar	30 (75%)	23 (79.3%)	7 (63.6%)
multi-lobar	6 (15%)	4 (13.8%)	2 (18.2%)
Interictal EEG:			
localizing	10 (25%)	6 (20.6%)	4 (36.3%)
regional	13 (32.5%)	9 (31%)	4 (36.3%)
falsely-localizing	11 (27.5%)	9 (5 T, 4 FT) (31%)	2 (1 T, 1 FT) (18.2%)
only-lateralizing	3 (5.5%)	2 (6.9%)	1 (9%)
falsely-lateralizing	2 (5%)	2 (6.9%)	0
normal	1 (2.5%)	1 (3.44%)	0
Ictal EEG:	32 pts	22 pts	10 pts
localizing	8 (25%)	5 (22.7%)	3 (30%)
regional	17 (53.1%)	11 (38%)	6 (60%)
falsely-localizing	1 (3.12%)	1 (T) (4.54%)	0
only-lateralizing	3 (9.4%)	3 (13.6%)	0
falsely-lateralizing	1 (3.1%)	1 (4.5%)	0
diffuse	2 (6.2%)	1 (4.5%)	1 (10%)

**Table 1.** (Continued).

	<b>Total pts (40 pts)</b>	<b>Adults (29 pts)</b>	<b>Children (11 pts)</b>
SEEG	22 (55%)	16 (55%)	6 (54.5%)
Side of surgery (R/L)	21/19	16/13	5/6
Localization of surgery:			
mesial	15 (37.5%)	10 (34.5%)	5 (45.4%)
lateral	14 (35%)	10 (34.5%)	4 (36.3%)
mesial-lateral	8 (20%)	7 (24.1%)	1 (9%)
opercular	2 (5%)	1 (3.44%)	1 (9%)
post-central gyrus	1 (2.5%)	1 (3.44%)	0
Histology:			
tumoural lesions	19 (47.5%)	15 (51.7%)	4 (36.3%)
DNET	9 (22.5%)	7 (24%)	2 (18%)
ganglioglioma	7 (17.5%)	6 (20.7%)	1 (9%)
other tumours	3 (7.5%)	2 (6.9%)	1 (9%)
MCD	13 (32.5%)	7 (24%)	6 (54.5%)
FCD I	2 (5%)	0	2 (18%)
FCD II	9 (22.5%)	7 (24%)	2 (18%)
TSC	1 (2.5%)	0	1 (9%)
PMG+SNH	1 (2.5%)	0	1 (9%)
gliosis	5 (12.5%)	4 (13.8%)	1 (9%)
cavernoma	3 (7.5%)	3 (10.4%)	0
Engel class:			
I	30 (75%)	21 (72.4%)	9 (81.8%)
Ia	23	14	9
Ib	1	1	0
Ic	6	6	0
IIa	3 (7.5%)	2 (6.9%)	1 (9%)
III	4 (10%)	4 (13.8%)	0
IV	3 (7.5%)	2 (6.9%)	1 (9%)
AEDS:			
stopped	17 (42.5%)	9 (31%)	8 (72.7%)
tapered	8 (20%)	7 (24%)	1 (9%)
unchanged	15 (37.5%)	13 (44.8%)	2 (18%)

pts: patients; yrs: years; imp: impairment; SPS: simple partial seizures; CPS: complex partial seizures; SGS: secondary generalized seizures; T: temporal; FT: fronto-temporal; R: right; L: left; MCD: malformations of cortical development; AEDs: antiepileptic drugs.

An invasive pre-surgical evaluation by means of SEEG was performed in 55% of patients, with a similar distribution in the two groups. In one case, this procedure was complicated by an intracranial haemorrhage and resulted in a hemianoptic visual field defect, along with a transitory sensitive hemisindrome.

The most frequent responses induced by electrical cortical stimulations in the PL structures, besides the simple somatosensory manifestations, consisted of vertiginous sensations and visual illusions (*table 3*), and were always obtained in adults. Vestibular sensations were clinically variable, while visual illusions mainly consisted of blurred vision and object motion. We excluded stimulations applied

within an anatomical lesion, which elicited known ictal symptoms or were associated with an after-discharge.

### MRI and histopathological features

MRI showed a discrete lobar/sub-lobar lesion in 30 cases and multi-lobar lesions in six cases, the latter consisting of malformations of cortical development in three cases, hypoxic-ischaemic insults in two, and multiple angiomas in one case. MRI was uninformative in four cases (three children).

Cortical malformations and benign tumors represented the commonest histological finding; the former

**Table 2.** (A) Aura (32 patients, 28 adults and 4 children). (B) Objective ictal signs.

A	
Sign	N° of Pts (total 40 pts)
Somatosensory	20 (62.5%)
paresthesias	15
illusions	4
disesthesias	2
Visual	10 (31.2%)
visual illusions:	9
metamorphopsia	4
blurred vision	2
macropsia	2
micropsia	2
amaurosis	2
positive elementary visual hallucinations	3
complex visual hallucinations	1
Vertiginous	9 (22.5%)
rotatory vertigo contr/ipsil	2-Mar
disequilibrium	2
sensation of falling	1
dizziness	2
Psychic	6 (18.7%)
Cephalic sensation	6 (18.7%)
Epigastric/thoracic	5 (15.6%)
Fear/anxiety	4 (12.5%)
Auditory	4 (12.5%)
Gustatory	2 (6.2%)
Pain	2 (6.2%)
Autonomic	1 (3.1%)

prevailed in the pediatric population and the latter in adults (54.5% versus 24%, and 51.7% versus 36.3%, respectively, non-statistically-significant).

