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Short communications

Progressive hippocampal sclerosis after viral encephalitis: Potential role of NMDA receptor antibodies

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ABSTRACT

Purpose: Survivors of viral encephalitis can develop refractory epilepsy and hippocampal sclerosis. Both the initial infectious insult and the secondary effects of recurrent seizures have been implicated in chronic disease progression. Recently, post-infectious autoimmunity, involved in acute relapses, has also been proposed as a pathomechanism for chronic disease progression. Our case series suggests a potential role of antibodies against the N-methyl-D-aspartate receptor (NMDAR) in chronic inflammatory disease beyond acute manifestations.
Methods: Retrospective chart review of four patients with epilepsy, hippocampal sclerosis following viral encephalitis and NMDAR-antibodies in CSF.
Results: The four patients were female, developed hippocampal sclerosis (in 3/4 in a step-wise progression) after Herpes simplex or Varicella zoster virus encephalitis and harboured immunoglobulin G antibodies against the NMDAR in their CSF. Two patients were treated with short-term immunosuppression but did not benefit.
Conclusion: This case series presents the first tentative evidence in support of chronic autoimmune inflammation driving disease progression after viral encephalitis beyond the known acute immune-mediated relapses. The anecdotal nature of the data does not, however, permit conclusive judgement on causality. Should our findings be replicated in larger cohorts, the treatment of post-infectious epilepsy could potentially be expanded to include immunosuppressive strategies in antibody-positive cases.

1. Introduction

Having survived viral encephalitis, patients often develop refractory epilepsy. In some cases hippocampal sclerosis and associated cognitive impairments are seen, though the pathomechanism of this secondary disease progression is still a matter of debate [1]. Encephalitis, particularly at an early age, can lead to mesial temporal lobe damage [2]. Post-encephalitic epilepsy itself could later cause or exacerbate hippocampal sclerosis [3]. Recently, acute encephalitis relapses one week to three months after Herpes simplex or Varicella zoster virus encephalitis (HSVE; VZVE) have been described as mediated by neural antibodies against the N-methyl-D-aspartate receptor (NMDAR) [4,5]. Whether post-infectious autoimmunity plays a role in long-term disease progression is unknown [1].

For early NMDAR-antibody mediated post-viral encephalitis, immunosuppression seems to be beneficial [6,7]. Antiepileptic polytherapy and potentially epilepsy surgery should be considered in the treatment of post-infectious epilepsy [1].

The following case series comprises four patients with post-encephalitic hippocampal sclerosis and immunoglobulin (Ig) G antibodies against the NMDAR in CSF. In analysing the findings, clinical course and treatment response, we aim to address the potential role of NMDAR antibodies in chronic post-infectious disease beyond acute manifestations.

Abbreviations: d, days; HSVE, herpes simplex virus encephalitis; Fc, fragment crystallisable; H+L, heavy and light chain; Ig, immunoglobulin; neg, negative; NMDAR, N-methyl-D-aspartate receptor; Pat., patient; pos, positive; VZVE, varicella zoster virus encephalitis; y, year.

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2. Materials and methods

A retrospective chart review was performed on four patients with epilepsy, NMDAR antibodies of IgG in CSF and a history of viral encephalitis treated at the Epilepsy Centres in Bochum and Bielefeld-Bethel in Germany as well as the Cantonal Hospital St. Gallen in Switzerland between 2012 and 2016. Patients were selected based on personal knowledge of the authors; a database containing the variables of interest (history of viral encephalitis, hippocampal sclerosis, NMDAR antibody positivity) was not available, so a systematic search to identify further cases was technically not possible. All data were obtained for clinical routine and not for research purposes. Publication of such data does not require approval by our Ethics Committees. Written informed consent was obtained from all patients. Fig. 1 presents a summary of relevant imaging and clinical data.

3. Results

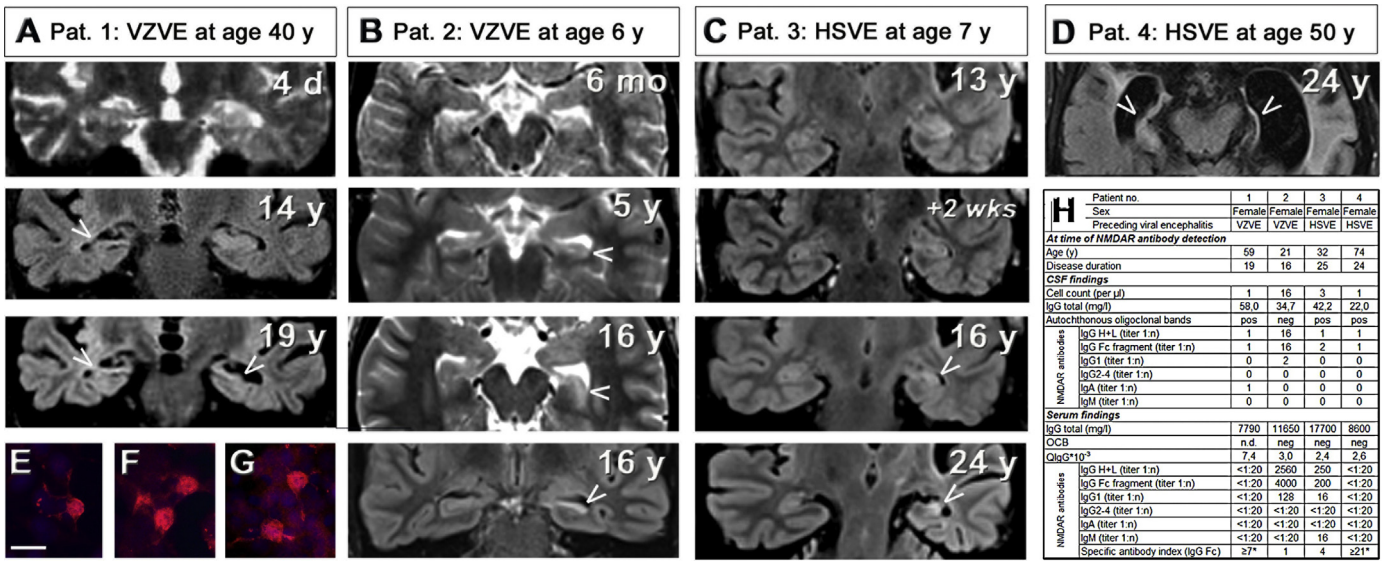
Patient 1 had suffered VZVE at the age of 39 with acute onset amnesia, disorientation, transient aphasia and seizures. She recovered fully after antiviral treatment. Four years later memory problems and temporal lobe seizures first reoccurred. During the following decade short term memory disturbance progressed and MRI showed both right hippocampal atrophy and left hippocampal hyperintensity. Three monthly steroid pulses on the suspicion of autoimmune encephalitis were without effect. Five years later, bilateral hippocampal sclerosis had evolved. Memory impairment was severe and seizures were pharmacoresistant. CSF analysis yielded IgG (and IgA) against the NMDAR. No further immunotherapy was offered.

