

Successful epilepsy surgery with a resection contralateral to a suspected epileptogenic lesion

Pavel Krsek¹, Michal Tichy², Milan Hajek³, Monika Dezortova³, Josef Zamecnik⁴, Milan Zedka¹, Radana Stibitzova⁵, Vladimir Komarek¹

¹ Department of Pediatric Neurology

² Department of Neurosurgery, Charles University, Second Medical School, Motol Hospital

³ MR Unit, Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine

⁴ Department of Pathology and Molecular Medicine, Charles University, Second Medical School, Motol Hospital

⁵ Department of Pediatric Neurology, Thomayer University Hospital, Prague, Czech Republic

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ABSTRACT – We report on a case of frontal lobe epilepsy in an eight-year-old girl. Seizure semiology and EEG indicated an epileptogenic zone localized in the mesial frontal structures, without clear-cut lateralization. MRI showed a lesion in the right cingulate gyrus, initially regarded as a hamartoma. Ictal SPECT did not have a localization value. MR spectroscopy revealed two metabolic abnormalities: one in the area of the MRI lesion and a second contra-laterally. Invasive monitoring using subdural electrodes covering the convexity and mesial part of the right frontal lobe including mesial strips with bilateral contacts was used. The invasive monitoring failed to localize ictal onset in the right hemisphere; however, electric stimulation induced seizures from electrodes facing the left supplementary sensorimotor area (“through” the *falx cerebri*). We re-implanted the electrodes over the left frontal lobe and the second invasive monitoring clearly localized the ictal onset zone in the left supplementary sensorimotor area, which was subsequently resected. Histopathology found MRI-negative focal cortical dysplasia. The contralateral lesion was reassessed as nonspecific enlargement of perivascular spaces. The patient has been seizure-free for more than two years.

[Published with video sequences]

Key words: frontal lobe epilepsy, MR spectroscopy, subdural electrode mapping, focal cortical dysplasia, MRI-negative focal epilepsy

Identifying the epileptogenic zone, defined as “the area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures” (Lüders *et al.* 2006, Palmieri 2006, Kahane *et al.*

2006) is the ultimate goal of the pre-surgical evaluation of epilepsy surgery candidates. A critical part of this process is the detection of the epileptogenic lesion, which is defined as the structurally abnormal area of the brain apparent on MRI (Wieser 1994, Engel



Correspondence:

P. Krsek, MD, PhD
Department of Pediatric Neurology
Charles University, 2nd Medical School
Motol University Hospital
V Uvalu 84
CZ 15006 Prague 5
Czech Republic
Tel.: (+00 420) 2 24433300
Fax: (+00 420) 2 24433339
<pavel.krsek@post.cz>

1996, Rosenow and Lüders 2001, Kuzniecki 2004, Urbach 2005). Removing a structural lesion is the surest way of producing a good surgical outcome, and complete excision is better than incomplete excision (Wyllie *et al.* 1987, Hader *et al.* 2004). However, the relationship between an abnormality detected on MRI and the extent of the epileptogenic zone is not always straightforward. In some lesions, the visible structural lesion may comprise only a portion of the pathological tissue. A typical example of such a lesion is focal cortical dysplasia (Palmini *et al.* 1991, Sisodiya 2000). Alternatively, functionally abnormal tissue that must also be excised for seizure relief could surround the structural pathology.

Complete absence of a specific focal lesion on MRI may render the work-up particularly difficult. Diagnostic protocols must rely on clinical semiology, EEG and functional imaging data. Intracranial EEG monitoring is frequently required (Duchowny *et al.* 2000). MRI-negative patients usually have a less favorable surgical outcome, but some recent studies have reported promising surgical outcomes (Siegel *et al.* 2000, Cukiert *et al.* 2001, Blume *et al.* 2004, Chapman *et al.* 2005).

The possibility that a structural lesion may be unrelated to the epilepsy must also be considered and the anatomo-electro-clinical correlations need to be established. However, scalp EEG is an imperfect tool and has a number of limitations. Among others, propagation of electrical activity along physiological pathways or through-volume conduction in extracellular spaces may give a misleading impression as to the location of the source of the epileptiform activity (Smith 2005). It is therefore critically important to appropriately evaluate all sources of information concerning localization of the epileptogenic zone.

