VGKC antibody-associated encephalitis, microbleeds and progressive brain atrophy

Kapina, Viktoria; Vargas Gomez, Maria Isabel; Vulliemoz, Serge; Landis, Theodor; Picard, Fabienne; Lalive d'Epinay, Patrice

How to cite

KAPINA, Viktoria et al. VGKC antibody-associated encephalitis, microbleeds and progressive brain atrophy. In: Journal of neurology, 2010, vol. 257, n° 3, p. 466–468. doi: 10.1007/s00415-009-5370-5

This publication URL: https://archive-ouverte.unige.ch/unige:21034
Publication DOI: 10.1007/s00415-009-5370-5

J Neurol (2010) 257:466–468
DOI 10.1007/s00415-009-5370-5

LETTER TO THE EDITORS

VGKC antibody-associated encephalitis, microbleeds and progressive brain atrophy

Viktoria Kapina · Maria-Isabel Vargas · Serge Vulliemoz · Theodor Landis · Fabienne Picard · Patrice H. Lalive

Received: 7 October 2009 / Revised: 16 October 2009 / Accepted: 19 October 2009 / Published online: 6 November 2009

Sir,

Limbic encephalitis (LE) is an autoimmune disorder which can be of paraneoplastic or non-paraneoplastic origin. Antibodies (Abs) against voltage-gated potassium channels (VGKC-Abs) have recently been reported to be a possible cause of non-paraneoplastic LE responding to immunosuppressive therapy [1–3]. However, this type of LE may affect more than the limbic-restricted region, since some cases are described with a rapidly progressing cortical atrophy [2, 4].

A 79-year-old man was admitted to our hospital because of auditory hallucinations, agitation, and confusion with spatiotemporal disorientation. Neurological examination was otherwise normal. His medical history included surgery for epidermoid cancer of the left lung 5 years earlier which was considered in complete remission according to oncological investigations. At admission, blood serologies for viruses and Lyme disease were negative. Paraneoplastic Abs including anti-GAD, -Hu, -Ri, -YO, -CV2/CRMP, -Amphiphysin, and -Ma2 were negative. Anti-phospholipid Abs including anti-cardiolipin, anti-beta 2 glycoprotein, and lupus anticoagulant were negative. In addition, Protein C and S, antithrombine activity, and activated protein C resistance were normal; factor V Leiden and factor II mutations were absent. A CSF analysis revealed 50 WBC/mm^3, elevated proteins to 0.83 g/L and oligoclonal bands matched in the serum. Serum VGKC-Abs were present at a high titer of 3,495 pM (normal range: 0–100, Radioimmuno assay detecting Kv1.1, 1.2 and 1.6 subtypes, laboratory of Prof. A. Vincent, Oxford, UK). There was no electromyographic sign of neuromyotonia, his Na level was normal in the serum and there was no antecedent of recent infective illness. The cerebral MRI at admission (Fig. 1**a**) showed a left hippocampus lesion with increased signal on coronal FLAIR sequences. Axial gradient echo T2-weighted MRI sequences showed the presence of cerebral microbleeds (CMBs) in cortical and subcortical regions which dramatically increased in number and size in the follow-up MRI performed 14 weeks later (Fig. 1**b**, **c**, **f**, **g**). This accumulation of CMBs was associated with signs of acute cortical necrosis which correlated with progressive brain atrophy (Fig. 1**d**, **e**, **h**, **i**). The clinical follow-up was characterized by partial seizures with secondary generalization, which required introduction of levetiracetam, as well as the development of memory impairment and aphasia (encoding ability 5 words: normal; verbal testing: 3/5 words immediate recall and 0/5 words 10 min later; visual testing: 2/5 objects immediate recall and 0/5 objects 10 min later; language testing revealed mostly a motor aphasia with alteration of the verbal fluency and some difficulties in comprehension of complex verbal orders). Clinical symptoms were eventually stabilized after high doses of IV corticosteroids and plasma exchanges (5 courses) were initiated (auditory hallucinations and agitation disappeared, but spatiotemporal disorientation, difficulties in comprehension of complex verbal