### Surgical resections and outcome

Twenty-one subjects underwent a right and 19 a left PL surgical resection. Mesial resections prevailed in the paediatric group and mesial-lateral resections prevailed in adults.

Transient post-operative morbidity was observed in 30% of patients (10 adults and 2 children) and consisted largely of focal motor-sensitive deficits contralateral to the side of the resection (nine cases) and Gerstmann syndrome (six cases). Permanent post-operative neurological deficits, in the form of quadrantanopsia, concerned two adults.

B	
Sign	N° of pts (total 40 pts)
Eye +/- head deviation	22 (55%)
contralateral	13 (32.5%)
ipsilateral	9 (22.5%)
Automatisms	17 (42.5%)
simple motor	3 (7.5%)
gestural	6 (15%)
oro-alimentary	3 (7.5%)
vocalization	3 (7.5%)
bipedal, ictal automatic locomotion	2 (5%)
Motor contralateral	35 (87.5%)
clonic	18 (45%)
dystonic /hypertonic	14 (35%)
negative myoclonus	3 (7.5%)
Version	3 (7.5%)
contralateral	2 (5%)
ipsilateral	1 (2.5%)
Autonomic	3 (7.5%)
Hypermotor	1 (2.5%)
Aphasia	5 (12.5%)
Post-ictal focal paresis	7 (17.5%)

More than one sign could coexist in the same individual.

After a mean follow-up period of 9.4 years (range: 3.1-16.7), 30 subjects (75%) were classified as Engel Class I (23 subjects; 57.5% in Class Ia) (*table 1*). Among the patients who underwent a SEEG procedure, 73% achieved seizure freedom.

In eight cases, a partial excision of the MRI-identifiable lesion was performed, leading to seizure freedom in 50% of cases. In seven cases, an incomplete resection of the EZ was carried out in order to avoid functional deficits; all patients achieved an unsatisfactory outcome (*figure 1*; *figure 3* from Liava *et al.* [2014]).

A greater number of children reached complete drug discontinuation after surgery; antiepileptic drugs (AEDs) were totally stopped in 73% of the paediatric versus 31% of the adult population ( $p=0.0305$ ), in which 24% of subjects maintained unmodified AEDs.

At a minimum of two years follow-up, for the subset of 25 seizure-free subjects (18 adults) with pre-operative impairment in specific cognitive domains (*supplementary table 2A*<sup>2</sup>), a complete recovery was seen in 51.5% of patients with right PL resections and 61.2% of left PLE subjects, whereas in all non-seizure-free patients, impaired pre-operative performance in cognitive functions still remained within a sub-average range (*supplementary table 2B*<sup>3</sup>).

<sup>2</sup> Available on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)

<sup>3</sup> Available on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)

**Table 3.** Subjective vestibular and visual manifestations induced by intracerebral stimulations in the parietal lobe.

Stimulation site	Vestibular symptoms (N° of patients)	Visual symptoms (N° of patients)
Precuneus	“falling flat” (1) subjective vertigo (2) disequilibrium (1)	blurred vision (3) macropsia + object motion (1) “a moving object” (1)
Intraparietal sulcus	body oscillations “like being on the sea” (2)	double vision (1) blurred vision (1) metamorphopsia (1)
Superior parietal lobule	subjective vertigo (1) cephalic subjective vertigo (1) “pulsation of the head” (1)	blurred vision + object motion (1) object motion (1)
Inferior parietal lobule	“falling into a vortex” (1)	blurred vision (1) object motion (1)
Supramarginal gyrus	“falling out of bed” (1) subjective vertigo (1) body oscillations “like being in a boat”(1)	blurred vision (1) “halo around the image” (1)
Parietal cingulum	“pulsation inside the head” (1)	blurred vision + object- motion (1)

### Outcome predictors

An incomplete resection of the EZ represented a statistically significant negative predictive factor for surgical outcome, whereas seizure frequency, the presence of SGS and multiple aura types, as well as an incomplete resection of the MRI-visible lesion, did not correlate with outcome (*table 4*).

The presence of localizing/regional interictal EEG significantly correlated with a favourable seizure outcome ( $p=0.007$ ), whereas ictal EEG did not represent a significant predictive element. None of the analyzed ictal clinical symptoms and signs correlated with outcome (data not shown), however, simple motor automatisms prevailed among non-seizure-free patients and bipedal automatisms and automatic locomotion were seen exclusively among the same group ( $p=0.0577$ ).

