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Brief Communications

Cognitive Deficits during Status Epilepticus and Time Course of Recovery: A Case Report

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Summary: We describe a young woman with progressive cognitive and neurological deficits during a parietal lobe status epilepticus (SE). Ictal FDG-PET showed left parietal lobe hypermetabolism and frontal lobe hypometabolism with concomitant EEG slowing. Cognitive and neurological deficits fully reversed more than 1 year after seizure remission, and were associated with normalization of FDG-PET and EEG. Our findings suggest that ictal hypometabolism and EEG delta activity at a distance from the epileptic focus were seizure-related phenomena, possibly representing inhibition in seizure propagation pathways, which could be responsible for the epileptic encephalopathy. **Key Words:** Epileptic encephalopathy—Cognition—Epilepsy—Surround inhibition—FDG-PET.

An epileptic encephalopathy is characterized by uncontrolled epileptic seizures associated with cognitive deterioration, and can occur both in children (Wirrell et al., 2005) and adults (Dodrill 2002; Helmstaedter et al., 2003; Thompson and Duncan 2005). The cause of the cognitive deterioration is unknown and may be due to antiepileptic drugs (AEDs), neuronal cell loss, the underlying etiology of the epilepsy or as a direct effect of seizures and epileptic activity. We describe a patient with prolonged status epilepticus (SE) and progressive cognitive deterioration, which slowly reversed after the control of epileptic seizures. We present evidence that this cognitive decline may be a seizure-related phenomenon, characterized by FDG-PET hypometabolism and EEG delta activity at a distance from the ictal onset zone, which we have called the surround inhibition zone (Nelissen et al., 2006; Van Paesschen et al., 2007).

CASE DESCRIPTION

The patient was a 25-year-old right-handed woman. Her gestation and birth were uneventful. She did not have a history of febrile seizures, meningoencephalitis, or cerebral trauma. Her early development was normal. There was no family history of epilepsy. The epilepsy started at the age of 14 years, and was characterized by isolated sensory simple partial seizures (SPS) (tingling sensations) and occasional myoclonic jerks affecting mainly her left leg, and vertiginous sensations. She had two secondarily generalized tonic–clonic seizures (SGTCS) that started with the paresthesias in the left leg. Several EEGs and an MRI scan of the brain were normal. She was treated with carbamazepine (CBZ) 200 mg b.i.d. for 2 years and remained seizure free for 7 years.

In January 2002, at the age of 21 years, she experienced progressively more frequent and prolonged daily SPS characterized by paresthesias in her right face and arm, and she noticed some difficulties typing with her right hand. Six weeks later, she had a SGTCS. CBZ was restarted and increased to 400 mg b.i.d. Despite the AED, the sensory SPS affecting the right face and arm continued relentlessly. After the SGTCS, she developed progressive speech difficulties and apraxia of the right hand over the ensuing 6 weeks. She became slow, and it took her more than 1 hour to dress in the morning. She was easily distracted, and developed memory problems. Since it was felt that her cognitive problems were due to CBZ toxicity, CBZ was tapered and discontinued after 1 week, and lamotrigine (LTG) was started at a dose of 25 mg b.i.d.

