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Excellent outcome after prolonged status epilepticus due to non-paraneoplastic limbic encephalitis

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Abstract

Limbic encephalitis (LE) is frequently associated with malignancy. Non-paraneoplastic LE is less common and in this form, voltage-gated potassium channel (VGKC) antibodies are usually found. However, in 2007 the spectrum was further extended by a report on four patients with presumed non-paraneoplastic LE in whom neither VGKC-antibodies nor other antibodies could be found (Samarasekera et al. 2007). Despite immunmodulatory treatment all these patients had severe neurological residual symptoms. Here we describe a further patient in whom extensive diagnostic procedures suggested non-paraneoplastic antibody-negative limbic encephalitis. Although this woman had prolonged status epilepticus during seven weeks, her outcome was excellent.

Key words : Antibodies ; intravenous immunoglobulins ; limbic encephalitis ; outcome ; plasma exchange ; status epilepticus.

Introduction

In limbic encephalitis (LE) with or without associated malignancy, temporal lobe symptoms such as confusion, amnesia and seizures develop subacutely. Diagnostic procedures exclude CNS tumors, infections and other etiologies, and MRI may show high signal intensities in one or both medial temporal lobes. Moreover, antibodies cross-reacting with tumor and CNS antigens can point toward an underlying malignancy. However, in the last years it has become evident that LE also exists without a causative malignant process. In 2004, two case studies demonstrated that non-paraneoplastic LE may be associated with voltage gated potassium channel (VGKC) antibodies (Thieben *et al.* 2004 ; Vincent *et al.* 2004). In 2007, the spectrum was further extended by a report on four patients with presumed non-paraneoplastic LE in whom neither VGKC-antibodies nor other antibodies could be found (Samarasekera *et al.* 2007). Although these patients made some recovery after immunomodulatory therapy, they all remained with substantial neurological deficits. Here we add another case without any of the known antibodies to intracellular neuronal antigens or VGKC. However, despite prolonged status epilepticus outcome in our patient was excellent.

Case report

In April 2006 a 31-year old woman had a partial seizure consisting of aura with fear and despair followed by motor convulsions with start in the left cheek and secondary generalization. The following three weeks the patient experienced insidious personality change with affective flattening and childish behavior, and several partial seizures with and without secondary generalization. Despite treatment with oral carbamazepine and intravenous phenytoin seizures continued. On referral to our neurological department, examination revealed a somnolent, disoriented and unconcerned patient with anterograde and retrograde amnesia. She had no focal neurological deficit, fever or meningism. Her prior history was unremarkable. Contrast-enhanced MR Imaging revealed no abnormalities, but EEG showed status epilepticus with a focus in the left temporofrontal lobe. CSF analysis revealed slight monocytosis. Intravenous aciclovir was prescribed and the patient was transferred to a neurological intensive care unit with continuous 24 h EEG monitoring. Following intubation she received intravenous penthotal to burst suppression. Subsequently, various antiepileptic agents including valproate, topiramate, phenobarbital and levetiracetam were added. Two attempts were made during the next three weeks to withdraw penthotal and extubate the patient. However, each time complex partial seizures and epileptic activity on EEG occurred.

Repeated CSF analysis showed ; mild pleocytosis (1-4 polycytes, 9-15 monocytes/10^{-6} l), 3-5 oligoclonal bands, slightly increased IgM-index and Interleukin 6, but normal albumin, glucose, blood brain barrier function, IgG-index and glial fibrillary astrocytic protein. Concentrations of neurofilament protein (< 250-8020 ng/l), Tau, phospho-Tau and beta-amyloid were increased only

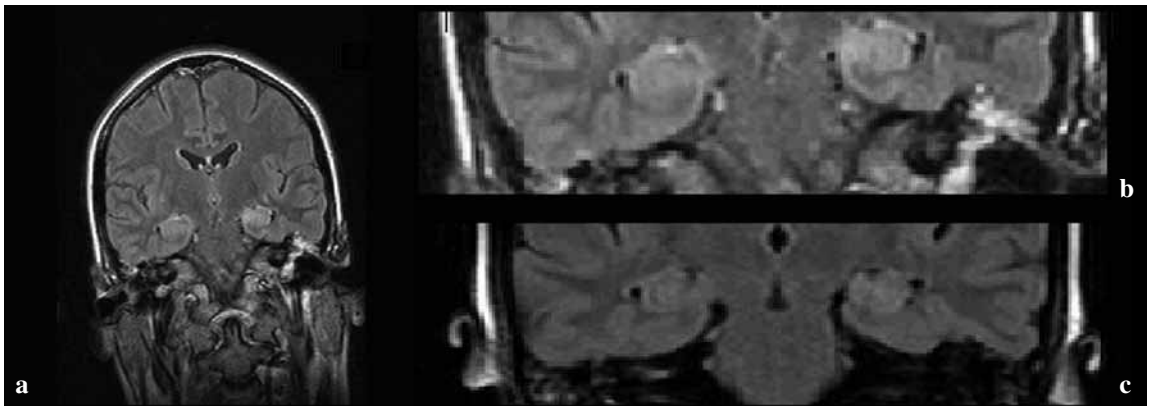

FIG. 1. — MRI with coronal FLAIR sequences shows high signal intensities in the hippocampus and gyrus parahippocampus bilaterally, consistent with the diagnosis of limbic encephalitis (a, b). Seven days later, following intravenous immunoglobulin treatment, these lesions are unchanged (MRI not shown). However, one week after repeated plasma exchange and seven weeks after debut of status epilepticus, regress of the temporal lesions is seen. Slight hippocampal atrophy is visible (c).