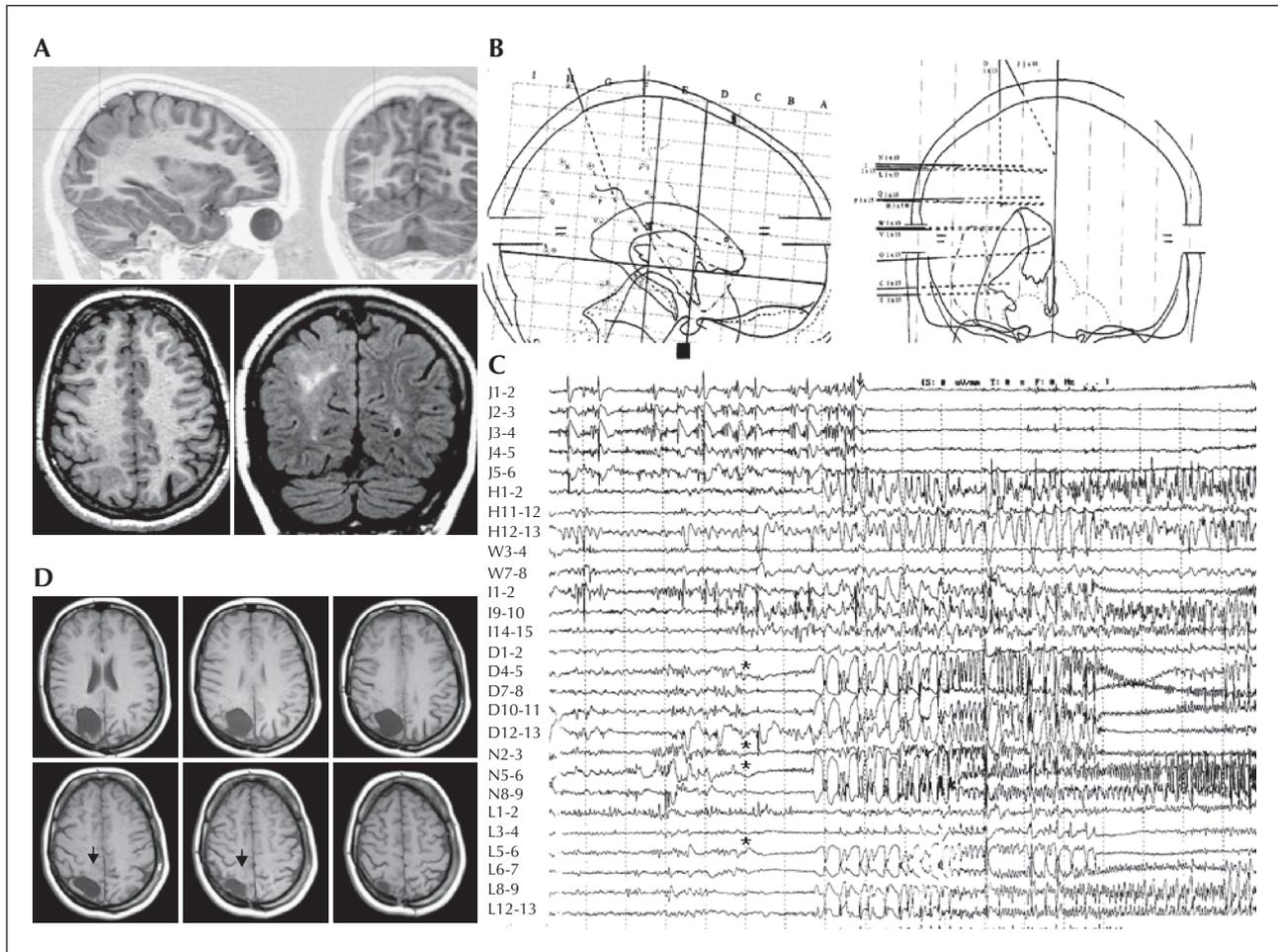
### Discussion

Parietal lobe epilepsy is not frequent in surgical series, however, its frequency may be underestimated, mainly because of misleading seizure semiology (Blume *et al.*, 1991; Salanova *et al.*, 1995; Ristic *et al.*, 2012) and consequent diagnostic difficulty. In fact, an important feature of PL seizures, highlighted in the literature and confirmed by our findings, is the polymorphism of ictal manifestations that accounts for the potential misdiagnosis of PLE, either with other localization-related epilepsies or even with non-epileptic psychogenic events (PNES).

In our series, the presence of variable ictal patterns, such as focal tonic or clonic seizure activity and seizures with automatisms, reflects the rapid seizure spread outside of the PL, either to the frontal or to the temporo-limbic structures. Indeed, focal motor contralateral signs, mostly clonic activity but also asymmetric posturing, never occurred as the leading ictal manifestation and did not correlate with post-surgical seizure outcome; these signs were exhibited by a large proportion of patients (87.5%), in line with previous series (45%-84%: Salanova *et al.*, 1995; Kim *et al.*, 2004a; Kim *et al.*, 2004b, Bartolomei *et al.*, 2011). Similarly, orolimentary automatisms were unrelated to outcome, apparently resulting from the secondary involvement of mesial temporal lobe structures, probably via the multiple anatomical connections existing among the PL and the hippocampal formation (Rushworth *et al.*, 2006; Olson and Berryhill, 2009).

Automatic motor behaviours, simple, but also bipedal automatisms and automatic locomotion, prevailed among non-seizure-free patients, reflecting the implication of an extended EZ, probably including large cortical-subcortical areas in the context of the frontoparietal system, the ictal involvement of which leads to the disinhibition of innate activities controlled by central pattern generators (Tassinari *et al.*, 2005).

Eye (with or without head) deviation represented the most frequent leading objective ictal sign (55%). This feature is probably related to the parietal eye field, located in the lateral intraparietal subregion, but also to the presence of a second eye field, identified in the medial parietal area, the stimulation of which also



**Figure 1.** MRI and SEEG of a patient with epilepsy originating from the parietal lobe who was shown to have FCD IIB. The patient had no significant family or personal antecedents. At neurological examination, osteotendineous reflex was slightly prominent in the left, with a moderate deficit of grafagnosia in both legs, and a presence of atonic events on the left at Mingazzini I. The patient was right-handed. Epilepsy onset occurred at eight years of age with a generalized seizure, afterwards, seizures were characterized by an initial sensitive-motor sensation of the left foot or, more frequently, an initial impression of “seeing weirdly” (“the ceiling becomes smaller and is moving towards me”), followed by eye deviation to the left (or, sometimes, to the right), flushing, diffuse hypertonia and clonias prevalently to the left, and no apparent post-ictal language deficits. EEG showed:

- interictal spike-waves over the right centro-parieto-occipital region;
- high-voltage spike or spike-wave on the right parietal region correlating with the negative myoclonus of the left arm (and frequently the left leg);
- ictal onset in the right centro-parietal region when associated with the major attacks (one seizure) and in the right centro-temporal region when associated with the visual auras (two seizures).

