J Neurol (2012) 259:582–584
DOI 10.1007/s00415-011-6229-0

LETTER TO THE EDITORS

Anti-NMDA receptor antibodies in a case of MELAS syndrome

Carsten Finke · Harald Prüss · Michael Scheel · Florian Ostendorf · Lutz Harms · Kathrin Borowski · Klaus-Peter Wandinger · Christoph J. Ploner

Received: 6 May 2011 / Revised: 9 August 2011 / Accepted: 16 August 2011 / Published online: 6 September 2011

Dear Sirs,

A 42-year-old man presented with new-onset headache, global aphasia, antero- and retrograde memory deficits, stereotypic behavior, agitation and an inappropriate foolish affect in July 2007. Immediate MRI revealed a T2w lesion in the left temporal lobe with cortical and subcortical involvement, compatible with encephalitis (Fig. 1). CSF analysis showed normal cell count and negative herpes simplex virus type I PCR while protein and lactate levels were elevated (protein: 1.36 g/l; normal: 0.15–0.45 g/l; lactate: 5.6 mmol/l; normal: 0.55–2.2 mmol/l). Repeated history taking revealed progressive bilateral hearing loss for 8 years. Additional MRI investigations showed a hyperintense appearance of the observed lesion in diffusion weighted images (DWI), mixed increased and decreased diffusion on apparent diffusion coefficient (ADC) maps, and a strong lactate peak in MR spectroscopy (Fig. 1). Further work-up revealed myopathic changes in several muscles on electromyography, elevated serum lactate during lactate stress test, hypertrophic cardiomyopathy, and signs of mitochondrial disease in muscle biopsy specimens (increased fuchsinophilia and COX-negative fibers). Family history was negative for mitochondrial disorders, but genetic analysis from leucocytes revealed a heteroplasmic m.3243A>G point mutation in mitochondrial DNA (heteroplasmy rate, 30%), compatible with a diagnosis of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). No other family members were tested. During the next few years, the patient developed focal epilepsy and progressive cognitive deficits. In 2010, he sustained a stroke-like episode of the left occipital cortex causing right homonymous hemianopia (Fig. 1). At this time, the initial clinical presentation was reconsidered and archived CSF/serum samples obtained 6 days after symptom onset in 2007 were analyzed for autoimmune antibodies. Antibodies were determined by means of a recombinant immunofluorescence assay employing NMDAR transfected HEK cells as described previously [1]. IgG-antibodies against NMDAR were detected in the patient's serum at a titer of 1:32 (score 2 according to Irani et al. [4]). No antinuclear antibodies (ANA) or antibodies against further neuronal surface antigens (i.e., AMPA receptor, GABAb-receptor) or VGKC-complex were detected in the patient's serum. On follow-up in 2010, NMDAR antibodies were negative both in serum and CSF. A body-CT revealed no malignancies.

Taken together, our patient presented with symptoms compatible with a first manifestation of MELAS syndrome in 2007 [2]. The patient's lesion in the left temporal lobe likely accounts for his aphasia, memory disturbances, and behavioral changes. Imaging characteristics suggest a stroke-like lesion associated with MELAS syndrome [3]. At the same time, however, the patient tested positive for anti-NMDAR antibodies that are considered highly specific

C. Finke (✉) · H. Prüss · F. Ostendorf · L. Harms · C. J. Ploner
Department of Neurology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
e-mail: carsten.finke@charite.de

M. Scheel
Department of Neuroradiology, Charité-Universitätsmedizin Berlin, Berlin, Germany

K. Borowski · K.-P. Wandinger
Institute for Experimental Immunology, EUROIMMUN, Lübeck, Germany

K.-P. Wandinger
Institute for Neuroimmunology and Clinical MS Research, Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Eppendorf, Hamburg, Germany

