RADIATING MULTIPLE SUBPIAL TRANSECTIONS FOR TREATMENT OF NONLESIONAL EPILEPSY IN CORTICAL ELOQUENT AREAS

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ABSTRACT:
Context and objectives
Epilepsy surgery in eloquent areas remains a challenge when the MRI is negative. In this context multiple subpial transections technique represents an alternative to the cortical resection. The aim of our study was to identify clinical and pathological features and the postoperative outcome of patients with nonlesional epilepsy and treated using radiating transections.
Methods:
This study is a series of 25 patients with MRI negative epilepsy treated by the radiating multiple subpial transections technique at Cliniques Universitaires Saint-Luc/Brussels. Specific study parameters were: seizures type, use of invasive EEGs, number of transections, histopathological findings, seizures trends and postoperative neurological deficits.
Results:
Our patients benefited an average of 37 transections (extremes 4-89) alone or associated with other procedures. Generalized seizures were observed in 64% of patients and 60% required invasive EEGs. In 48% of cases, the histopathological examination performed on intraoperative specimens was non-contributory. Minor permanent neurological deficit was noted in 2 patients. Seizures evaluation showed a favorable outcome in 72% of cases with total suppression in 9 patients (36%).
Conclusion:
Our Patients with non-lesional epilepsy in eloquent areas are characterized by a high incidence of generalized seizures, extensive use of invasive EEGs, and nearly half non-contributory histopathological analyzes. Radiating transections perfomed alone or in association with other procedures provide their seizures suppression in at least one third of cases with low morbidity.

Keywords: *Epilepsy Surgery - Magnetic resonance imaging - multiple subpial transection*

Introduction:

About 30% of epilepsy patients do not respond to well-conducted medical treatment [1]. These patients become potential candidates for surgical treatment and should be evaluated using neuroimaging. In this context, MRI is a cornerstone and the discovery of a clearly identified lesion is a key factor in determining surgical strategy[1,2,3,4].

However, in many cases MRI does not reveal any lesions[5,6]. In this situation, the surgical strategy becomes more complex to define, especially when the epileptogenic focus is located in an eloquent cortical area[7,8]. The possibilities of surgery in this case are represented by, among others, resective surgery, multiple subpial transections (MST) and thermo-coagulation. However the latter technique is less practiced than the first two[8,9].

When it is indicated, extensive resection involves the risk of a major neurological deficit counterbalancing the surgical treatment benefit. In contrast, minimal resection often leads to ineffective treatment[8,9]. MST performed alone or in combination with other techniques seems to compensate the limitations of resective surgery. Indeed, this technique, which consists in performing vertical cortical micro-disconnections to suppress the horizontal epileptogenic discharges propagation, makes possible to reduce the risk of neurological deficits related to resective surgery in functional areas. In addition, transections can be performed on large areas of the cortex, thus increasing the potential of seizures control[10,11].

In the refractory epilepsy center of the Cliniques Universitaires Saint-Luc in Brussels (Belgium), we practice radiating MST (rMST) instead of the parallel transections described by Morell[11,12]. The present study is based on 25 patients who undewent rMST for treatment of epilepsy in cortical functional areas with no MRI lesions. Its objective is to identify the clinical and pathological specificities as well as the post-operative outcome of this group of patients with so-called non-lesion epilepsy.

Methods:

From January 2003 to January 2009, 62 patients had to benefit from the MST for treatment of refractory epilepsy at the Cliniques universitaires Saint-Luc in Brussels. Among them, 25 patients, who constitute the population of the present study, had no lesions demonstrated on MRI 1.5 (9 patients) or 3.0 Tesla (16 patients).

The records of all these patients were discussed at the multidisciplinary meetings of the refractory epilepsy center, which included neurosurgeons, neurologists, epileptologists, neuro-radiologists, neuropediatricians and neuropsychologists. Preoperative evaluation of patients included: neurological examination, standard EEG data and video recordings, morphological and functional MRI, sometimes PET-SCAN with fluoro-deoxy-glucose or methionine as well as neuropsychological examination and Wada test in some cases.

