Original article

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Pilomotor seizures and status in non-paraneoplastic limbic encephalitis

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ABSTRACT – *Background and aims.* To describe an unusual clinical presentation of a patient with voltage-gated potassium channel Ab- positive, non-paraneoplastic limbic encephalitis. *Methods.* We performed video-EEG monitoring, structural MRI, ^{18}F-FDG-PET, ^{1}H-MRS, neuropsychological testing and antibody serology. *Results.* A 42-year-old male patient presented in an acute phase of non-paraneoplastic limbic encephalitis confirmed by MRI, with antibodies to voltage-gated potassium channels. His pilomotor status was pharmacoresistant to antiepileptic drugs, but responded to corticosteroid and azathioprine treatment. The MRI findings improved. The pilomotor seizures recurred when the immunosuppressive therapy was discontinued after 18 months. MRI at that time was consistent with hippocampal sclerosis. Complete seizure control was achieved after reintroduction of steroids. *Conclusion.* Pilomotor seizures were the predominant seizure type in this case of non-paraneoplastic limbic encephalitis. Immunosuppressive therapy may provide recovery including seizure control. However, long-term immunosuppression may be necessary to prevent relapse. Hippocampal sclerosis and chronic epilepsy might evolve as sequelae of limbic encephalitis.

Key words: non-paraneoplastic limbic encephalitis, pilomotor seizures, laboratory diagnosis, clinical course, hippocampal sclerosis, VGKC antibodies

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Pilomotor activity is a rare ictal manifestation and is classified as a subtype of autonomic seizures. It occurs either uni- or bilaterally and is often accompanied by other symptoms including all types of partial seizures, but particularly autonomic seizures. Pilomotor seizures originate predominantly in the temporal lobe (Green 1984, Baumgartner *et al.* 2001, Stefan *et al.* 2003, Loddenkemper *et al.* 2004), although other seizure origins have been described (Brody *et al.* 1960, Seo *et al.* 2003, Cutts *et al.* 2002).

Limbic encephalitis is a distinct clinical-pathological entity, which affects, as suggested by the name, mainly the medial limbic part of the temporal lobes. The clinical presentation comprises impaired memory

functions, behavioral abnormalities and epileptic seizures. T2-weighted magnetic resonance imaging (MRI) shows increased signal intensity in the hippocampal formations. Limbic encephalitis has often a paraneoplastic origin and is most commonly associated with small-cell lung cancer (SCLC); less frequently with testicular cancer, thymoma, Hodgkin's disease, non-SCLC, and breast, colon, and bladder cancer. In the majority of patients with paraneoplastic limbic encephalitis, specific autoantibodies (mainly to Hu, Ma2 and CV2/CRMP5) are detected in the serum and cerebrospinal fluid (CSF). Idiopathic limbic encephalitis is less frequent (Khan and Wieser 1994, Bien *et al.* 2000) and has a much better prognosis of recovery following immunotherapy. Recently, an association between reversible, non-paraneoplastic limbic encephalitis and high levels of voltage-gated potassium channel antibodies (VGKC-Ab) has been described (Vincent *et al.* 2004).

We report the case of a patient who was diagnosed with pilomotor seizures due to non-paraneoplastic limbic encephalitis.

Case study

Clinical history

A 42-year-old, previously healthy, right-handed businessman without personal or family history of epilepsy or neurological diseases was admitted in 2002 because of frequent bouts of piloerection, cold shivering and flushing lasting from a few seconds to a few minutes, on one or both sides of the body. Goose bumps were more prominent on the left arm and the face. These episodes were either isolated or were associated with fear, olfactory hallucinations and arrest reactions. Longer seizures were associated with disorientation and amnesia for the ictal episode. During the first two weeks, the patient also suffered from excessive night sweats. These episodes initially occurred about once a week, but then their frequency rapidly increased over few days reaching the stage where they kept recurring every few minutes. In this status-like state, the patient presented psychotic symptoms; fear, illusions, delusions of persecution, and paranoid thinking. Memory functions deteriorated rapidly. Retrograde amnesia was severe and the patient was not able to retain any new information. Antiepileptic drug (AED) therapy was started, but despite AED-polytherapy (carbamezepine, benzodiazepines, phenytoin, gabapentin, phenobarbital, levetiracetam, and valproic acid alone and in combination), seizures persisted.