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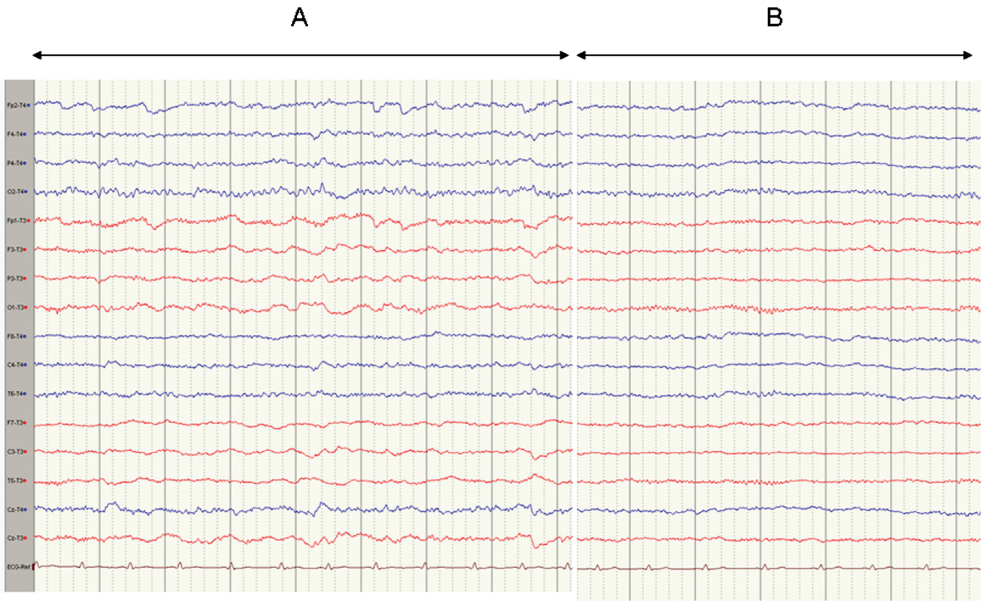

FIG. 1. EEG during and after simple partial SE. Mid-temporal referential montage. Blue: right hemisphere derivations, red: left hemisphere derivations. (A) Recording of April 17, 2002, during simple partial SE. There was an excess of polymorphic, medium voltage delta activity over both hemispheres, which was much more pronounced on the left. Alpha rhythm was present on the right, but not the left. (B) Recording of July 19, 2004, more than 2 years after SE. This part of the recording was normal, with disappearance of the excess slowing and lateralisation, and presence of bilateral alpha rhythm during eye closure. Time base: 30 mm/s; sensitivity (of original recording): 100 μV/cm; high cut: 30.0 Hz; low cut: 0.5 Hz.

Subsequently, she had two SGTCS in two days, and on the third day (April 4, 2002), she was hospitalized because of convulsive SE, which lasted more than 30 min and was controlled with IV lorazepam 4 mg and IV phenytoin 1,000 mg. Clobazam 10 mg t.i.d. was started. Afterwards, the cognitive decline was at its worst. She had severe memory difficulties, aphasia and apraxia of the right hand. At this point, she was transferred to our hospital for a second opinion for a rapidly progressive dementia with seizures.

On admission (April 10, 2002), she complained of continuous paresthesias in the right arm and face, speech and memory problems and apraxia of the right hand. On examination, she was alert and cooperative. Mini mental state examination was 13/30. She was disoriented in place and time, had short-term memory problems, serial sevens was not possible, she had naming and comprehension difficulties, was able to read "close your eyes," but did not understand it, and was unable to write and draw a figure. Her right hand was apraxic. Cranial nerves were intact. Fine finger movements were diminished on the right. Otherwise, motor testing was intact, as were deep tendon reflexes, sensory testing and gait.

On clinical grounds, we suspected simple partial SE of the left parietal lobe. An EEG demonstrated delta slowing mainly over the anterior derivations, which was more pronounced on the left, but no epileptic activity (Fig. 1A). An ictal FDG-PET (April 12, 2002) showed an area of hypermetabolism in the left parietal lobe, and confirmed the clinical diagnosis (Fig. 2A). In addition, large areas of hypometabolism were present in the frontal lobes, left more than right. A 1.5 T MRI (T_1- and T_2-weighted axial and coronal images, FLAIR, and MPRAGE) was normal. Examination of CSF was normal (including cells, protein, glucose, lactate, oligoclonal bands, gram stain and culture, IgG index and screen for herpes simplex virus, Epstein-Barr virus, varicella-zoster virus, cytomegalovirus, toxoplasmosis, *Borrelia burgdorferi*, HIV, and 14-3-3 protein). Serum virology was normal. Serum vitamin B1, B12, and folate were normal. Thyroid function was normal and thyroid antibodies were not present. Screening tests for Tay-Sachs disease, beta-galactosidase-1 deficiency, Gaucher disease, Niemann-Pick disease, and MELAS syndrome were negative. Axilla biopsy did not provide evidence for Lafora's disease or lipofuscinosis.