In the majority of cases, the epilepsy setting was complemented by realization of invasive EEG (EEGi) followed by a video recording. We used subdural and intra-parenchymal electrodes separately or in combination, depending on the case. In contrast to the usual practice of intra-parenchymal electrodes placing using the stereotactic frame, all our EEGi were performed under neuro-navigation (BrainLab, Germany) (Fig 1). Similarly, instead of performing a craniectomy for subdural electrodes placement, we place them through a linear channel shape craniotomy (Fig. 2). These two techniques make it possible to avoid performing a large craniotomy before the proper epilepsy surgery. The location of the electrodes is checked by MRI in the immediate postoperative period (Fig. 3). After recording by video EEG, only the removal of the subdural electrodes requires general anesthesia. The craniotomy channel is then covered with acrylic cement. The removal of the intra-parenchymal electrodes takes place at the patient's bed by simple withdrawal.

Whenever the surgical option was taken by the multidisciplinary team, patient and / or his / her family were convened for a preoperative discussion. The potential risks of surgery, the benefits and the expected results were clearly explained during the tandem consultations bringing together the epileptologist and the neurosurgeon responsibles of epilepsy center. The operative program was set only after obtaining consent.

The surgical procedures were performed under neuro-navigation coupled to the operating microscope and electro-corticographic guidance. We used a 24 contacts subdural electrode for intra-operative electro-corticography. We practice a modified MST technique which consists of radiating transections from a single cortical entry point instead of the parallel transections described by Morell[10]. The details and particularities of this technique as well as the specific protocol of general anesthesia used were developed in an earlier article[12].

General study parameters were: sex as well as age at surgery, age of onset and duration of epilepsy, seizures types, surgical procedure, hemisphere and Brodmann areas (BA) concerned, the invasive EEG use and number of transections. The postoperative evaluation performed between 3 and 9 years included the existence of permanent neurological deficit and pathological findings, the evolution of seizures according to the modified Engel classification. Patients were thus divided into 4 classes. The first three classes were considered favorable: class I (total seizures suppression), class II (seizures reduction rate between 75 and 99%), class III (seizures reduction rate between 50 and 74%). Class IV, which included patients with a seizures reduction rate of less than 50%, was considered unfavorable. In the present study, and because of the small sample size, Class II and III, which represent an improvement between 50% and 99%, were put together.

Non-parametric Mann Withney test was used to compare the evolution of seizures between our 25 patients and the remaining 37 patients in the general rMST population (62 patients) in whom MRI was positive. While the two-fold comparison test was used to compare the frequency of generalized seizures, the use of invasive EEGs, and noncontribution of pathological analysis between these two populations. Pathological examination was considered non-contributory whenever either lesions were absent or an aspecific lesion was noted. The statistical significance level was set at $p \leq 0.05$.

Results:
Of our 25 patients with non-lesional epilepsy in eloquent cortical areas, 15 were male and 10 female, with a sex ratio of 3/2. Their mean age at surgical treatment was 18.7 years with an average duration of epilepsy of 10.7 years. The age of seizures onset varied between 0 and 36 years with an average of 8.7 years (Table 1).

Sixteen patients (64%) had generalized seizures while the remaining 9 (36%) had partial seizures. This frequency of generalized seizures was found to be higher than in the 37 patients with lesional epilepsy (35%) with a statistically significant difference ($p = 0.00$). EEGi was practiced to localize the epileptogenic focus in 60% of cases (Table 1). A total of 44 electrodes were implanted, including 29 subdural and 15 intra-parenchymal. This proportion of EEGi is greater than in patients with positive MRI in whom EEGi was used in only 27% of cases. This difference is also statistically significant ($p = 0.00$).

In 60% of cases, transections were performed on the right hemisphere. The ascending frontal and parietal gyri were the most affected, respectively in 68 and 64% of cases. Wernicke (BA 22, 39 and 40) and Broca (BA 44) areas were concerned respectively in 28 and 5% of the cases. For these language areas, radiating transections were performed on the dominant hemisphere (left).