MRI (A) showed a probable dysplastic lesion in the right centro-parietal cortex in its superior and posterior portion. In order to better delineate the limits of the EZ and its relation with eloquent areas, an SEEG (see stereotactic implantation scheme in [B]) was performed (electrodes and corresponding structures investigated are outlined below) and showed an ictal onset (see seizure trace in [C]) in the superior parietal lobule, namely in the contacts N2-3, N5-6, L6-7, D4-5 (stars), followed by a fast and consistent involvement of the paracentral lobule (electrode J; arrow) and by rhythmic fast activity arising asynchronously from different sites of the dysplastic lesion and spreading to the inferior parietal lobule, precuneus, and cingulate gyrus. Low-frequency cortical stimulations of electrode J induced clonic jerks of the leg and hand, and confirmed that electrode J indeed was implanted in the paracentral lobule. As a consequence of the intracerebral neurophysiological and anatomic-functional findings, an incomplete resection of the dysplastic lesion (arrows in [D]) and epileptogenic zone was performed at 24 years of age. Histology revealed FCD IIB. The patient was classified as Engel class IVa from surgery, despite a vagal stimulator recently implanted. At last follow-up visit (14 years post-surgery), neuropsychological examination showed an amelioration of visual-motor planning abilities.

The cerebral structures investigated by each electrode in the stereotactic scheme (B) are listed from mesial to dorsal surfaces; the numbers of each electrode in the trace montage follow the same direction (1 to 15: mesial to dorsal). P: cingulate gyrus, inferior parietal lobule; H: cingulate gyrus, postcentralgyrus; I: cingulate gyrus, postcentralgyrus; V: cingulate gyrus, supramarginalgyrus; W: supramarginalgyrus; C: para-hippocampal gyrus, hippocampus, middle temporal gyrus; E: fusiform gyrus, inferior temporal gyrus; L: precuneus, lesion, inferior parietal lobule; N: precuneus, superior parietal lobule; O: lingual gyrus, middle occipital gyrus; J: paracentral lobule; D: lesion, superior parietal lobule; Q: cuneus, superior parietal lobule.

**Table 4.** Outcome predictors.

		<b>Engel class I (30 pts)</b>	<b>Non-Engel class I (10 pts)</b>	<b>P value</b>
Age at onset	(mean in years)	6.7	6.7	0.863
Age at surgery	(mean in years)	23.8	23.6	0.838
Duration	(mean in years)	16.6	16.9	0.606
Surgery in childhood	yes no	9 (81.8%) 21 (72.4%)	2 (18.2%) 8 (27.6%)	0.696
Seizure frequency	high mid low	10 (66.7%) 7 (77.7%) 13 (81.2%)	5 (33.3%) 3 (22.3%) 2 (18.8%)	0.652
MRI	negative unclear focal multifocal	0 2 (66.7%) 23 (76.7%) 5 (83.3%)	1 1 (33.3%) 7 (23.3%) 1 (16.7%)	0.464
Presence of SGS	yes no	19 (67.8%) 11 (91.7%)	9 (32.2%) 1 (8.3%)	0.23
Aura	no single multiple	4 (100%) 11 (64.7%) 15 (78.9%)	0 6 (35.3%) 4 (21.1)	0.442
Interictal EEG	localizing regional only-lateralizing falsely-localising falsely-lateralising normal	8 (80%) 13 (100%) 2 (66.7%) 6 (54.5%) 0 1 (100%)	2 (20%) 0 1 (33.3%) 5 (45.5%) 2 (100%) 0	0.007
Ictal EEG (32 pts)	localizing regional only-lateralizing diffuse falsely-localising falsely-lateralising	6 (75%) 14 (82.4%) 2 (66.7%) 2 (100%) 1 (100%) 0	2 (25%) 3 (17.6%) 1 (33.3%) 0 0 1 (100%)	0.542
SEEG	no yes	14 (77.8%) 16 (72.7%)	4 (22.2%) 6 (27.3%)	1
Localization of resection	mesial lateral mesial-lateral opercular post-central	11 (73.3%) 11 (78.6%) 5 (62.5%) 2 (100%) 1 (100%)	4 (26.7%) 3 (21.4%) 3 (37.5%) 0 0	0.918
Residual MRI lesion	no yes	26 (81.2%) 4 (50%)	6 (18.8%) 4 (50%)	0.089
Residual EZ	no yes	30 (90.9%) 0	3 (9.1%) 7 (100%)	0.000006
Histology	tumours FCD gliosis others	15 (78.9%) 7 (63.7%) 4 (80%) 4 (80%)	4 (21.1%) 4 (36.3%) 1 (20%) 1 (20%)	0.899

provokes eye movements (Pierrot-Deseilligny *et al.*, 2004). Eye-head deviation was ipsilateral in 41% of cases, almost equally distributed among seizure-free and non-seizure-free subjects.

A higher incidence of ipsilateral deviation in parietal seizures with respect to other focal epilepsies has been reported in the literature (Kim *et al.*, 2004b; Binder *et al.*, 2009) and in one study (Bartolomei *et al.*, 2011), the prevalence of ipsilateral version was described.

Ictal semiological polymorphism also concerned subjective symptoms; as many as 72% of patients, more frequently with right PLE, reported more than one kind of aura. Polymorphism of aura was not correlated to an unfavourable surgical outcome; a possible explanation could be attributed to the well-established role of the PL in the processing and integration of polysensory information (Seitz and Binkofski, 2008). In addition, the ability to recall all the different kinds of subjective manifestations may imply that the initial discharge remains confined to the PL, without spreading to adjacent or deeper structures or to the contralateral side, thus preventing a loss of awareness and, consequently, the amnesia for the auras (Abou-Khalil, 2008).