Investigations

On admission, the detailed **neurological** examination was normal except for numerous catch-up saccades during smooth pursuit eye movements. The **neuropsychological** examination showed severe, bilateral memory deficits with retro- and anterograde amnesia, weak encoding and retrieval abilities.

Interictal video-EEG revealed slight slowing of the background activity with mixed alpha and theta activity. Several pilomotor **seizures,** occurring spontaneously or provoked by hyperventilation, were registered. Clinically these seizures manifested with mostly bilateral and rarely unilateral piloerection (more often on the left than on the right side), sweating and fear, and were accompanied in the EEG by ictal theta pattern, alternating between the sides, mostly on the left, but also on the right and frequently with contralateral propagation *(figure 1)*. In unilateral pilomotor seizures, the EEG pattern was ipsilateral.

T2-weighted, fast spin echo inversion recovery (FSEIR) and FLAIR magnetic **resonance imaging** (MRI) showed hyperintense signal alterations in both hippocampi, the left being more affected than the right *(figure 2)*.

CSF contained four white blood cells and normal protein and glucose. No oligoclonal bands and no *Cytomegalovirus* or *Herpes simplex* virus was found in the PCR of the CSF.

Blood examination including baseline hematology and biochemistry was normal. Serum electrophoresis indicated slightly decreased albumin and alpha-2 globulin and increased gamma globulin.

Auto-antibodies for RF, ANA, p-/c-ANCA, anti-DNA-, anti-Ro-, anti-La-, antiphospholipid-, antineuronal-, anti-ribosomal P-, anti-Hu-, anti-Yo-, anti-Ri-, anti-amphiphysin, anti-myelin-associated-glycoprotein-antibodies were negative.

Serum levels of AFP, beta-HCG and CEA were normal.

CT of the chest and the abdomen, MRI of liver, sonography of kidneys and testes, serum protein electrophoresis and bone marrow puncture revealed no evidence of a neoplasm.

Clinical course and follow-up examinations

With the first antiepileptic drug, carbamazerpine, the patient developed a severe rash and had low serum Na^+ values. The status-like state stopped after intravenous benzodiazepines and phenytoin were administered. However, seizures persisted despite treatment with the combination of valproate, levetiracetam and phenytoin at high doses. The history and the clinical findings of complex partial seizures including pilomotor seizures and antero- and retrograde amnestic deficits in association with the MRI and electrophysiological findings suggested limbic encephalitis of unknown origin. Since an intensive search for a neoplastic process was negative, we postulated an "idiopathic" genesis. An immune-mediated inflammatory process was suspected and 1000 mg of methylprednisolone /day i.v. were given for five days, followed by oral steroids, that were gradually tapered off over a one-year period. This resulted in cessation of psychotic symptoms and marked seizure reduction. Almost complete cessation