V. Kapina · S. Vulliemoz · T. Landis · F. Picard · P. H. Lalive (✉)
Division of Neurology, Department of Neurosciences, University Hospital of Geneva and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland
e-mail: patrice.lalive@hcuge.ch

M.-I. Vargas
Division of Neuroradiology, University Hospital of Geneva and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland

P. H. Lalive
Laboratory Medicine Service, Department of Genetics and Laboratory Medicine, University Hospital of Geneva and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland

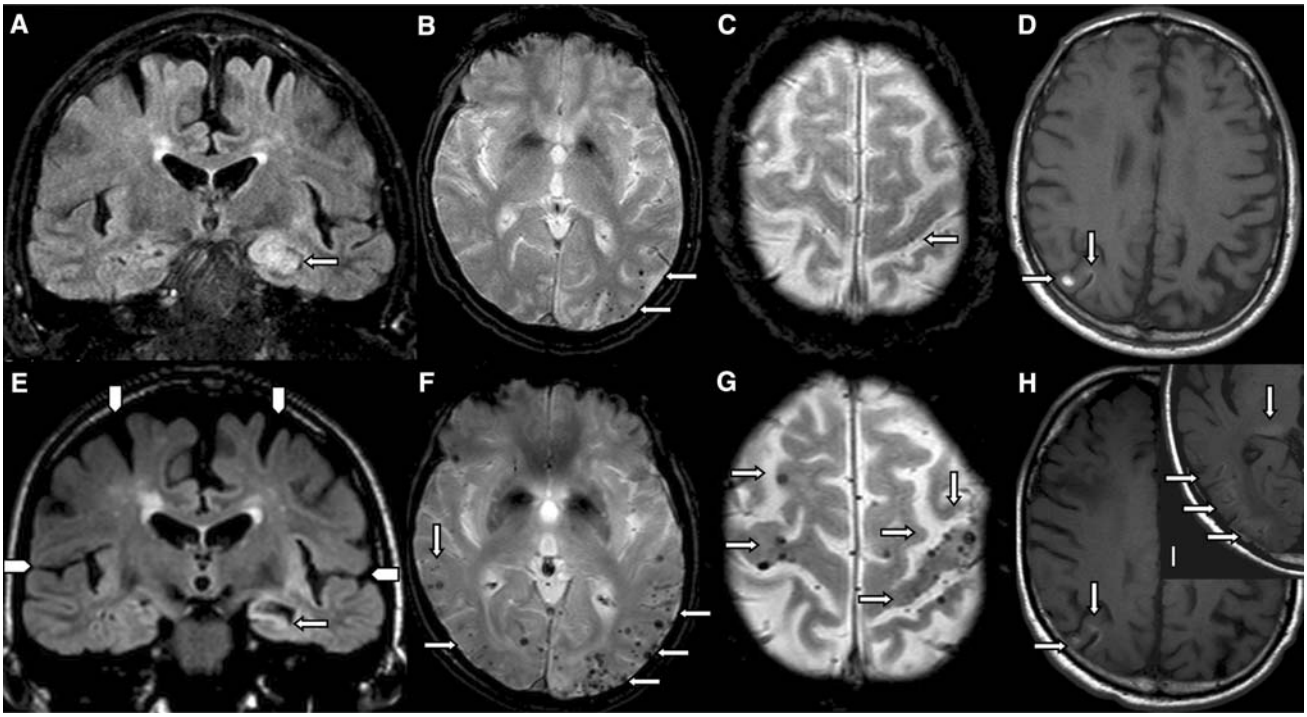

Fig. 1 Brain MRI at admission (**a**–**c**), 8 weeks (**d**), and 14 weeks (**e**–**i**) after admission. Increased signal and enlarged left hippocampus on coronal FLAIR image (**a**, *arrow*). Axial gradient echo T2-weighted MRI sequences showed the presence of few CMBs in cortical and subcortical regions (**b**, **c**, *arrows*) which dramatically increased in number and size in the follow-up MRI performed 14 weeks later (**f**, **g**, *arrows*). This accumulation of CMBs correlated with the progressive cortico-subcortical atrophy seen 14 weeks after admission (**e**, *arrowheads*). Signs of acute necrosis were detected in T1-weighted sequences in the right parietal cortical region 8 weeks (**d**, *arrows*) and 14 weeks (**h**, *arrows*) after admission. Areas of necrosis were also diffusely detected in other regions including the right temporal lobe and the thalamus (**i**, *arrows*)

orders and memory impairment persisted), which correlated with a decrease of VGKC-Abs to 359 pM.