The most frequently reported aura in our series was a well-described *lateralized somatosensory manifestation* (37.5%). In line with the literature (Williamson *et al.*, 1992; Sveinbjornsdottir and Duncan, 1993), the somatosensory disturbance occurred more frequently contralateral to the side of seizure origin, but also ipsilaterally or bilaterally, indicating that this symptom does not always have a reliable lateralizing value. Although somatosensory aura is highly suggestive of parietal seizures, it could be found in other posterior cortex epilepsies (Williamson *et al.*, 1992; Sveinbjornsdottir and Duncan, 1993; Guldvog *et al.*, 1994), as well as in MTL (Tuxhorn, 2005), while previous studies have demonstrated that the presence of somatosensory aura involving the peripheral extremities and the face, with sparing of the proximal extremities, may suggest a secondary sensory area origin (Penfield and Jasper, 1954). Moreover, somatosensory sensations are also elicited with stimulation of the SMA (Guldvog *et al.*, 1994) and somatosensory aura was found in 12% of patients with focal epilepsy, irrespective of the localization (Tuxhorn, 2005). Other frequent types of aura in our series were vertiginous sensations (22.5%) and visual illusions (28%), the former found exclusively among the seizure-free subjects (not statistically significant). *Vestibular manifestations* are reported in 10-23.5% in previous studies (Salanova *et al.*, 1995; Kim *et al.*, 2004b; Bartolomei *et al.*, 2011) and are described either as pure labyrinthine symptomatology or as dizziness. Vestibular symptoms have been reported in seizures involving the superior parietal cortex (Bartolomei *et al.*,

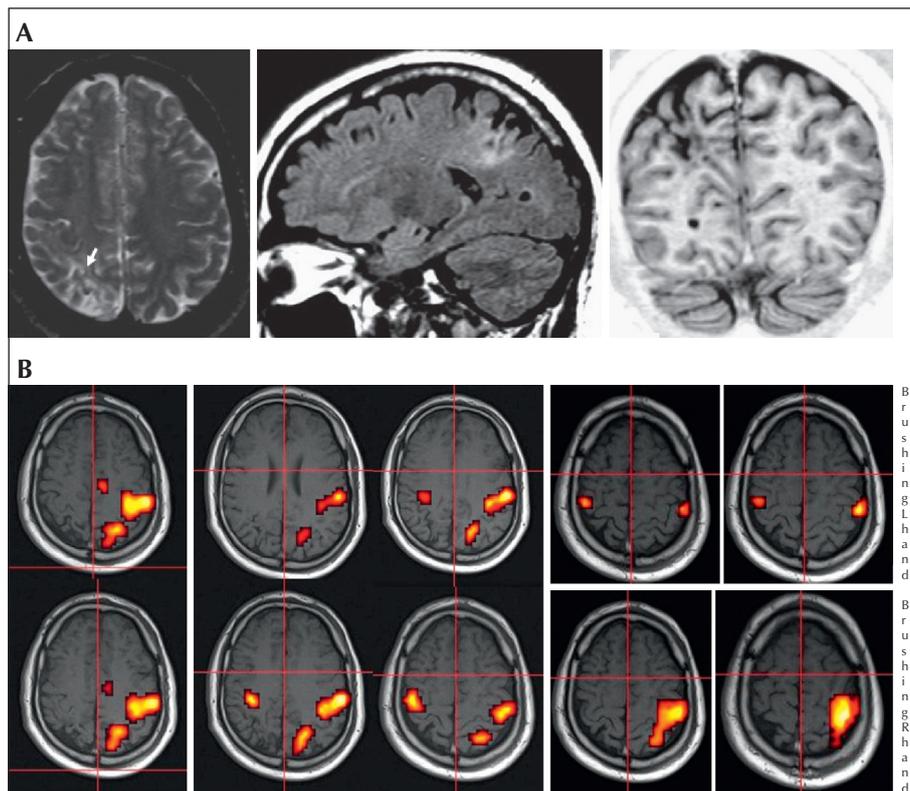
2011), induced by cortical stimulations of the vestibular region located in the temporal-parietal junction (Kahane *et al.*, 2003), but also the intraparietal sulcus (Blanke *et al.*, 2000). In our series, nine patients experienced vestibular sensations after stimulation without after-discharges at distinct sites in the PL, either in the mesial or lateral aspect, with variable clinical description depending on the stimulation site (table 3). Interestingly, four of these patients reported vertiginous sensations when stimulating the area of precuneus close to the cingulate sulcus; the stimulation of the same area induced vertiginous symptoms in four of 28 patients in the series of Kahane *et al.* (2003), probably suggesting that this well-circumscribed area, apparently inside BA7, might be part of the vestibular region and might correspond to the monkey's vestibular cingulate region.

*Visual illusions* elicited by stimulation of the PL structures were described mainly (87%) as object motion and blurred vision, and concerned almost equally mesial and lateral structures. Moving visual sensations were previously evoked by stimulation of the basal temporal-occipital, the mesial parietal-occipital, or the temporal-parietal-occipital junctional region using subdural grid electrodes in a series of 23 patients with epilepsy (Lee *et al.*, 2000).

A *vague cephalic sensation* was reported relatively frequently (19%) in our series. This subjective manifestation, which (especially when not followed by clear-cut epileptic signs) underscores the potential misdiagnosis of PL seizures with non-epileptic events, was linked to an epileptogenic area located either in the lateral part of the PL (three cases), in the mesial aspect (two cases), or both (one case).