We present a case of MRI-negative focal epilepsy, initially complicated by an assumed brain lesion.

Case report

Our patient, a girl born in 1995 at term and after a normal delivery, had no family history of epilepsy or any other neurological disorder. Developmental skills were normal. The first unprovoked seizure occurred at the age of five years. They were stereotyped, characterized at onset by a difficult-to-describe, non-lateralized sensation. Later she developed seizures without any warning. The seizures consisted of mild anteflexion of the upper half of the trunk and a tonic semi-flexion of the upper limbs, with changeable asymmetry. Consciousness was fully preserved. The episode lasted approximately ten seconds; frequency was high from the start: up to 40 seizures per 24 hours.

The patient was initially followed at a local pediatric department: CT scan showed no brain lesion, EEG demonstrated non-specific epileptiform abnormalities. Treatment with a combination of carbamazepine and valproic acid was initiated and she remained seizure-free over the

following two years. Her behavior and global development were normal.

The seizures recurred in January 2003, at the age of seven years. They had similar semiology, except for the absence of the above-mentioned aura. The asymmetric tonic posturing of the upper and lower limbs was variable and did not allow lateralization. Version of the head occurred infrequently. The majority of the seizures occurred during sleep. Seizures when awake were typically triggered by positive emotions. The frequency of her seizures was again high, usually up to a dozen per 24 hours. Her epilepsy became markedly drug resistant: treatment with valproic acid, carbamazepine, lamotrigine, topiramate, vigabatrin, levetiracetam, phenytoin and primidone in different combinations was ineffective. The worst aggravation of the condition occurred in December 2003, when the maximal frequency of seizures reached 244 per 24 hours, despite intensive intravenous medication. At the time of surgery, the girl received a combination of primidone, valproic acid and carbamazepine.

The neurological examination was unremarkable. EEG showed abnormally slow background activity and occasional midline fronto-centro-parietal low-voltage spikes. Epileptiform activity was more frequent during non-REM sleep. It again comprised midline, fronto-centro-parietal spikes and, moreover, long trains of rhythmic 4-5 Hz activity with an inconstant spike component in the fronto-central regions, however, with a clear-cut left preponderance. These episodes typically preceded seizures during sleep (*figure 1*). Ictal EEG changes were characterized by diffuse flattening of the amplitude and subsequent rhythmic activity in the midline; we classified them as non-lateralizing (*figure 2*). Detailed video EEG analysis of seizure semiology revealed that the majority of seizures were characterized by extension of the right upper and left lower limb, and that nocturnal seizures usually terminated with automatisms of both upper limbs such as touching the blanket and the genitals. Based on EEG and seizure semiology, we concluded that seizures originated from the supplementary sensorimotor area (SSMA) and cingular region; however, laterality was not clear (*see video sequence 1*).

Neuropsychological testing confirmed normal intelligence but highlighted a prominent attention deficit, probably related to the very high frequency of seizures. MRI showed on T2-weighted images a hyperintense signal over the right cingulate gyrus, interpreted to be a hamartoma (*figure 3A*). Interictal and ictal ^{99m}Tc -ECD SPECT were not confirmatory.

The patient underwent ^1H MR spectroscopic examination using the chemical shift imaging (CSI) technique. CSI spectra were obtained in the transverse plane using a volume preselected PRESS-CSI hybrid sequence with the following parameters: FOV 160x160 mm, 16x16 steps, TR/TE = 1500/135 ms, 1 acquisition, slice thickness 20 mm, and nominal voxel volume of 2 mL. Concentrations of