Neuropsychological testing (April 18, 2002) confirmed severe memory and frontal executive functions deficits, and naming difficulties during the simple partial SE (Table 1).

On admission to our hospital, she was taking LTG 25 mg b.i.d., phenytoin 100 mg b.i.d., and clobazam 10 mg t.i.d. LTG was increased and 10 days after admission (April 20, 2002), she became seizure free, i.e., the tingling sensations in her right arm and face stopped, on LTG 100 mg b.i.d. From that day, a gradual improvement in cognition (aphasia, apraxia, memory problems, and frontal executive functions deficits) was noticed, which was documented by repeated neuropsychological assessments (Table 1). An EEG on April 26, 2002 showed a normal occipital alfa rhythm and admixture of excess low voltage 1–2 Hz delta waves on the left, with accentuation of the

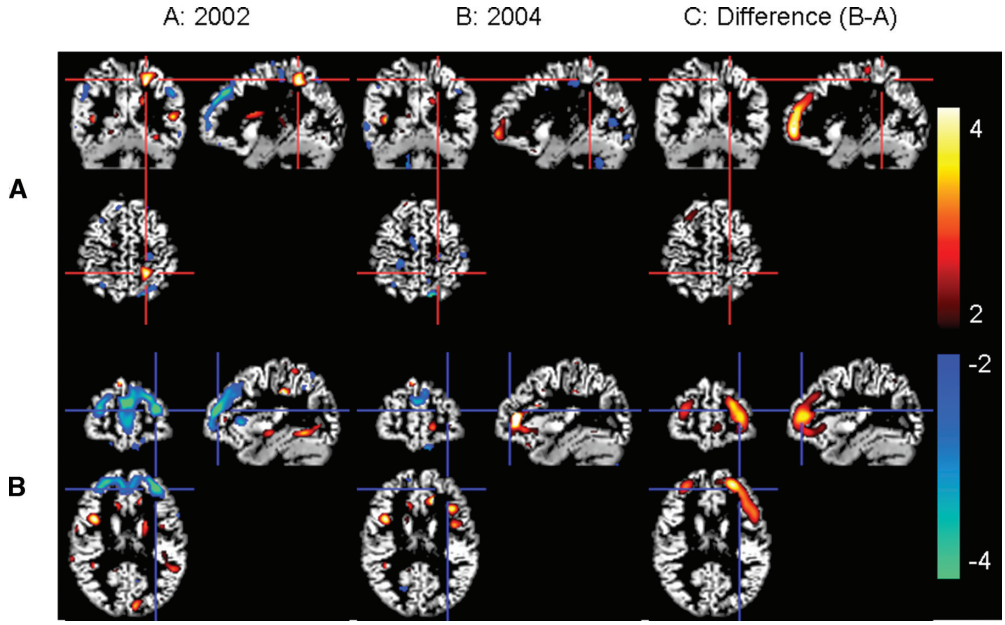

FIG. 2. FDG-PET during and after simple partial SE. The PET images were reconstructed using an anatomy-based reconstruction algorithm analyzed semiquantitatively after normalization to white matter activity, and compared with a normal age- and gender-matched control group (for more details see Baete et al., 2004a, 2004b; Nelissen et al., 2006). Regions of significantly increased (>2 SD, orange-red) and decreased (<2 SD, blue-green) metabolism, compared to normal controls, are projected on a reconstructed PET image. The top row (a) shows the results in the left parietal region (red crosses) and the bottom row (b) in the left frontal region (blue crosses). FDG-PET during the simple partial SE (A, April 12, 2002) showed hypermetabolism in the left parietal region (Aa), consistent with ictal activity, and large regions of hypometabolism affecting predominantly the frontal lobes (Ab). The FDG-PET during remission of epilepsy (B, 2004) showed resolution of the left parietal hypermetabolism (Ba) and frontal lobe hypometabolism (Bb). The difference image between the two PET scans (C) showed the largest (>2SD) increases in metabolism (orange-red) in the frontal lobes, left>right (Cb), during remission of the epilepsy compared with the simple partial SE.