Number of transections varied between 4 and 89 with a calculated average of 37 transections per patient. Ten patients (40%) benefited from rMST alone while in 60% of cases, rMST were associated with other procedures. In the latter case, disconnection was more frequent (in 28% of cases) followed by cortectomy (16%). Details on surgical procedures, pathological findings and postoperative outcome are given in Table 2.
The pathological analysis of the surgical specimens showed an absence of lesions in 24% of cases. Similarly, in about a quarter of patients (24%) the histopathological findings were aspecific. In total, 48% of histopathologic analyzes were not contributory (compared with 14% in the case of positive MRI with a statistically significant difference, $p = 0.002$). In patients with specific lesions (44%), the most common was gliosis (28%). While cortical dysplasia was less frequent (12%). Two patients (8%) did not receive a pathological examination.
In postoperative follow-up, which varied from 3 to 9 years, permanent neurological deficit was observed in 2 patients (8%). This was a superior quadranopsia relative to a temporal disconnection and therefore not directly related to the rMST as well as a discrete facial paresis in relation to the rMST practiced on the ascending frontal and the pre-motor areas.
Seventy-two per cent of patients had a favorable outcome, of whom 9 (36%) were free of any seizures (class I). The remaining 9 patients (36%) had more than 50% improvement in their seizures (Class II and III). Seven patients (28%) were considered class IV because of the marked lack of improvement in seizures. Compared to the group of 37 patients with lesional epilepsy in whom classes I, II + III and IV had respectively, 46, 38 and 16% of patients, we observed a decrease in the number of patients in class I and an increase of those of class IV in the non-lesion epilepsy. However, this difference is not statistically significant at the different classes (p-value of 0.44, 0.88 and 0.26 respectively).

Discussion:
Refractory epilepsy surgery in functional cortical areas remains a challenge for neurosurgical teams. This challenge seems easier when neuroimaging helps to clearly identify the seizures origin lesion. The situation becomes more complex when the neuroimaging investigations, in particular the MRI, turn out to be negative. Many studies have had to demonstrate the less favorable seizures outcome in these patients with so-called non-lesional epilepsy compared to lesional epilepsy[13,14,15]. In order to improve the control of seizures in non-lesional epilepsy, some neurosurgical teams have resolved to carry out increasingly extensive resections. However, these resections are accompanied by a high rate of neurological complications counterbalancing the surgical treatment benefits[7,8,16]. Although considered as palliative surgery, MST, which represent an alternative to resective surgery in eloquent cortical areas, reduce the risk of neurological deficits and provide seizure suppression in at least 1/3 of the

cases[8,9,10,12]. Our MST technique consists in practicing 3 to 5 radiating transections from a single arachnoid-subpial penetration point, which makes it possible to minimize surgical trauma to the cortex and to reduce the risk of bleeding[12].

The aim of the present study was to identify the clinical and pathological specificities as well as the post-operative evolution of patients with so-called non-lesion epilepsy treated using the rMST technique.

Regardless of the surgical technique to be applied, patients with non-lesional refractory epilepsy should be considered as a particular group of candidates for surgery[7,17,18]. In our series, they are characterized by a high incidence of generalized seizures (64% of patients versus 35% in the MRI + group). As shown in Table 1, the frontal and parietal lobes were the most incriminated at the seizure origin in our study population. Indeed, generalized seizures appear to be more frequent in extra-temporal epilepsies than in temporal epilepsy, given that extra-temporal epileptogenic foci having a greater tendency to spread epileptic discharges[8,13,14,16].
The identification of the seizures origin focus constituting the key point of the surgical strategy represents a real stumbling block for non-lesional epilepsy[16,19,20]. These patients often require further explorations, including the use of EEGi[21]. In our series, 60% of patients benefited from the implantation of a total of 44 invasive electrodes followed by a video recording. In Chapman study, 63% of patients required the use of EEGi to define the surgical strategy[21]. The broad use of EEGi was also highlighted by Tobochnik in his study of neo-cortical non-lesional epilepsy[7]. In Kim series about resection in eloquent cortical areas, all patients benefited from EEGi[22].

The pathological analysis of our intraoperative specimens showed a significant proportion of cases of absence of lesions (24%) and aspecific lesions (24%), representing 48% of non-contributory examinations. Chapman noted 54% of aspecific lesions in 24 patients with non-lesional epilepsy[21]. In Dorward's study focused on pediatric population, pathological examination was normal in 42% of patients[17]. Although dysplasia was recognized as the most common lesion in negative MRI, both in our series and in Bell's, gliosis was more frequent in patients with positive histopathology[5,14].

Post-operative neurological deficit related to rMST was observed only in 1 patient in our study (4% of patients) and this was a minor deficit. MST performed alone or in combination with other techniques, are recognized as inducing low postoperative morbidity[9,10,23]. Indeed, in a comparative study of studies focused on MST, Ntsambi and his colleagues observed deficit rates between 0 and 23%[12]. This is in contrast to resective surgery where deficit rates ranging from 5.5% to 52% were noted[8,12,20,22].

