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LETTER TO THE EDITORS

Anti-NMDA receptor encephalitis triggered by epilepsy surgery

Judith N. Wagner[1] · Gabriele Schwarz[1] · Gertraud Puttinger[1] · Anna Maria Hengsberger[1] · Stefan Guggenberger[1] · Serge Weis[2] · Johannes Trenkler[3] · Martin Aichholzer[4] · Tim J. von Oertzen[1]

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Dear Sirs,

We report on a patient diagnosed with anti-NMDA receptor (NMDAR) encephalitis after epilepsy surgery. We argue that the encephalitis was directly induced by brain surgery, which would render it the first such case published.

A 40-year-old male had suffered from HSV1-encephalitis (HSVE) at the age of 3 years and subsequently developed drug-resistant frontal lobe epilepsy. Previous partial resection of the left frontal lobe had resulted in incomplete remission. After detailed presurgical evaluation, a frontoopercular part of the left precentral gyrus was resected. PCR for HSV1 performed on the specimen was positive, suggesting latent HSV1 infection. MRI 2 days post-surgery was unremarkable except for postinterventional alterations (Day 2, Fig. 1).

On day 3, the patient developed semiologically new seizures and pronounced dysarthria and dysphagia. MRI on day 8 showed vasogenic edema of the left subcentral gyrus and a new small cortical diffusion restriction in the rolandic area of the right hemisphere which remained unchanged on an MRI on day 42. Cerebrospinal fluid (CSF) analysis revealed slight lymphocytic pleocytosis (10 cells/µl). The varicella-zoster-IgG-CSF/serum-index (AI) was somewhat elevated (2.49), but VZV-PCR was negative. The HSV1/2-IgG-AI and -PCR were unremarkable. Phenytoin, benzodiazepines and dexamethasone were introduced and the patient was discharged to a rehabilitation unit on day 45.

Due to severe progressive dysarthria and dysphagia, the patient was transferred back to our hospital on day 56. Subsequently, the patient developed a new paresis of the right arm. An MRI on day 56 revealed progress of the lesions (Fig. 1). CSF analysis showed 17 cells/µl. The HSV1-IgG-AI was elevated (4.47), HSV-PCR remained negative. Therapy with acyclovir was initiated, but no clinical response ensued. 12 days later, serum and CSF NMDAR antibodies returned positive (1:32 and 1:10). Antibodies against Hu, Yo, Ri, PNMA2, CV2, amphiphysin, PCA2, TR, SOX1, Zic4, recoverin, GAD, and anti-glial nuclear antibodies as well as anti-CASPR2-/GABA B-/LGI1-/AMPA-GluR1/2- and DPPX-antibodies were negative.

Due to lack of clinical improvement and deterioration of MRI findings after steroid treatment and plasmapheresis (Day 85, Fig. 1), immunosuppressive therapy with rituximab and cyclophosphamide was started (Fig. 1). With this regimen, the patient's MRI and clinical presentation improved markedly (Day 121, Fig. 1). On day 170, NMDAR antibodies were negative in the serum and significantly reduced in the CSF (1:1).

In summary, we present a patient who was diagnosed with anti-NMDAR encephalitis shortly after epilepsy surgery. Two pathomechanisms are feasible:

(1) HSVE was reactivated by epilepsy surgery with subsequent induction of anti-NMDAR encephalitis. This series of events would fit well with previous reports on these entities [1–5, 10].
(2) Anti-NMDAR encephalitis was directly induced by brain surgery.

We favor the latter hypothesis: in most published cases of post-operative HSV1 reactivation, CSF HSV1-PCR was positive, and symptoms resolved after treatment with acyclovir [1]. In our patient, repeated CSF HSV1-PCR was negative.

✉ Judith N. Wagner
Judith.Wagner@kepleruniklinikum.at

[1] Department of Neurology 1, Kepler University Hospital, Johannes Kepler University Linz, Wagner-Jauregg-Weg 15, 4020 Linz, Austria

[2] Department of Neuropathology, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria

[3] Department of Neuroradiology, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria

[4] Department of Neurosurgery, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria