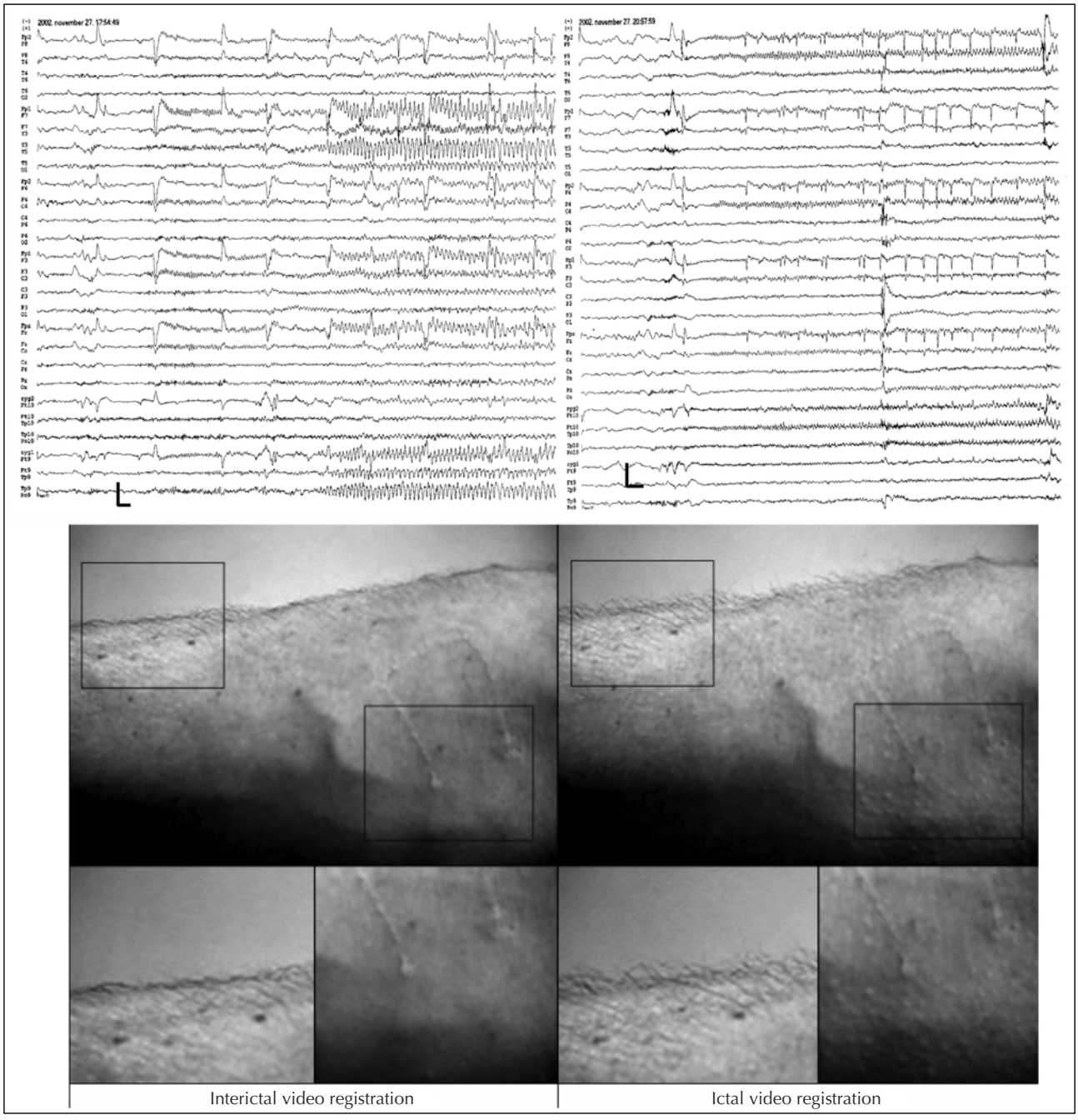

Figure 1. *Top:* scalp EEG of two seizures: a) ictal theta pattern over the left temporal lobe, b) ictal activity over the right temporal lobe. *Bottom:* simultaneous video recording of the right forearm showing the ictal piloerection and the appearance of goose bumps.