In our series, a large proportion of subjects (70%) exhibited secondarily generalized seizures, most commonly within the first year of illness; this feature is in concordance with previous series (65-84%; Kim *et al.*, 2004a; Kim *et al.*, 2004b; Binder *et al.*, 2009), suggesting that secondary generalization is more frequent in PLE than in other epilepsies. Even if this feature prevailed among non-seizure-free subjects, it did not represent a statistically significant negative predictor for outcome, suggesting that, unlike temporal lobe epilepsy where a preoperative history of SGS significantly reduces the likelihood of being seizure-free (Cleary *et al.*, 2012), SGS in extratemporal lobe epilepsy do not preclude postoperative seizure remission.

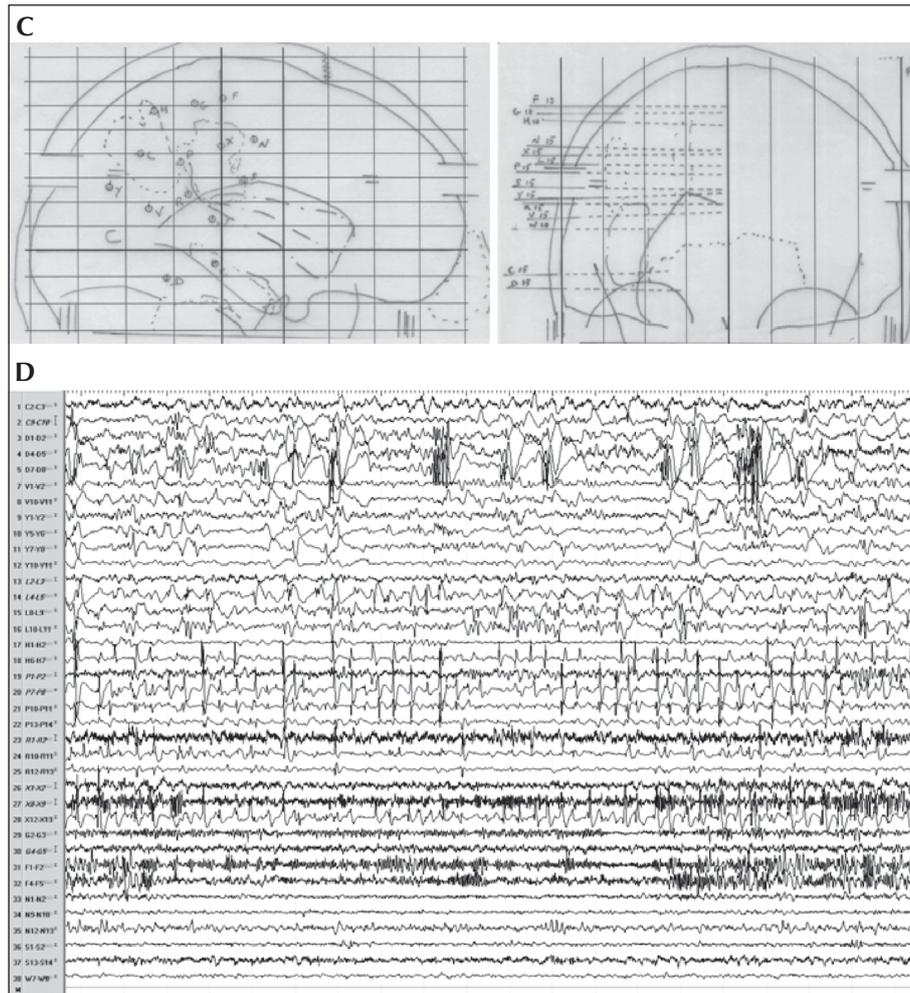
The total resection of EZ was a statistically significant predictive factor for surgical outcome and in six of our cases (60% of the non-seizure-free patients), the failure of surgery to control seizures was anticipated during the presurgical evaluation regarding the inability to entirely remove the epileptogenic, yet functional, cortex (figure 1; figure 3 from Liava *et al.*, 2014). Intracerebral mapping of putative epileptogenic



**Figure 2.** MRI, fMRI and SEEG of a patient with epilepsy originating from the parietal lobe who was shown to have right parietal ulegria and gliosis. The patient was born before term (34 weeks of gestation) with normal delivery. There were no focal neurological deficits, although agnosia digitorum was present with moderate cognitive impairment involving specific deficits in: problem-solving abilities, verbal fluency, visuo-spatial memory, visuo-motor planning, and facial recognition. The patient was ambidextrous. Epilepsy onset occurred at eight months of age, with annual seizures, frequently facilitated by fever and characterized by diffuse hypertonia and staring or eye-head deviation, as well as constant secondary generalization. At the time of the presurgical evaluation at 31 years of age, the seizures had a monthly frequency, and their semiology consisted of an initial tingling-like sensation localized to the fingers of the left hand with a centripetal direction up to the shoulder, and afterwards towards the left foot, followed by eye and head deviation either to the right (more frequently) or to the left, and left arm hypertonia. Interictal EEG showed spike-waves over T4-T6 and P4-T6 and asynchronous spikes over C4-P4, constantly involving Pz, while ictal EEG showed a right temporo-parietal initial rapid discharge. MRI (A) revealed right parietal ulegria, involving both the inferior parietal lobule and the post-central gyrus, including the underlying white matter (arrow: Rolandic sulcus). fMRI (B) showed an activation of the left primary motor area, the left SMA, and a left post-central area during the finger-tapping (F-T) task of the right (R) hand; an activation of a left post-central area and the primary motor area, bilaterally, with greater extent and intensity on the left, during finger-tapping of the left (L) hand; an activation of the left somatosensory area during brushing of the right hand; and an activation of two small areas, bilaterally, none of which corresponded to the theoretical position of the somatosensory area in the right post-central gyrus during brushing of the left hand. The activated sensorimotor areas did not appear to be contiguous with the ulegric lesion.