As mentioned above, several studies have had to demonstrate the low seizures resolution in the so-called non-lesional epilepsy surgery in general. Some studies non specifically focused on MST have found that MST performed in addition to resection were associated with less favorable outcome[8,16,17]. Compared to the group of 37 patients with MRI+, our 25 patients were characterized by a decreasing rate of Class I (36% versus 46%) and an increase in Class IV (21% against 16%). However, this difference is not statistically significant, so we can consider that the results of radiating MST performed alone or in combination with other techniques may be similar to those of lesional epilepsy in eloquent cortical zones. At least 1/3 of patients may obatin seizures freedom. Our rate of class I patients (36%) is comparable to that reported by Smith (37.5%) on MST in extra-temporal epilepsy[23]. It is slightly higher than that of the meta-analysis of Ansari and his colleagues (33.7%) on the surgery of non-temporal non-lesional epilepsy in children[16].

Conclusion:

Our patients with non-lesional refractory epilepsy in eloquent cortical areas represent a particular group of candidates for surgery. They are characterized by a high incidence of generalized seizures, and the extensive use of EEGi for the setting of the epileptogenic focus. In almost half of cases, pathological analysis is not contributory. Radiating MST performed alone or in combination with other techniques allow to provide them seizure suppression in at least 1/3 of cases with low postoperative morbidity.

Disclosure of conflicts of interest: the authors have any conflict of interest to disclosure

Table.1: General characteristics of patients treated using radiating multiple subpial transections (rMST)

	MRI (–) group (N=25)		MRI (+) group (N=37)	
Sex				
M	15 (60)	-	27 (73)	-
F	10 (40)	-	10 (27)	-
Age at surgery (years)	-	18,5; 14 (0,25-55)		20,6 ; 21 (0,25-52)
Onset age (years)	-	8,7 ; 7 (0-36)		9,2 ; 11 (0-51)
Epilepsy duration (years)	-	10,5 ; 9 (1-28)		12,1 ; 11 (0,25-38)
Seizures types				
Generalized	16 (64)	-	13 (35)	-
Partial	9 (36)	-	24 (65)	-
iEEG[a] use	15 (60)	-	10 (27)	-
Cerebral hemisphere concerned				
Rigth	15 (60)	-	19 (51)	-
Left	10 (40)	-	18 (49)	-
Cortical eloquent areas				
FA[b] (BA[c] 4)	17 (68)	-	21 (57)	-
PA[d] (BA3, 2, 1)	16 (64)	-	20 (54)	-
SMA[e] (BA 6)	7 (28)	-	0	-
Wernicke (AB 22, 39, 40)	7 (28)	-	0	-
Broca (AB 44)	5 (20)	-	2 (5)	-

[a] iEEG: invasive electro-encéphalogram; [b] FA: frontal ascending gyrus; [c]BA: Brodmann area
[d] PA: parietal ascendin gyrus ; [e]SMA : supplementary motor area

Table.2: Surgical procedures, pathological description and patients outcome in nonlesional epilepsy

	n (%)	Mean ; Median (extremes
Procedures		
rMSTa[a]	10 (40)	-
rMST[b] *+ Disconnection*	7 (28)	-
rMST + Cortectomy	4 (16)	-
rMST + Electrocoagulation	1 (4)	-
rMST+ Combination[b]	3 (12)	-
Transection number	-	37 ; 40 (4-89)
Pathological description		
Gliosis	7 (28)	-
No specific lesions	6 (24)	-
No lesion found	6 (24)	-
Cortical dysplasia	3 (12)	-
Spongiosis	1 (4)	-
Not performed	2 (8)	-
Permanent neurological deficit		
Minor	2 (8)	-
Major	0 (0)	-
Outcome *(Engel Classes)*		
Class I	9 (36)	-
Class II + III	9 (36)	-
Class IV	7 (28)	-