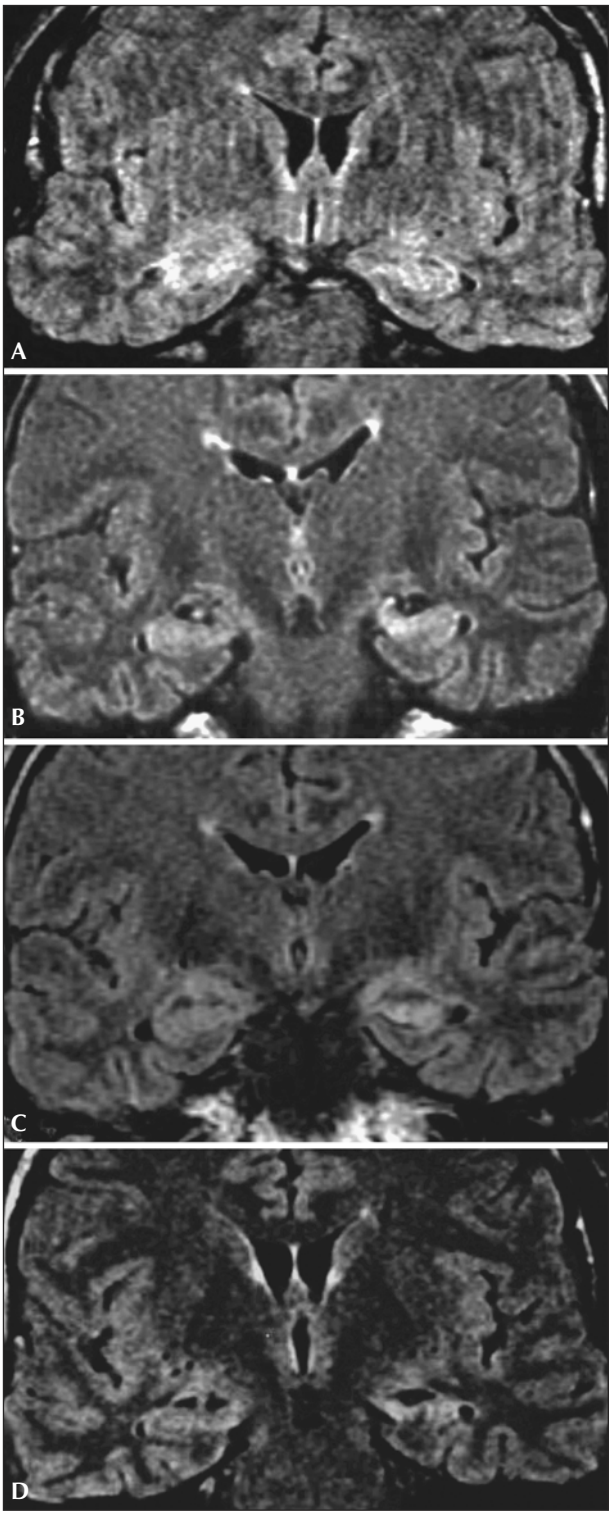

Figure 2. Coronal MRI sections showing the initial high signal intensity in bilateral hippocampal formations, left more than right, and the evolution over time. **A**) FLAIR MRI at the time of the acute phase. **B**) Fast spin echo inversion recovery (FSEIR) at admission. **C**) FLAIR MRI at the time of remission. **D**) FLAIR MRI at the time of relapse.

of the seizures was achieved only after addition of azathioprine.

Six months after admission, the patient felt much better and had partially returned to his professional activities. Although the patient reported only minor memory deficits and his psychomotor and non-verbal memory functions were improved significantly, verbal learning and recall performances were still markedly impaired according to the formal neuropsychological examination.

The control EEG at this time showed isolated, bi-temporal alpha-theta runs, but normal alpha background activity with no epileptiform activity.

^{18}F-FDG-positron-emission-tomography showed left temporal hypometabolism *(figure 3)*. ^{1}H-NMR-Spectroscopy of the brain revealed reduced NAA/(Cr+Cho) quotient in the posterior part of the left hippocampus, resulting in a pathological asymmetry index and indicating neuronal loss or neuronal dysfunction in this region *(figure 4)*. The T2-weighted MRI at this time still showed hyperintense signal alterations in the left hippocampus, but less intense compared to the first MRI. The hyperintense signal changes in the right hippocampus were no longer present.

After one year of immunosuppression, first the steroids, and six months later the azathioprine were discontinued. While on azathioprine only, occasional bouts of gooseflesh recurred, which were always triggered emotionally. When azathioprine was stopped, the piloerection attacks became frequent, 10-20 per day. During these pilomotor seizures, the patient remained fully conscious. The epileptic nature of these attacks was re-confirmed by video EEG. Neuropsychological testing at the time of relapse showed intact visuospatial memory and further slight improvement in verbal learning, with a persisting deficit in verbal recall. The repeated MRI revealed definite high signal on the left. Steroid treatment was started again and the patient became seizure free. VGKC antibodies were measured only after the recurrence of seizures (and the re-initiation of steroids), and were positive at 481 pM (normal values <100 pM).