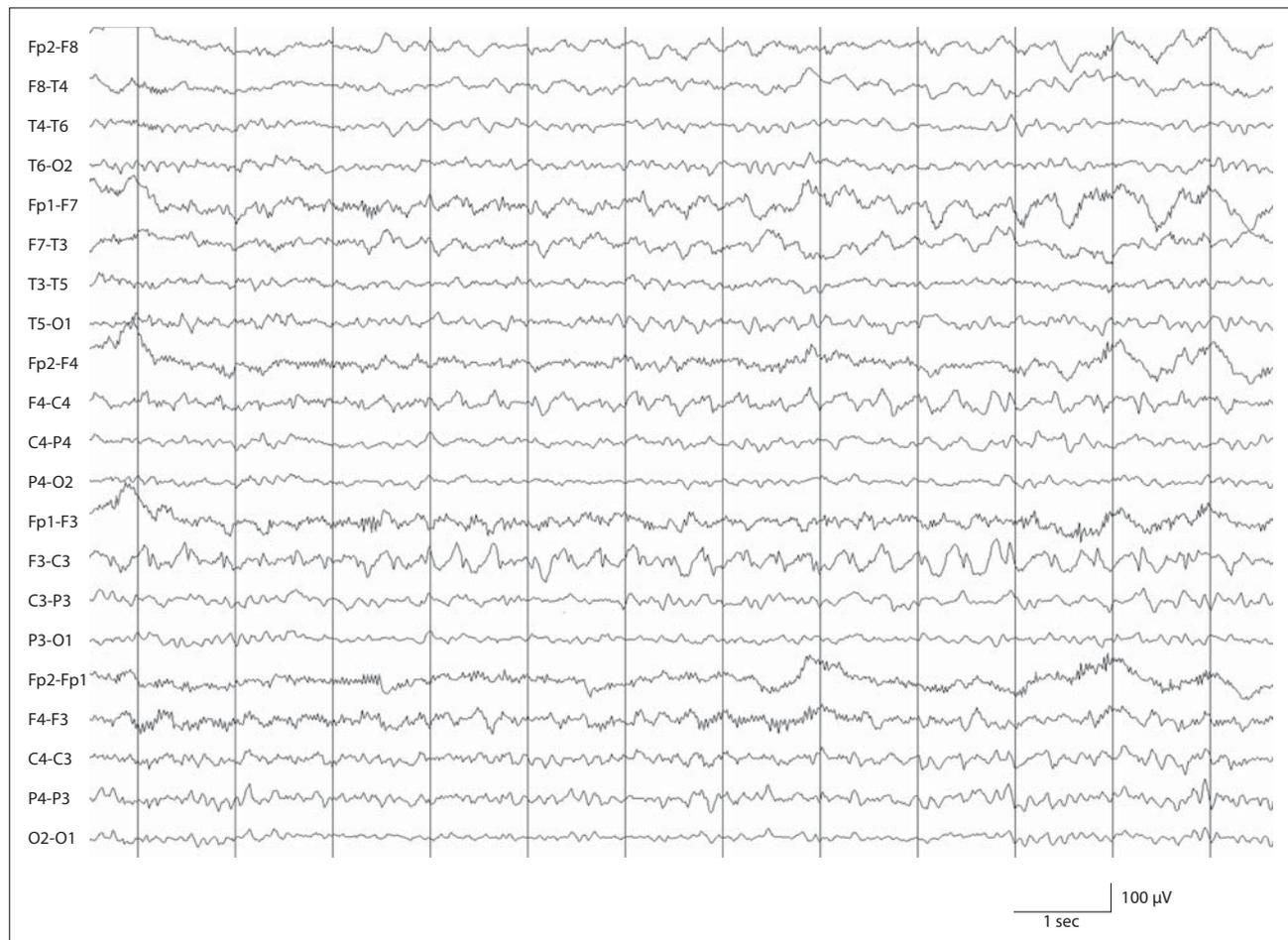


Figure 1. Sleep EEG performed at age 7.5 years showing an episode of rhythmic SW complexes in the fronto-central regions with a left preponderance.

N-acetylaspartate (NAA), (phospho)creatine (Cr) and choline compounds (Cho) in laboratory units [mM] and their ratios were used for the calculation of metabolic maps (Jiru *et al.* 2006). The investigation showed visible metabolite abnormalities in both frontal lobes (*figure 3B, C*). The first co-localized with the MRI lesion, the second was localized in the MRI-negative area of the left frontal lobe.