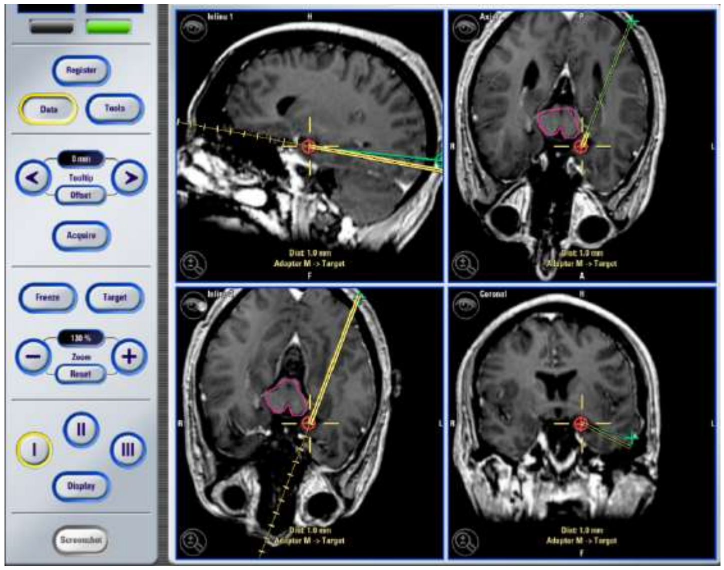
[a] rMSTa : radiating muliple subpial transections performed alone
[b] rMST : radiating muliple subpial transections

Figures legends:

Fig 1 : Mesio-temporal electrode placement under neuro-navigation guidance (Brainlab) showing target, trajectory and brainstem that must be protected.

Fig 2: Subdural electrodes placement (a et b) via a linear craniotomy and using neuro-navigation guidance.

Fig 3: MRI post-operative imaging showing intraparenchymal (rigth mesio-temporal) and subdural (left frontal) electrodes locations



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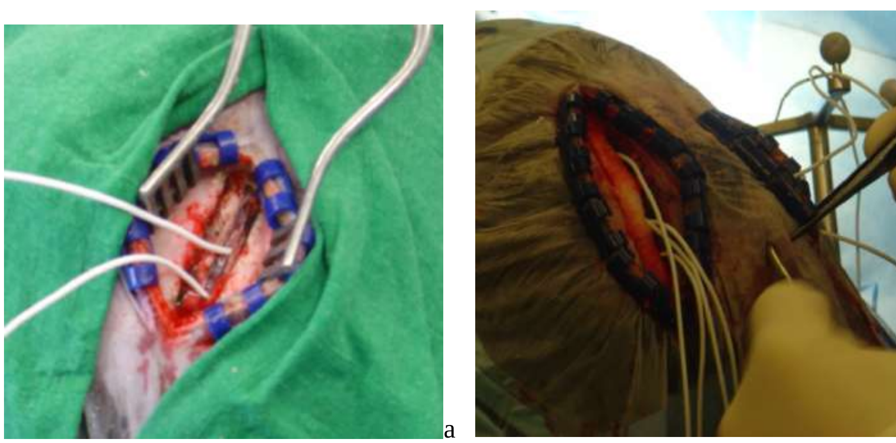
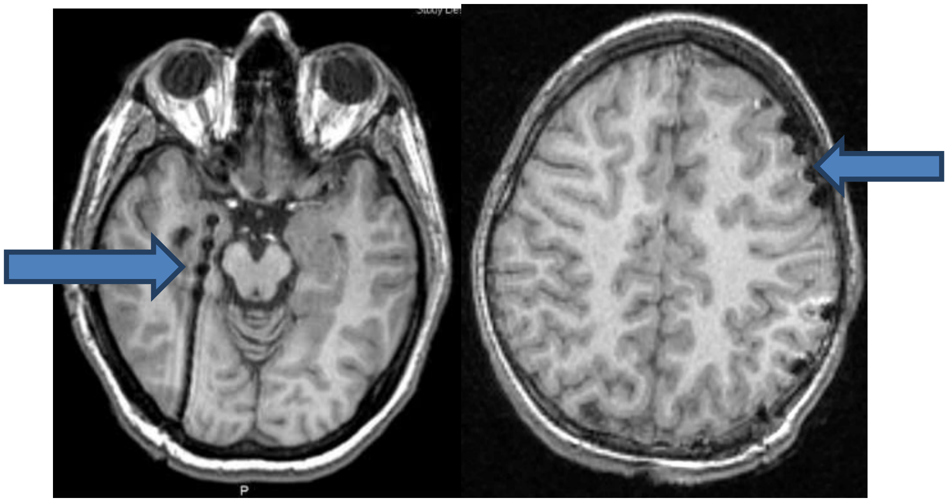


a b

Fig 2: Subdural electrodes placement (a et b) via a linear craniotomy and using neuronavigation guidance.



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