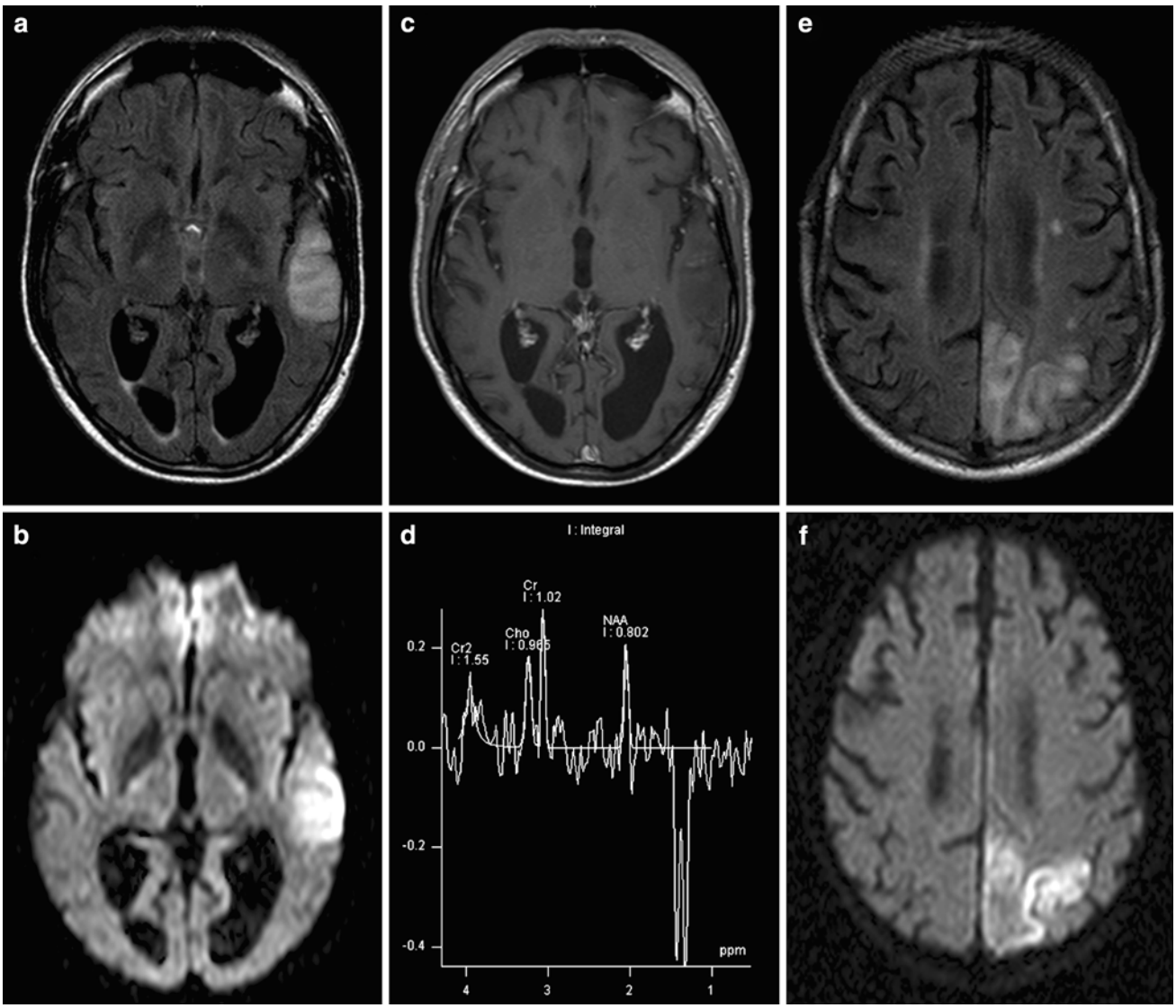

Fig. 1 MR imaging 2007: Left temporo-parietal lesion with cortical and subcortical edema in FLAIR (**a**), hyperintense appearance in DWI (**b**), and no Gd-enhancement of the lesion in Gd-enhanced T1 (**c**). Proton magnetic resonance spectroscopy of the lesion exhibits a strong lactate signal (inverted double peak at 1.3 ppm, TE = 135 ms) and reduced NAA signal (**d**). MR imaging 2010: New ischemic left parieto-occipital lesion (with cortical and subcortical edema) in FLAIR (**e**) and hyperintense appearance in DWI (**f**)

for anti-NMDAR encephalitis. Intriguingly, the initial clinical syndrome was also compatible with a diagnosis of anti-NMDAR encephalitis [4, 5]. Although many patients with NMDAR encephalitis suffer from severe disease courses, milder *formes frustes* with predominance of psychiatric symptoms, memory disturbances, seizures, or dyskinesias have been described [5]. Hence, among others, NDMAR encephalitis is a relevant differential diagnosis in MELAS patients. It must be noted, however, that in classical NMDAR encephalitis, antibodies are always present in the CSF, which was not the case in our patient. In our case, different potential clinical constellations must be considered. A coincidence of MELAS syndrome and anti-NMDAR encephalitis is possible, but appears unlikely facing the low incidence of both diseases. Likewise, an autoimmune response against NMDAR secondary to the left temporal lobe lesion is unlikely, since anti-NMDAR antibodies were detected already a few days after symptom onset. On the other hand, an association of MELAS with autoimmune disease has repeatedly been reported, e.g. with autoimmune hyperthyroid disease [6], anti-GAD-associated diabetes mellitus [7], antiphospholipid antibody syndrome [8], and autoimmune polyglandular syndrome [9]. This is the first report of a potential association of anti-NMDAR encephalitis with MELAS. However, these findings are preliminary and further studies are required that systematically analyze sera from early cases of MELAS.

Conflict of interest None.

References

1. Wandinger KP, Saschenbrecker S, Stoecker W et al (2011) Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. J Neuroimmunol 231:86–91
2. Pavlakis SG, Phillips PC, DiMauro S et al (1984) Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a distinctive clinical syndrome. Ann Neurol 16:481–488
3. Matthews PM, Andermann F, Silver K et al (1993) Proton MR spectroscopic characterization of differences in regional brain metabolic abnormalities in mitochondrial encephalomyopathies. Neurology 43:2484–2490
4. Irani SR, Bera K, Waters P et al (2010) N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 133:1655–1667
5. Dalmau J, Lancaster E, Martinez-Hernandez E et al (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10:63–74
6. Corman V, Rorive M, Hennen G et al (2001) Clinical case of the month. MELAS syndrome. Revue Médicale De Liège. 56:681–684
7. Huang CN, Jee SH, Hwang JJ et al (1998) Autoimmune IDDM in a sporadic MELAS patient with mitochondrial tRNA(Leu(UUR)) mutation. Clin Endocrinol 49:265–270
8. Li HY, Yang WS, Tai TY et al (2003) A diabetic subject with MELAS and antiphospholipid syndrome. Diabetes Care 26:2218–2219
9. Ohno K, Yamamoto M, Engel AG et al (1996) MELAS- and Kearns-Sayre-type co-mutation with myopathy and autoimmune polyendocrinopathy. Ann Neurol 39:761–766