In May 2004, the patient underwent an invasive investigation following implantation of subdural electrodes. Since we regarded ictal onset from the neighborhood of the MRI lesion as probable, the electrodes were initially placed in the convexity and the mesial part of the right fronto-central region. Midline strips with bilateral contacts (recording the activity of the right hemisphere subdurally and the activity of the left hemisphere epidurally – through the *falx cerebri*) were used. Continuous monitoring failed to show ictal onset during spontaneous seizures, and, moreover, electric stimulation of the right hemisphere induced neither seizures nor epileptiform afterdischarges. We also tried to

stimulate using mesial electrodes facing the *falx cerebri*. Analgesic drugs were administered because of painful sensations during the stimulation. At an intensity of 7mA, a typical seizure with a tonic extension of the right upper extremity was induced from electrodes facing the left SSMA (*see video sequence 2*).

We decided to re-implant electrodes over the left fronto-central region. Electrodes from the first implantation were retained, which allowed simultaneous recording from the convexity and mesial structures of both hemispheres. The second invasive monitoring reliably demonstrated the localization of the seizure onset zone in the left SSMA (*figure 4*); moreover, typical seizures were induced here using electric stimulation at an intensity of 3 mA. The total length of both invasive monitorings was 14 days. No complications occurred.

A limited resection of the left SSMA and pre-motor cortex was performed. No neurological and cognitive deficits were encountered following surgery. Postoperative MRI