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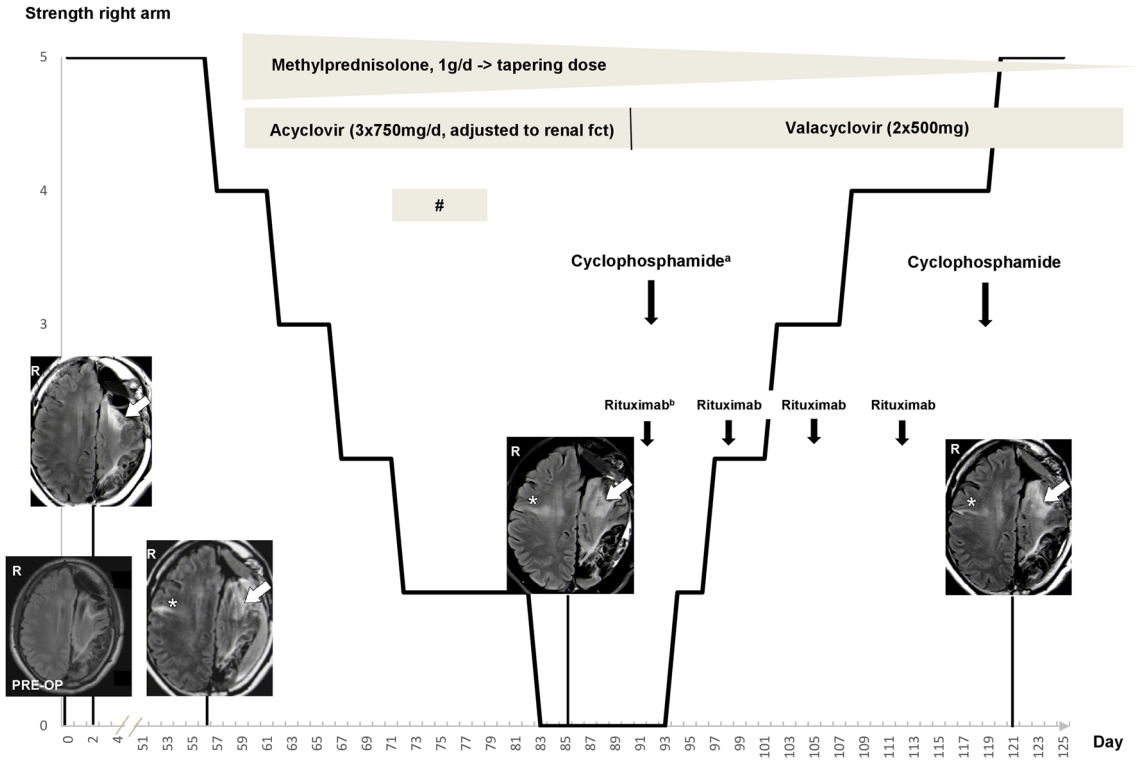

Fig. 1 Course of clinical and imaging findings. The day of surgery was defined as day 0. The strength of the right arm was chosen as index symptom for better quantifiability (Oxford grading scale of muscle strength was used). Full clinical examinations were available for days 1, 3, 7, 8, 9, 51, 56, 72, 77, 80, 81, 83, 85, 90, 93, 97, 101, 108, and 120; values in between are estimates. FLAIR 3T-MR images are shown for days 3 ("PRE-OP"), 2, 56, 85, and 121. Next to extensive left-hemispheric gliotic and cystic parenchymal defects and a subdural hygroma, they show progressive (days 56 and 85) and receding (day 121) lesions adjacent to the resection area (white arrow) and in the right central region (asterisk). [#]Plasmapheresis: five sessions, plasma exchange of 40 ml/kg body weight per session. [a]750 mg/m^2 body surface area. [b]375 mg/m^2 body surface area

We propose that progressive dysarthria and dysphagia constituted the first symptoms of the anti-NMDA receptor antibodies, which would place the onset of antibody-related symptoms between days 45 and 56. This time frame resembles the latency of 41 days described in a detailed work-up on post-HSVE anti-NMDAR encephalitis and the median latency of 39 days (range 12–51 days) in a review on eight teenagers/adults [6, 7]. The relatively long symptom-free interval may be due to secondary mechanisms triggered by antibody-mediated internalization of NMDA receptors such as homeostatic downregulation of inhibitory synapses [8]. The patient's symptoms and MRI changes did not improve on prolonged antiviral treatment, but only after escalation of immunosuppressive therapy. Clinical and MRI remission correlated with a significant reduction in NMDAR antibody levels. Hence, despite of this study's limitation—the absence of presurgical anti-NMDAR titres—ample evidence points towards direct induction of anti-NMDAR encephalitis without an intermediary viral reactivation.

We propose that the paresis of the right arm resulted from the lesion in the left motor cortex. A left-hemispheric subdural effusion (i.a. MRI day 56) showed merely subtle signs of space occupation and lacked correlation of its size with the extent of the right arm paresis, thus it is unlikely to have caused the brachial motor deficits. The dysarthria and dysphagia were most likely due to a bilateral opercular syndrome. Interestingly, a patient presumed to suffer from "chronic herpes simplex encephalitis"—most likely reflecting a case of post-HSVE anti-NMDAR-encephalitis—with very similar symptoms and imaging features has been described [9].

Anti-NMDAR-encephalitis following HSV1 encephalitis may be caused by release of intracellular antigens due to non-specific viral or parasitical neuronal lysis [10, 11]. In analogy, antigen release secondary to surgical trauma may trigger the same autoinflammatory cascade. Anti-NMDAR encephalitis after resection of melanocytic naevi has been described, suggesting a similar pathomechanism [12]. These antigens may either be true autoantigens or particles of latent HSV1, acting via molecular mimicry. Hence, brain surgery in patients with a history of HSV1 encephalitis should be very carefully indicated.

Compliance with ethical standards

Conflicts of interest Dr. Wagner received travel funds from Boehringer Ingelheim and Daiichi Sankyo as well as personal fees from UCB. Dr. Trenkler reports grants and personal fees from Medtronic, grants from Microvention, and grants from Stryker. Dr. von Oertzen reports personal fees and non-financial support from Eisai Pharma GmbH Vienna, grants, personal fees and non-financial support from UCB Pharma GmbH Vienna, non-financial support from Medtronic Austria GmbH, grants, personal fees and non-financial support from Novartis Phama, personal fees from Roche Pharma, personal fees from Biogen Idec Austria, personal fees from Liva Nova, personal fees from Sanofi-Aventis GmbH, and grants from Grossegger & Drbal GmbH. The other authors report no disclosures.

Ethical standards The authors declare that they acted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The individual presented in this case report gave his informed consent to its being submitted for publication.

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