temporarily. Extensive PCR and antibody screening for various virus, bacteria and fungi in CSF and blood were negative. Repeated routine blood assays were normal. Slightly enhanced amounts of complement factors 3, 3 d and 4, TNF-α, Interleukin 6 and α-1-antitrypsin were noted. Apart from a minor increase of ANA titer (< 80-640) with subsequent normalization, screening for mitochondria and smooth muscle cell antibodies, ANCA, antibodies against thyroid peroxidase and thyroglobulin, antiprotease 3, rheumatoid factor, anti-cardiolipine and cryoglobuline was negative. Of note, repeated analysis revealed no antibodies against neuronal antigens (Hu, Ri, Yo, PCA-2, amphiphysin, CRMP5/CV2, Ma-2, VGKC Kv 1.1, 1.2 and 1.6). However, a second MR three weeks after debut of status epilepticus showed high signal lesions in the hippocampus and parahippocampal gyrus bilaterally (fig. 1a, 1b). No contrast loading was seen. A diagnosis of refractory status epilepticus due to LE of unknown origin was made.

Following an unsuccessful course of intravenous immunoglobulins and a third MRI showing unchanged temporal high signal intensities, plasma exchange (PE) was performed once a day for a period of five days. Four days later, no epileptic activity was recorded on 24 h EEG. Penthothal was tapered off. The next day a fourth MR brain showed regress of temporal signal activity (fig. 1c). Ten weeks after her first seizure and seven weeks after debut of status epilepticus, the patient was finally extubated. She remained seizure-free on topiramate, levetiracetam, phenytoin and phenobarbital and intravenous methylprednisolone 1000 mg for three days, once per month. Our patient made an excellent recovery without residual neurological or neuropsychological deficits. At the time of writing in April 2008 she is free of seizures on a combination of topiramate 200 mg and levetiracetam 1000mg once daily. She works again as a concierge. Despite extensive, repeated work-up including a whole-body FDG-PET Imaging study 18 months after symptom debut, no malignant process has been detected.

Discussion

In this report the typical clinical course with initial amnesia and personality changes followed by complex partial seizures of temporal lobe origin is well consistent with LE. Although hippocampal signal increase seen on MRI might have been due to the seizures per se this is also a typical feature of LE. In addition, extensive diagnostic procedures revealed no other cause for prolonged status epilepticus. Furthermore, the evolution of temporomesial abnormalities from swelling seen on the second and third MRI to atrophy seen on the fourth study has indeed been described for non-paraneoplastic antibody-negative LE (Bien and Elger 2007). The excellent outcome after plasma exchange strongly implies a non-malignant cause, since immunosuppression has only temporary, if any effects in paraneoplastic LE (Bien and Elger 2007). Indeed, paraneoplastic LE associated with refractory epilepsy appears to be the most aggressive and rapidly fatal form [6]. Our diagnostic search for occult malignancy included whole-body PET scan 18 months after symptom debut thereby exceeding the current suggestions (Bien and Elger 2007). We therefore feel assured about the non-paramalignant state of our patient. Besides, all the well-established, commercially available antineuronal antibodies were absent, which is consistent with non-paraneoplasic LE. Every previous similar report has been published as recently as in 2007 (Bataller *et al.* 2007 ; Bien and Elger 2007 ; Samarasekera *et al.* 2007), suggesting that this condition is underdiagnosed. However, the question arises whether or not antibodies against neuronal antigens were present. We excluded repeatedly the established paraneoplastic antibodies, but that does not rule out the possibility

that hitherto unrecognized antibodies to neuronal antigens may have been present in our patient. Such unrecognized antibodies might also have been at work in previously reported patients with non-paraneoplastic LE (Bataller *et al.* 2007 ; Bien and Elger 2007 ; Samarasekera *et al.* 2007), in whom the established antibodies neither could be found. In contrast to our patient, all these patients were left with marked cognitive deficits and persistent seizures, which might point to different pathogenic etiologies. We did not test for the recently reported autoantibodies to the novel cell-membrane antigens (nCMAg) (Bataller *et al.* 2007). However, nCMAg-postive patients usually have an associated malignant process (Bataller *et al.* 2007).

The extent of MRI changes in LE does not necessarily correspond to clinical outcome. We have recently treated another patient with prolonged status epilepticus and presumed non-paraneoplastic antibody-negative LE. This 29-year old previously healthy woman had repeatedly normal MRI of the brain, which is relatively unusual for LE (Bien and Elger 2007), but has been well-described (Gultekin *et al.* 2000 ; Espay *et al.* 2006). This patient had residual temporal lobe deficits with severe amnesia, which was in striking contrast to the excellent outcome of our first patient who had both transient and residual MRI changes.

In conclusion, this case report suggests that firstly, non-paraneoplastic antibody-negative LE must be included as a differential diagnosis in status epilepticus of temporal lobe origin and that secondly, the extent of MRI changes does not necessarily correspond to the degree of remaining neurological deficits. Thirdly, and most importantly, outcome can be excellent despite severe status epilepticus.

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