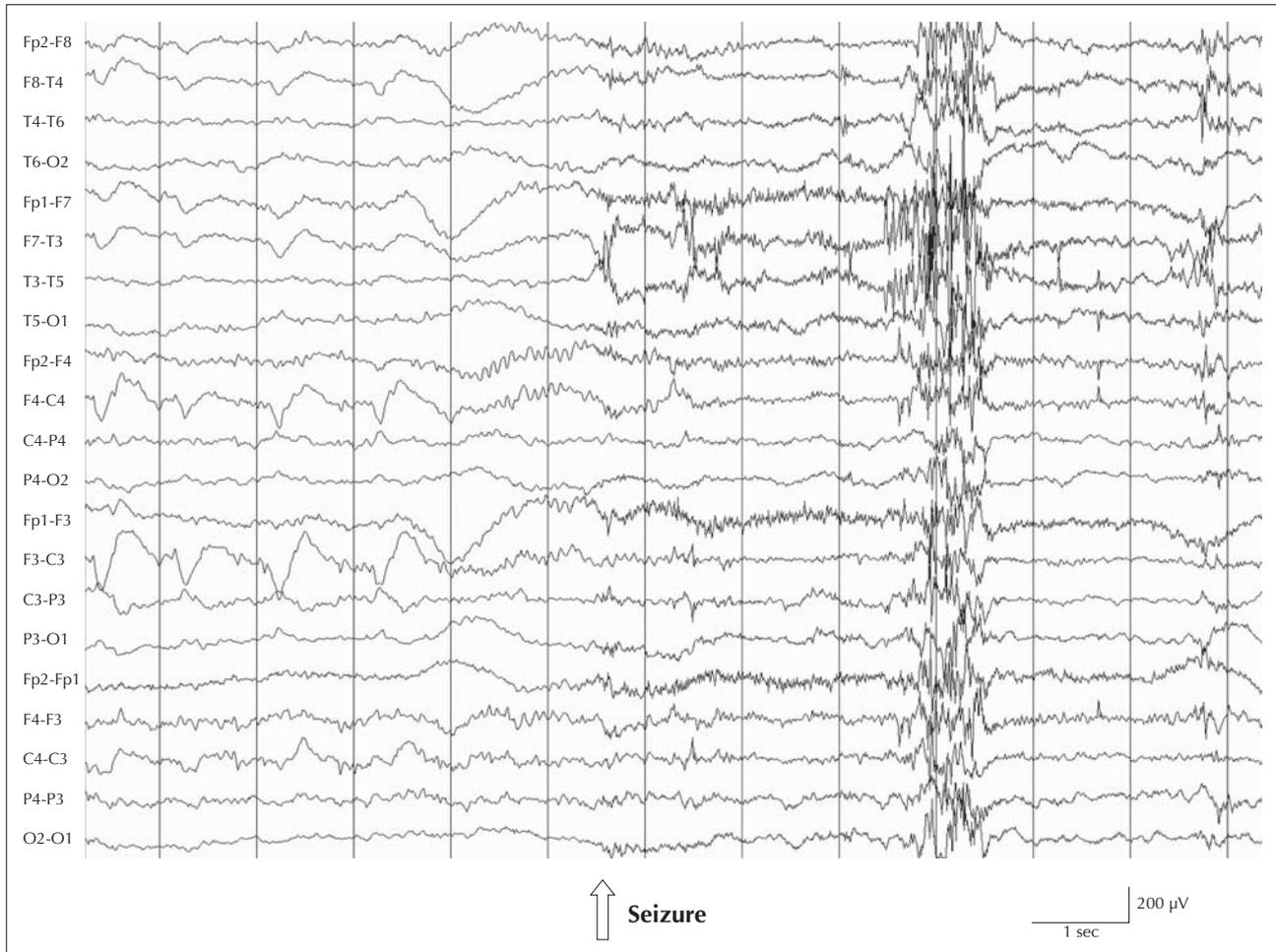


Figure 2. Ictal EEG. The arrow depicts the clinical onset of the seizure. The seizure was preceded by rhythmic bilateral fronto-central SW complexes evolving into generalized flattening of the amplitude with bifrontal non-lateralized rhythmic activity partially obscured by artifacts.

revealed no complications (*figure 3D*). Histological examination of the resected brain tissue found an MRI-undetected focal cortical dysplasia (FCD). According to the new classification of FCD (Palmini *et al.* 2001), the finding was evaluated as FCD type 2B (because of the presence of both dysmorphic neurons and balloon cells). No signs of FCD were present in the margins of the resected tissue.

During a 28 month, post-operative follow-up, no seizures have been reported. Repeated EEGs were free of epileptiform discharges and the background activity has gradually improved. The last EEG tracing displayed only minimal non-specific abnormalities. Primidone was completely withdrawn, valproic acid is being reduced and the dose of carbamazepine was also lowered. A thorough neuropsychological evaluation conducted at the age of ten showed normal intelligence quotient and absence of significant cognitive deficits.

Discussion

We report on an atypical case of frontal lobe epilepsy with SSMA-type seizures. Seizure semeiology was characteristic of SSMA seizures, which are usually frequent, brief, predominantly during sleep, with abrupt tonic posturing of the extremities and preserved consciousness (Williamson and Jobst 2000, Ikeda *et al.* 2002). Drug resistance is another characteristic feature of this type of focal epilepsy. It was reported that detailed analysis of videos could provide useful lateralizing clues such as version of the head and eyes during secondary generalization (Wyllie and Bass 1996). In our patient, lateralization based on semeiology was not evident; however, prevailing tonic extension of the right upper extremity was an important sign.

Scalp EEG findings in patients with SSMA seizures are usually inconclusive or show only infrequent interictal spikes over the midline which could be the result of sleep