An SEEG investigation of the right centro-parieto-temporal cortex was performed (see stereotactic scheme in [C]; electrodes and corresponding structures investigated are outlined below) demonstrating the presence of:

- subcontinuous spike-waves (D) involving the post-central gyrus (X12-13), the intermediate-external aspect of the inferior parietal region (external contacts of R and intermediate-external contacts of P) and the posterior part of precuneus (L4-5), and polyspikes in the fusiform gyrus and inferior temporal gyrus (electrode D), while activity in the precentralgyrus (X8-9) was free of interictal abnormalities;
- subclinical paroxysms (E) arising from the inferior parietal area (see fast activity from intermediate-external contacts of electrodes L and P), in the intermediate-external aspect of the parieto-occipital junction (see flattening at electrodes Y and V), but also in the inferior temporal and fusiform gyri (see rhythmic bursts of high-voltage polyspikes at electrode D);
- ictal onset, either similar to the subclinical paroxysms or, more frequently, characterized by a high-voltage spike (F) immediately followed by fast activity of very low voltage involving the majority of electrodes, more pronounced in the intermediate contacts of L, D, P and external contacts of V and R.



**Figure 2.** (Continued) Electrical cortical stimulations of the supra marginal gyrus and the post-central gyrus induced the habitual aura, and revealed a normal function of the motor area and a partially functional somatosensory area. Invasive neurophysiological and anatomo-functional findings permitted to delineate an epileptogenic zone localized in the intermediate-external part of the parietal region and involving the post-central gyrus in the superior aspect, as far as the parietal-occipital junction in the inferior aspect (C), the total resection of which led to complete seizure freedom (Engel class Ia) without motor-sensitive deficits. Post-operative visual field testing revealed a predicted, incomplete left inferior quadrantanopsia. Histopathological analysis revealed the presence of gliosis. Neuropsychological evaluation at five years of follow-up showed an amelioration of verbal fluency, visuo-motor planning, facial recognition, and problem-solving abilities.

The cerebral structures investigated by each electrode in the stereotactic scheme (C) are listed from mesial to dorsal surfaces; the numbers of each electrode in the trace montage follow the same direction (1 to 15: mesial to dorsal). F1-2: anterior part of paracentral lobule; F3-5: superior part of precentralgyrus; G1-3: posterior part of paracentral lobule; G4-7: superior part of postcentralgyrus; H1-6: anterior part of superior parietal lobule; W1-5: transverse temporal gyrus; W6-7: posterior part of superior temporal gyrus; D1-5: intermediate part of fusiform gyrus; D6-11: posterior part of inferior temporal gyrus; N1-2: posterior part of central gyrus; N9-13: intermediate part of precentralgyrus; S1-2: posterior part of central gyrus; S11-15: inferior part of postcentralgyrus; X1-2: posterior part of paracentral lobule; X7-9: intermediate part of precentralgyrus; X11-14: postcentralgyrus (lesion). P1-2: posterior part of central gyrus; P6-11: lesion; P12-15: supramarginalgyrus; R1-2: posterior part of central gyrus; R10-11: lesion; R12-15: supramarginalgyrus; C1-3: intermediate part of hippocampus; C11: posterior part of middle temporal gyrus; L1-4: posterior part of precuneus; L5-7: lesion; L8-11: posterior part of inferior parietal lobule; V1-2: posterior part of precuneus; V9-15: angular gyrus (lesion); Y1-3: anterior part of cuneus; Y5-6: lesion; Y7-10: superior occipital gyrus.