Interestingly, follow-up MRI revealed that some patients with VGKC-Abs-associated LE may present with rapidly progressing cerebral atrophy that exceed the temporal lobes [2, 4]. It is nevertheless unclear from the recent literature whether specific MRI sequences able to detect CMBs were carried out or not on these patients. The MRI follow-up of our patient is in accordance with these previous observations as witnessed by a global decline in cerebral volume over 14 weeks. Gradient echo T2-weighted MRI sequences showed CMBs which fulfilled the radiological criteria of the Microbleed Study Group [5]. The significant increase of cortical CMBs over this short period of time correlated with signs of acute cortical necrosis. Thus, cortical CMBs might be at the origin of the rapid and diffuse cortical atrophy seen in some patients with VGKC-Ab-associated encephalitis.

CMBs are often described in association with hypertensive vasculopathy or cerebral amyloid angiopathy [5]. Hypertensive vasculopathy is typically associated with CMBs in the basal ganglia, thalamus, brainstem and the cerebellum [6], whereas cerebral amyloid angiopathy is commonly associated with a lobar distribution of CMBs [6, 7]. Since our patient had no history of high blood pressure and CMBs were exclusively detected in lobar areas, amyloid angiopathy could explain the presence of the cortical CMBs.

Auto-Abs such as anti-phospholipid Abs may also cause CMBs. In our patient these Abs were tested negative. Interestingly, a recent histopathological report of a patient with anti-VGKC encephalitis describes the presence of parenchymal and perivascular B cells, supporting the possibility of a humoral-mediated disease process [9]. In this regard, an alternative hypothesis could imply a direct link between VGKC-Abs and CMBs: K^+ channels are highly expressed in vascular smooth muscle and endothelial cells in the microcirculation of tissues, including the blood brain barrier, and play an important role in the vascular homeostasis [8]. Thus, it could be hypothesized that VGKC-Abs bind to K^+ channels in the brain cortical microvessels and induce a perturbation of vascular homeostasis leading to vasoconstriction, which in turn may provoke CMBs, necrosis, and progressive atrophy. Nevertheless, this hypothesis will require further investigations to be confirmed.

In conclusion, our observation suggests that the presence of CMBs should be explored in patients with VGKC-Ab-

associated LE using appropriate MRI sequences. Conversely, patients presenting a rapid increase of CMBs without a clear origin could be tested for VGKC-Abs.

Conflict of interest statement The authors report no conflicts of interest.

References

1. Buckley C, Oger J, Clover L et al (2001) Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol 50:73–78
2. Vincent A, Buckley C, Schott JM et al (2004) Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 127:701–712
3. Thieben MJ, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S (2004) Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. Neurology 62:1177–1182
4. Schott JM, Harkness K, Barnes J, della Rocchetta AI, Vincent A, Rossor MN (2003) Amnesia, cerebral atrophy, and autoimmunity. Lancet 361:1266
5. Greenberg SM, Vernooij MW, Cordonnier C et al (2009) Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 8:165–174
6. Fazekas F, Kleinert R, Roob G et al (1999) Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol 20:637–642
7. Knudsen KA, Rosand J, Karluk D, Greenberg SM (2001) Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology 56:537–539
8. Jackson WF (2005) Potassium channels in the peripheral microcirculation. Microcirculation 12:113–127
9. Khan NL, Jeffree MA, Good C, Macleod W, Al-Sarraj S (2009) Histopathology of VGKC antibody-associated limbic encephalitis. Neurology 72:1703–1705