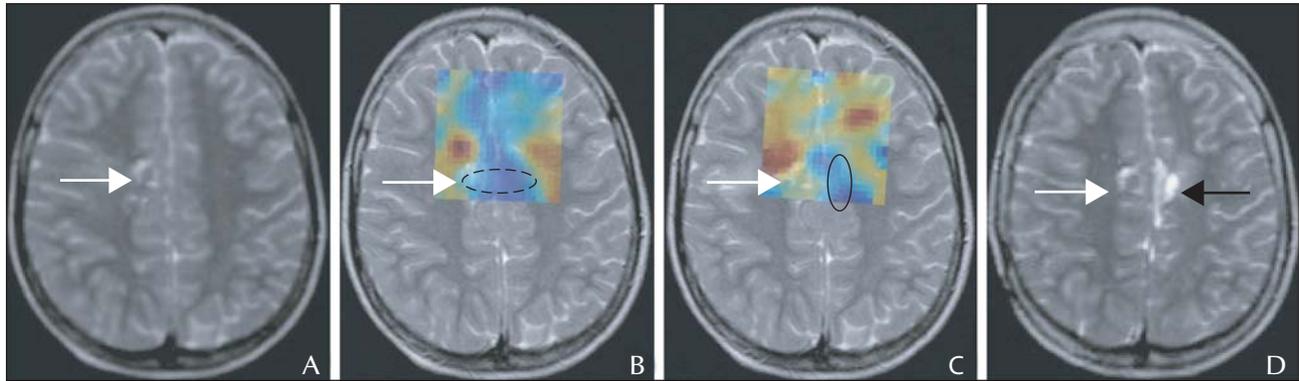


Figure 3. Transversal T2 weighted images (turbo-spin echo sequence, TR/TE = 4400/99 mm, slice thickness = 5 mm, FOV = 260x260 mm) used for CSI localization. **a** – transversal slice with the lesion described as a hamartoma (white arrow); **b** – transversal slice with metabolic map of ratios Cho/Cr, the area labeled by dashed ellipse was assumed as metabolic abnormality with increased Cr concentration (similar symmetrical decreasing of metabolite ratios was observed for NAA/Cho); **c** – minimum in metabolic map of ratios NAA/Cr (black ellipse) corresponds well with the position of the resection cavity (black arrow) demonstrated at the figure **d** – T2w image two years after the resection. Low and high values of metabolite ratios in CSI maps correspond to the blue and red color, respectively.

(Wyllie and Bass 1996, Ikeda *et al.* 2002). Moreover, ictal EEG changes are often subtle and obscured by EMG artifacts, and do not always enable reliable lateralization. Wyllie and Bass (1996) reported on the importance of prolonged sleep EEG in a patient on reduced antiepileptic medication. Runs of vertex spikes which are frequently asymmetric with higher amplitude over one side may be evident. In their series, the asymmetry always agreed with a lateralization hypothesis based on ictal EEG, MRI or PET. We eventually supported this result. Our patient exhibited long episodes of predominantly left-sided rhythmic activity during sleep. Initially, we interpreted this activity incorrectly as originating from the right hemisphere but detected on the left side due to an oblique dipole.

Because of the frequently vague localization of the epileptogenic zone based only on EEG-clinical characteristics, high-resolution MRI plays a critical role in the evaluation process of epilepsy surgery candidates with SSMA seizures. Surgical outcome is usually good when EEG and MRI data are convergent, whereas the seizure control is poor when imaging data are negative or not concordant with EEG findings. It is important to keep in mind that SSMA seizures could be caused by the ictal spread to the SSMA from adjacent “silent” areas (Ikeda *et al.* 2002). MRI-negative cases are nevertheless not uncommon among patients with SSMA seizures; e.g. six of 11 patients in the series by Wyllie and Bass had normal, preoperative MRI (Wyllie and Bass 1996).

In our case, the suspicion of an MRI lesion located in the right cingulate gyrus seemed to be related to the localization of the epileptogenic zone since we expected seizure onset in the mesial frontal area. The nature of the lesion was however, obscure from the beginning. It was originally described as a hamartoma. This false interpretation led to the wrong decision concerning subdural electrode implantation. Based on repeated consultations concern-

ing the findings, we eventually concluded that the MRI abnormality reflected an atypically enlarged perivascular space. An important message of our present report is that MRI lesions, presumably causing epilepsy, should always be interpreted with caution and that several readings may be needed.

Even though re-evaluation of the MRI scans did not reveal pathology at the site of the resection (in the left SSMA). This is rather surprising given the type of histopathology (focal cortical dysplasia type 2B), since MRI is usually reported to be highly sensitive to this type of brain lesion (Lawson *et al.* 2005). The reason for the normal MRI in our patient could be the small size of the cortical malformation as well as the small number of balloon cells found.

Ictal SPECT could be a useful method of seizure-onset localization in patients with SSMA seizures (Laich *et al.* 1997). Nevertheless, visible hyperperfusion was not found in our case. The most plausible explanation is that the duration of seizures (usually ten seconds) was too short to induce detectable ictal hyperperfusion (Van Paesschen 2004).