TABLE 1. *Neuropsychological test results*

	Normal control values: mean (SD)	April 18, 2002	June 3, 2002	Aug. 12, 2002	Dec. 16, 2002	Jan. 23, 2006
Memory						
AVLT						
Sum	*59 (7)*	**29**	**41**	**42**	55	55
Delayed	*12 (2)*	**4**	**7**	10	10	12
Recognition	*14 (1)*	13	14	12	**11**	14
RVDLT						
Sum	*53 (8)*	**18**	**35**	45	69	60
Recognition	*14 (1)*	**11**	15	15	15	15
Digit span forward	*6*	**4**	**4**	6	7	**5**
Digit span backward	*4*	**2**	**2**	**3**	5	5
Attentional/frontal functions						
Bourdon						
Average row time (seconds)	*12.3 (1.6)*	**20.0**	**14.9**	10.9		10.4
Average row deviation time (seconds)	*1.26 (0.46)*	**3.78**	1.66	1.05		1.20
Omissions	*7 (7)*	2	2	1		1
Errors	*0 (0)*	1	0	0		0
Stroop interference factor	*<27.2*	**39.8**	−26.4	8	−10.6	−5
Trail making						
Version A (s)	*<42*	**83**	38	34	40	19
Version B (s)	*<94*	**389**	**197**	**100**	66	53
Letter verbal fluency	*47 (12)*	**17**	**26**	39	41	45
Animal fluency	*<12*	16	16	21	23	18
Language						
Boston Naming Test	*49/60 (82%)*	**26/40 (65%)**	**37/50 (74%)**	**19/30(63%)**	**48/60 (80%)**	53/60 (88%)

Note: Values more than 2 SD from the mean of the normal control values are indicated in bold.
AVLT, auditory verbal memory test; RVDLT, Rey visual design learning test.

lateralization during hyperventilation. Neuropsychological testing 8 months (December 16, 2002) after SE still revealed residual deficits in memory and naming. According to family members, it took more than 1 year before she had fully recovered. After 1 year, she was able to resume her studies, and obtained a Master Degree in Economics. Clobazam was gradually tapered and discontinued after 1 year. During an attempt to discontinue AEDs 2 years after SE, there probably was a recurrent nocturnal seizure (April 2004), and the dose of AEDs was increased again. The FDG-PET scan was repeated 2 years after SE (July 16, 2004) (Fig. 1B). The area of hypermetabolism in the left parietal lobe was no longer present, and the hypometabolism in the frontal lobes had resolved. An EEG (July 19, 2004) had improved considerably (Fig. 2B), but still showed a mild excess of 5 Hz theta and 2 Hz delta activity in left temporal derivations with accentuation during hyperventilation. A 3T MRI scan of the brain showed a small hyperintense area in the cortex of the right parietal lobe on FLAIR, consistent with a small focal cortical dysplastic lesion. The epilepsy remained well controlled at the latest follow-up. EEG 3 years after the SE (January 15, 2005) and neuropsychological evaluation 4 years after SE (January 23, 2006) were within normal limits.

In summary, the chronology of the semiology was as follows: sensory simple partial SE affecting right arm and face without cognitive deficits (lasting 6 weeks starting January 2002) → isolated tonic clonic seizure (mid February 2002) → sensory simple partial SE with some cognitive deficits (mid February to March 2002) → two tonic clonic seizures and convulsive SE (April 2–4, 2002) → sensory simple partial SE with severe cognitive deficits (April 5–20, 2002)→ seizure remission and recovery of cognitive deficits over more than 1 year (April 21, 2002 to mid 2003).

DISCUSSION

This patient presented with an epileptic encephalopathy, i.e., progressive cognitive decline associated with epileptic seizures. We excluded encephalitis, neurodegenerative diseases, and metabolic causes. Since a small focal cortical dysplasia was present in the right parietal lobe, we speculate that a small focal cortical dysplasia in the left parietal lobe, not visible on MRI, might have been responsible for the SE (Molyneux et al., 1998). Although AEDs may have cognitive side effects, lateralized findings, such as the right-sided apraxia and aphasia, could not be explained by AED toxicity. Also, improvement in cognition occurred after an increase in AEDs during SE, and the dosages of AEDs were not changed in the first year after remission of epileptic seizures, when the major improvements in cognition occurred.