Two years after the first examination the patient reported a further clear-cut improvement in his state. He no longer suffered physical restrictions and his memory functions had improved so much that he was able to work full time in his previous position as manager. Under an antiepileptic treatment with phenobarbital and levetiracetam, he continued to have rare, short-lasting episodes of piloerection, but without any other accompanying symptoms. Further follow-up examinations yielded no evidence of a neoplasm.

VGKC antibodies were measured again 26 months after the acute phase, and six months after the second trial of steroid discontinuation A an anti-VGKC antibody titer of 3031 pM was evident. At that time, the patient had daily pilomotor seizures, the MRI showed no deterioration and memory functions were still improving. The patient refused reintroduction of immunosuppressants.

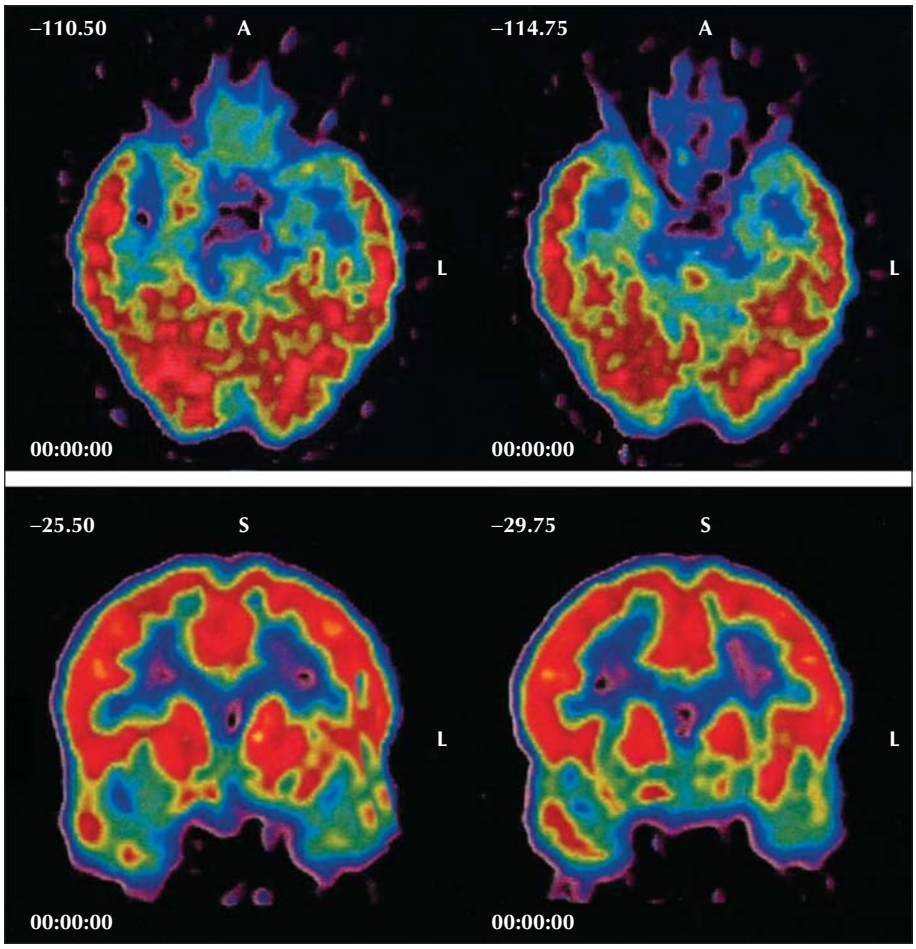

Figure 3. Transverse and coronal ^{18}F-FDG-positron-emission-tomography sections, showing a left temporal hypometabolism.