MR spectroscopy (^1H MRS) provided important additional data for the presurgical evaluation of our patient. Metabolite abnormality (characterized by symmetrically decreased Cr/Cho and NAA/Cho ratios, and asymmetry in NAA/Cr ratio) in mesial parts of both frontal lobes was found. The right-sided metabolic abnormality corresponded to the MRI findings and probably reflected the changes in cell metabolism in the enlarged perivascular space. The left-side abnormality was however, localized in an area which appeared normal on MRI. Postoperative correlation of results demonstrated that the position of the resection cavity matched with the left hemisphere metabolite changes corresponding mostly to decreased

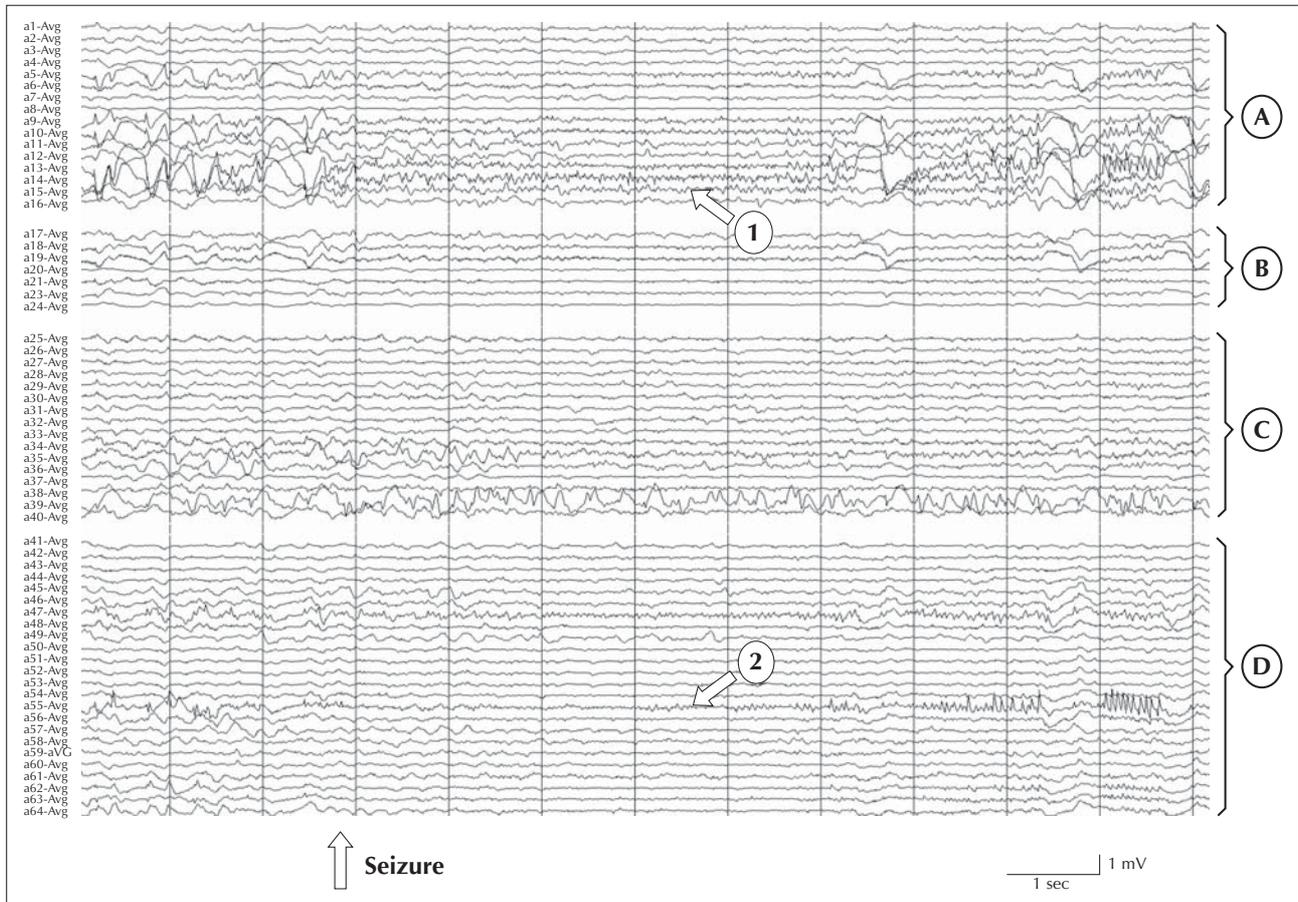


Figure 4. Invasive monitoring of the seizure from bilaterally placed, subdural electrodes (A – the left mesial fronto-central region subdurally; B – the left mesial fronto-central region epidurally; C – the right mesial fronto-central region subdurally; D – the left fronto-central convexity). Preceding rhythmic epileptiform discharges evolving into low-voltage fast activity credibly localize ictal onset to the left supplementary sensorimotor area (1). The seizure pattern is almost absent in electrodes recording the same left mesial frontal area epidurally, through the *falx cerebri*. Note the late spread of the seizure activity to the left primary motor area (2).

NAA/Cr ratio. ^1H MRS therefore correctly indicated MRI-undetected cortical malformation.

Only a few studies have suggested that ^1H MRS could be useful in the presurgical evaluation of patients with extratemporal epilepsy without apparent MRI lesions (Garcia *et al.* 1995, Stanley *et al.* 1998, Lundbom *et al.* 2001). We recently reported on seven patients with MRI-undetectable focal cortical dysplasia (Krsek *et al.* in press). ^1H MRS correctly lateralized the epileptogenic zone in all cases and localized it in five of them. It seems that in some patients ^1H MRS could be more sensitive than conventional MRI for the detection of discrete malformations of cortical development.

The course of the invasive monitoring of the patient was remarkable for at least three reasons. Firstly, adding or repositioning intracranial electrodes during an invasive study is usually regarded as a risky procedure. However, it has been recently reported that in patients who had unsuccessful, initial, intracranial evaluation, adding or repositioning

intracranial electrodes within a short-term interval allowed a good surgical outcome in one half of the patients (Lee *et al.* 2004). In Lee's series, no additional morbidity or death occurred during the second exploration. We confirmed the results of this study since our patient would not have been rendered seizure-free without the second implantation of the subdural electrodes over the opposite hemisphere.