The time course of the cognitive deficits, which became obvious only after SGTCS, and were maximal after CSE, suggested a causal relationship between SGTCS and cognitive decline, confirming previous observations (Dodrill 2002; Thompson and Duncan 2005). It is of interest that cognitive functions in our patient started to recover only on the day that complete cessation of seizure activity was obtained, suggesting that ongoing SPS prevented cognitive recovery.

Although the underlying neurobiology of FDG-PET hypometabolism is not well understood, recent studies have stressed that interictal FDG-PET hypometabolism represents a dynamic seizure-related phenomenon, that can disappear when seizures are controlled (Joo et al., 2005; Benedek et al., 2006; Nelissen et al., 2006), as in our patient. EEG slow activity was most marked over the left frontal lobe and coincided with the region of most severe hypometabolism, confirming observations of Altay et al. (2005). Although it has generally been assumed that the region of predominant FDG-PET hypometabolism contains the epileptogenic zone, evidence has been mounting that the region of predominant hypometabolism is actually at a distance from the epileptogenic zone (Juhasz et al., 2000; Nelissen et al., 2006), as in our patient. Several of the neuropsychological and neurological deficits in our patient could be explained by frontal lobe dysfunction, and could be seen as the functional correlates of the frontal lobe hypometabolism and EEG slowing. This observation confirms the findings of McDonald and colleagues (2006), who reported that resting frontal lobe metabolic values were strong predictors of executive functioning in patients with epilepsy.

Ictal EEG remains normal in around 80% of SPS, and does not exclude the diagnosis (Devinsky et al., 1988), as in our case. The clinical diagnosis of simple partial SE was confirmed by FDG-PET, which is in agreement with previous observations (Meltzer et al., 2000; Abou-Khalil et al., 2005; Palmini et al., 2005). In our patient with left parietal lobe SE, the region of increased metabolism in the left parietal lobe was consistent with ongoing seizure activity and could explain the continuous paresthesias reported by our patient. The area of increased metabolism returned to normal when seizures were controlled.

The time course of seizure activity, cognitive, neurological, EEG, and PET changes in our patient provided evidence supporting the hypothesis of surround inhibition in epilepsy. We have defined surround inhibition as a dynamic, i.e., seizure-related, defense mechanism against seizure propagation, which is present in seizure propagation pathways, characterized by hypometabolism on FDG-PET, and responsible for functional deficits, that may be reversible upon cessation of seizure activity (Nelissen et al., 2006). Seizure propagation from a parietal lobe focus is often into the frontal lobe resulting in motor seizures and SGTCS (Salanova et al., 1995), as in our patient. Our observation that parietal lobe hypermetabolism was associated with frontal lobe hypometabolism confirmed the PET findings of De Tiège and colleagues in patients with

continuous spikes and waves during sleep (DeTiège et al., 2004), and suggested that seizure propagation pathways became hypometabolic only after seizure propagation had occurred.

We postulate that hypermetabolism in the parietal lobe was secondary to increased neuronal activity at the focus, and that inhibitory projections beyond the focus resulted in inhibition in surrounding neuronal activity (leading to areas of hypometabolism) (Jueptner and Weiller 1995).

In longitudinal studies of cognition in epilepsy, it has been noted that recovery of cognitive deficits occurred when seizures were controlled for prolonged periods of time (Dodrill 2002; Helmstaedter et al., 2003; Thompson and Duncan 2005), as we found. We postulate that recovery from cognitive decline can to a large extent be explained by resolution of surround inhibition after remission of epileptic activity. Our data demonstrate that cognitive decline in epilepsy may be in the first place a functional and reversible, rather than a structural and irreversible problem (Oyegbile et al., 2006), stressing the importance of seizure freedom. The longitudinal follow-up of our patient demonstrated that important gains were made within the first weeks, but that full recovery took more than 1 year. The time course of resolution of FDG-PET hypometabolism, EEG slowing and cognitive functions after SE warrants further study, and will be important for the revalidation of patients after SE.

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