Discussion

Our patient is another example of VGKC antibody-positive, non-paraneoplastic limbic encephalitis. Many features of the disease are consistent with those published by Bien *et al.* (2000), and Vincent *et al.* (2004), including the male sex, the severe drug-induced rash, and the low serum Na^+ values. We did not find any clinical, laboratory or imaging evidence of malignancy, although this cannot be completely ruled out because of the length of the follow-up. However, the recovery after immuno-therapy and the relapse after its discontinuation support our assumption of an immune-mediated process, which was confirmed by VGKC Ab positivity.

To our knowledge, this is the first description of video-EEG documented, pilomotor seizures associated with limbic encephalitis. Ictal pilomotor activity has been found to be associated with tumors, infectious diseases of the CNS, metabolic disorders, cortical malformations, and postoperative and post-traumatic states (review in Roze *et al.* 2000). Ictal piloerection is typically associated with seizures originating in the temporal lobe (Green 1984, Lesser *et al.* 1985, Brogna *et al.* 1986, Tyndel *et al.* 1986, Ahern *et al.* 1988, Dupuy and Deroome 1989, Scopetta *et al.* 1989, Munari *et al.* 1995, Yu *et al.* 1998, Baumgartner *et al.* 2001, Sa'adah *et al.* 2002, Stefan *et al.* 2003, Loddenkemper *et al.* 2004), and an incidence of 3.6% in patients with temporal lobe epilepsy has been reported (Stefan *et al.* 2002). However, ictal pilomotor activity associated with frontal, fronto-parietal, fronto-temporal or parieto-occipital seizure origin has also been described (Scopetta *et al.* 1989, Seo *et al.* 2003, Féré 1904, Cutts *et al.* 2002, Brody *et al.* 1960).

The neuroanatomical substrate of ictal pilomotor erection is not known. Normal pilomotor activity is regulated by the central autonomic network, which includes the hypothalamus as the principal regulatory center, as well as the insula, medial prefrontal cortex, periaquaeductal gray matter, pontine parabrachial complex, nucleus of the tractus solitarius and ventrolateral medulla.

In human and animal studies, piloerection was observed during electrical and pharmacological stimulation of the