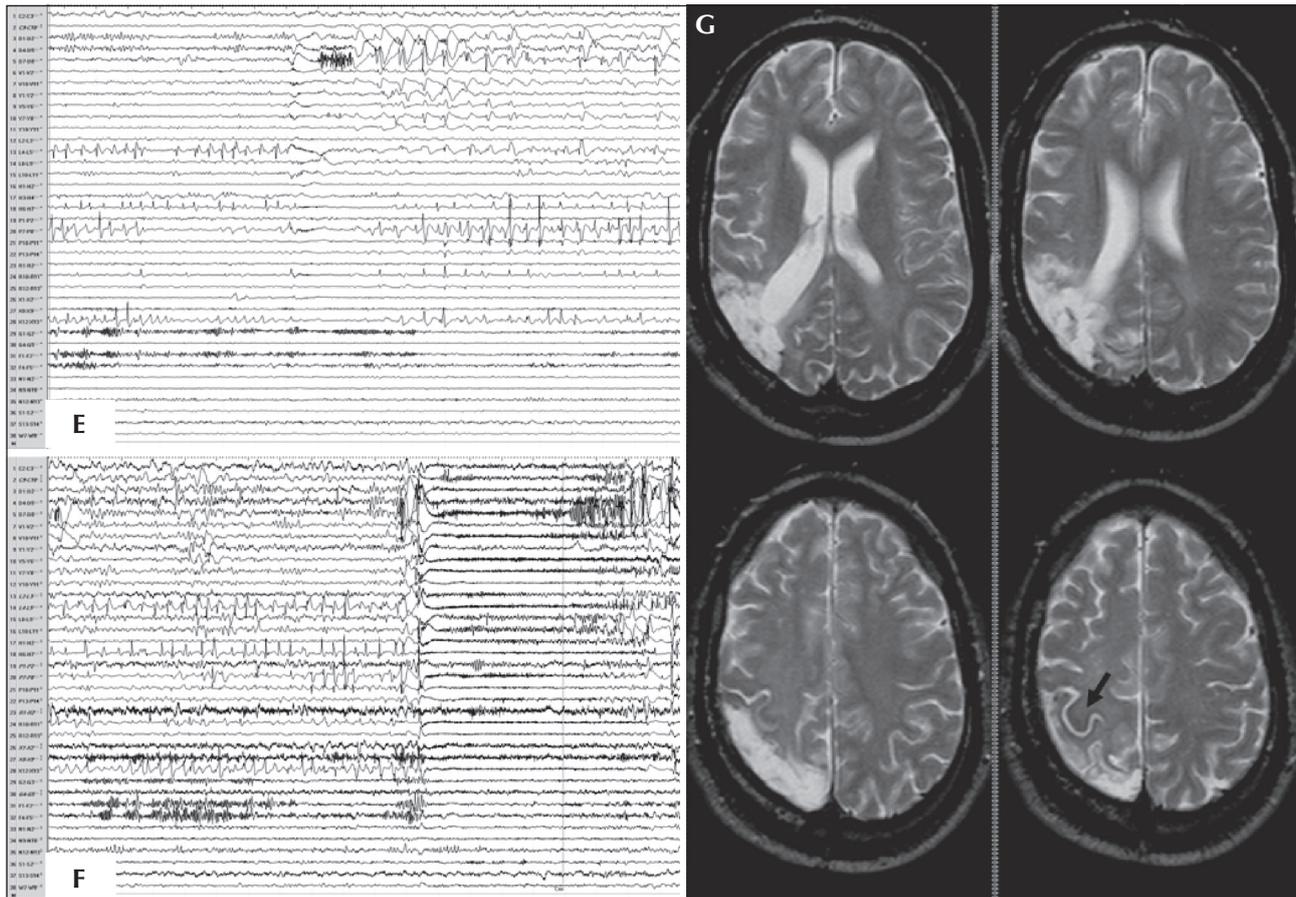


Figure 2. (Continued)

lesions, potentially intersected with functionally eloquent areas, was the cornerstone for the complete excision of the EZ and consequently for surgical success (figure 2).

A problematic definition of the extent of the epileptogenic focus is also attributed to the tendency of multiple EEG spread patterns and the non-localizing scalp EEG findings in parietal seizures (Williamson *et al.*, 1992; Ristic *et al.*, 2012). In fact, the presence of large association areas in the PL and its elaborate connectivity to various distant regions reasonably account for these EEG features, and probably account for a relatively higher incidence of invasive procedures in PLE compared with other focal epilepsies. This is the case in our series, where 55% of patients required a presurgical SEEG evaluation. It is notable, however, that in our series, interictal EEG contributed to the formulation of a well-framed seizure-focus hypothesis in 57.5% of subjects, of whom 91.3% achieved freedom of seizures. In fact, the presence of well-localizing/regional features on interictal EEG correlated significantly ( $p=0.007$ ) with a favourable seizure outcome.

Interestingly, all subjects had seizure onset in paediatric age, thus depicting PLE as a paediatric disorder. In our series, the paediatric group exhibited more frequently personal antecedents, neurological impairment, higher seizure frequency, as well as more dysplastic lesions. Despite these features, children had better outcome compared with adults, and a significantly greater number of children reached complete drug discontinuation after surgery, compared with the patients who received surgery in adulthood. Therefore, this could imply that a longer duration of focal epilepsy is correlated to worse seizure prognosis after resective surgery, in concordance with previous studies (Dalmagro *et al.*, 2005; Liava *et al.*, 2012), which might be related to the fact that deviations from normal interactions between networks, as well as more extended dysfunctional areas and/or decreased plasticity, are more likely with a longer duration of epilepsy (Bartolomei *et al.*, 2008). In this regard, it might be suggested that an earlier indication of surgery could increase the percentage of surgical success and of achievement of complete post-operative “drug freedom” (Francione *et al.*, 2012).

In both paediatric and adult groups, after two years of follow-up, seizure freedom was associated with a striking post-operative improvement or even complete recovery of preoperative specific neuropsychological deficits in a remarkably high number of subjects, thus indicating the deleterious effects of chronic epilepsy on the cognitive functions. This was particularly evident in the domain of mnemonic performances; 65% of patients with preoperative impairment in visuo-spatial memory and 50% of those with impairment in verbal memory presented a complete remission of deficits after two years of follow-up. Globally, all but five adults and four children exhibited pre-operative memory deficits. Indeed, our data provide further evidence of the role of the parietal structures in memory, already demonstrated by functional neuroimaging, either by means of PL activations to various mnemonic demands (Olson and Berryhill, 2009) or through anatomical linkages in white matter tractography between PL and frontal and temporal lobe areas (Rushworth *et al.*, 2006).

## Conclusion

Surgical management of PLE, significantly aided by high-resolution neuroimaging and, frequently, by invasive neurophysiological evaluation, may attain excellent results.

A subtotal resection of the EZ, due to functional constraints, is relatively frequent in PLE and intracerebral mapping might be essential in order to perform tailored resections and determine prognosis.

An earlier surgical referral may increase the chances of seizure control and complete post-operative drug discontinuation.

The presence of multiple types of aura in the same patient does not appear to represent a negative predictive factor of surgical outcome, but a characteristic feature of PL seizures. □

## Disclosures.

The authors have no conflict of interest to disclose.

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## TEST YOURSELF



- (1) Is the percentage of seizures originating from the parietal lobe underestimated?
- (2) Is the presence of multiple kinds of aura a contraindication or a negative prognostic factor for surgery in the parietal lobe?
- (3) Is eye and/or head deviation always contralateral in parietal lobe seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, [www.epilepticdisorders.com](http://www.epilepticdisorders.com), under the section "The EpiCentre".