Secondly, the induction of a typical seizure by electric stimulation epidurally "through" the *falx cerebri* could be regarded as a surprising phenomenon. To our knowledge, there is no previous description of a similar stimulation procedure in the literature. The reliability of the event was verified by consequent direct stimulation from a subdurally-placed electrode at a lower current intensity. Although we do not recommend the routine use of such stimulation (especially given the resulting painful sensations) it may be acceptable in selected cases.

Thirdly, the invasive monitoring demonstrated the propagation of both interictal discharges and seizure activity from the SSMA to the primary motor cortex. The epileptiform activity probably propagated from the SSMA to the primary motor cortex through subcortical circuits since electrodes recording the activity at these sites were separated by silent ones. The study corresponds with the observations of Baumgartner *et al.* (1996) who found that the time lag between the SSMA and the primary motor cortex averaged 25 ms for interictal spikes and 100 ms for ictal discharges. This time lag is too large to be attributed to intracortical volume conduction.

Considering all of the above-mentioned difficulties, the outcome of the epilepsy surgery is surprisingly favorable. On a reduced dosage of antiepileptic medication, the child has been seizure-free for more than two years. This result could positively influence our decision-making regarding surgical treatment of future difficult-to-treat cases of frontal lobe epilepsy.

Koepp and Woermann, 2005 ; Palmiini *et al.* 2004 ; Sammaritano *et al.* 1987. □

Legends for video sequences

Video 1. Two spontaneous seizures during sleep. The seizures consisted of a short tonic extension of the upper limbs, leaning of the upper half of the trunk and finally distal automatisms of the hands. In the second seizure, the right-sided preponderance of the tonic convulsion is apparent.

Video 2. Seizure induced by electric stimulation at 7 mA from epidural electrodes facing the left supplementary sensorimotor area through the *falx cerebri*. The stimulation was performed when subdural electrodes were placed over the right frontal lobe only. The girl first denotes a painful sensation during the stimulation. The tonic convulsion of the right upper limb simultaneously with the version of the eyes to the right followed. The doctor asked the girl to remember the word "telephone". The patient repeated the word at the end of the video.

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