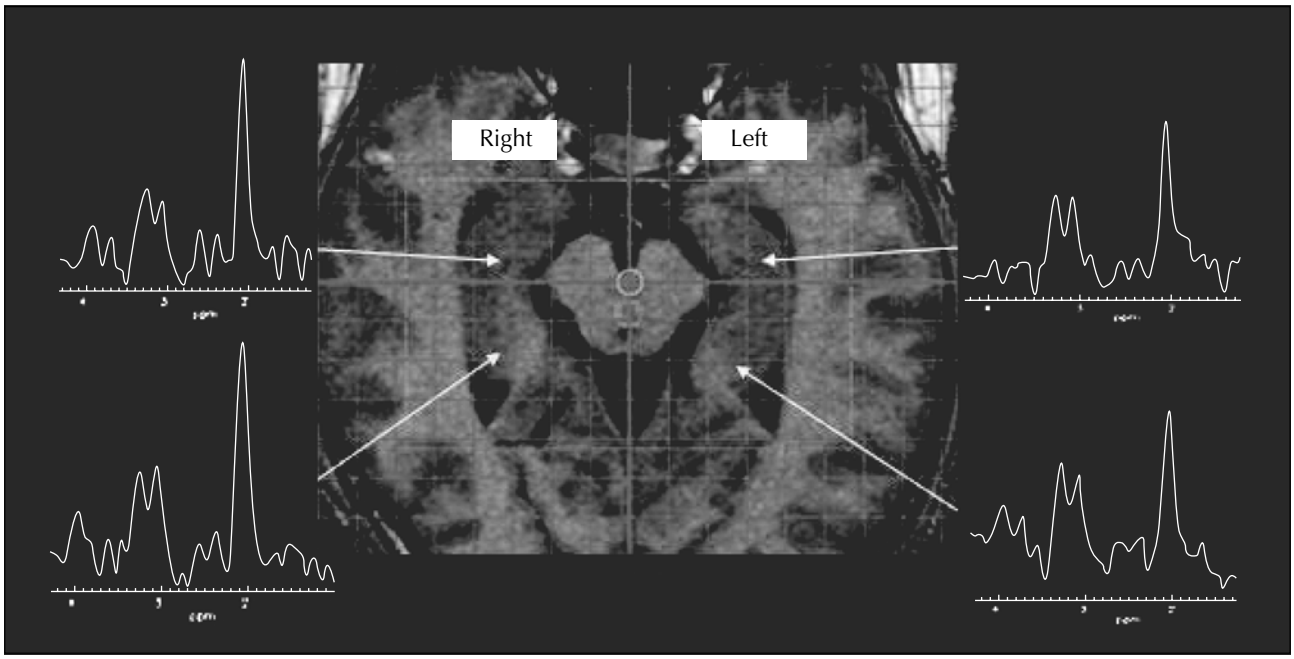

Figure 4. 1H-MRS. Spectroscopic measurements were performed with a 2D MRSI sequence (TR/TE = 1500/144 ms) using PRESS volume pre-selection (15 mm axial, 60 mm left-right, 100 mm anterior-posterior) with 24x24 phase encoding steps and a 210 mm^2 FOV angulated along the long axis of the hippocampus, covering both hippocampi. The spectra displayed show a clear NAA reduction, most prominently in the posterior part of the left hippocampal formation compared to the right hippocampal formation.

insula (Freeman and Schachter 1995), of the hypothalamus (Walker 1939), of the hippocampus and amygdala (Fish *et al.* 1993, Kaada *et al.* 1954), and of the cingulate gyrus (Smith 1945, Ward 1948). Involvement of the premotor area has been suspected as well (Lindsley and Sassaman 1938, Green 1984, Andermann and Gloor 1984). However, spread of ictal discharges from the temporal lobe or insular cortex to the hypothalamus (or related hypothalamic nuclei) has to be considered. The prominence of autonomic symptoms in temporal lobe epilepsy is explained by the strong limbic-hypothalamic connections (Walker 1939, Liporace and Sperling 1998, Wieser 1987). While unilateral ictal piloerection might indicate ipsilateral seizure onset (Loddenkemper *et al.* 2004), bilateral ictal piloerection is of no lateralizing value. Our patient displayed simple partial pilomotor seizures, which were more prominent and frequent on the left, as in most previously published cases (Stefan *et al.* 2002, Takeda *et al.* 2001, Dove *et al.* 2004).

In the series of Vincent *et al.* (2004), only one out of 10 patients relapsed. Immunological re-activation may have caused the seizure recurrence in our patient, since the seizures reappeared with tapering of the immunosuppressive therapy and ceased on reintroduction. However, neither MRI findings of inflammation nor deterioration of memory was noticed at the time of seizure recurrence. The development of hippocampal sclerosis, apart from the temporal atrophy, as described by Vincent *et al.* (2004), might be interpreted as a residuum of the previous LE, which causes chronic temporal lobe epilepsy with the same type of pilomotor seizures that occurred during the acute phase.

Our patient was pharmacoresistant to antiepileptic drugs as were the patients described by other authors. The memory disturbance experienced by our patient is still improving after the long-term steroid treatment, which is consistent with its beneficial effect on the neuropsychological state as observed by Vincent *et al.* (2004). However, the intensity of the memory problems have varied according to seizure frequency. On the other hand, cognitive disturbances have been more severe and irreversible in most instances of paraneoplastic limbic encephalitis.

Conclusions

Non-paraneoplastic LE might be more frequent than previously thought, and may present as seizures. Pilomotor seizures may be the predominant seizure type associated with limbic encephalitis. Psychotic features may appear transiently during the acute phase of the disease. Prolonged immunosuppressive therapy may provide almost complete recovery. However, relapse may occur after discontinuation of immunosuppressive therapy, and hippocampal sclerosis and chronic epilepsy might evolve as sequelae. This case study draws attention to the possibility

of a subacute immunological basis for other cases of focal epilepsies. □

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