Patient 2 was a 6-year-old girl whose hippocampi were not grossly atrophic 6 months after VZVE. Post-encephalitic seizures were controlled by carbamazepine. She was cognitively impaired but could attend regular school. Five years later, she developed new learning problems and again single focal seizures. MRI showed left hippocampal atrophy that progressed subsequently. CSF analysis revealed NMDAR IgG immunoreaction. Since then, she has had on average six pharmacoresistant left temporal lobe seizures per year. Immunotherapy was not offered.

Patient 3 had HSVE at age of seven and developed subsequent pharmacoresistant epilepsy, dense right-sided hemiparesis and mild aphasia. At age 20, she went into left-frontal status epilepticus. MRI revealed multiple old post-encephalitic neocortical lesions (not shown) and left hippocampal swelling which resolved upon status control. She had persistent, pharmacoresistant clonic seizures on left and right extremities. Three years after status, there was left sided hippocampal sclerosis. Twenty-four years after HSVE, MRI showed a further increase of the left-sided hippocampal sclerosis. Four months of oral prednisolone therapy upon NMDAR IgG (and IgM) antibody detection (starting at 80 mg/d, tapered over four months to 10 mg/d) and subsequent rituximab treatment (1000 mg twice) did not improve epilepsy or cognition.

Patient 4 had acute HSVE at the age of 50 that caused epilepsy and severe cognitive deficits. At age 74, transient vertigo and gait impairment led to hospital admission but remained unexplained. MRI showed neocortical post-encephalitic lesions and bilateral hippocampal atrophy. Earlier MR images were unavailable. Lumbar puncture revealed NMDAR IgG antibodies. No immunotherapy was offered.

In summary, the presented cases have in common the clinical constellation of epilepsy, hippocampal sclerosis and NMDAR-IgG-antibodies in CSF in the context of an encephalitis due to a member of the Herpesviridae many years previously. Two of the patients had VZVE and two HSVE; all were women (as are most patients with "classical" anti-NMDAR encephalitis). Sequential MRIs were available for Patients 1–3. In those, delayed-onset progressive hippocampal atrophy had developed in a stepwise fashion. Whether the bilateral hippocampal sclerosis of patient 4 was an immediate consequence of the encephalitis or developed later remains unknown. In two patients (1 and 3) the co-occurrence of NMDAR antibodies and hippocampal sclerosis led to the suspicion of a secondary autoimmune process, prompting immunosuppressive treatment. In both cases, no benefit was achieved.



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Patient no.	1	2	3	4
Sex	Female	Female	Female	Female
Preceding viral encephalitis	VZVE	VZVE	HSVE	HSVE
At time of NMDAR antibody detection				
Age (y)	59	21	32	74
Disease duration	19	16	25	24
CSF findings				
Cell count (per µl)	1	16	3	1
IgG total (mg/l)	58,0	34,7	42,2	22,0
Autochthonous oligoclonal bands	pos	neg	pos	pos
NMDAR antibodies: IgG H+L (titer 1:n)	1	16	1	1
NMDAR antibodies: IgG Fc fragment (titer 1:n)	1	16	2	1
NMDAR antibodies: IgG1 (titer 1:n)	0	2	0	0
NMDAR antibodies: IgG2-4 (titer 1:n)	0	0	0	0
NMDAR antibodies: IgA (titer 1:n)	1	0	0	0
NMDAR antibodies: IgM (titer 1:n)	0	0	0	0
Serum findings				
IgG total (mg/l)	7790	11650	17700	8600
OCB	n.d.	neg	neg	neg
QIgG*10^3	7,4	3,0	2,4	2,6
NMDAR antibodies: IgG H+L (titer 1:n)	<1:20	2560	250	<1:20
NMDAR antibodies: IgG Fc fragment (titer 1:n)	<1:20	4000	200	<1:20
NMDAR antibodies: IgG1 (titer 1:n)	<1:20	128	16	<1:20
NMDAR antibodies: IgG2-4 (titer 1:n)	<1:20	<1:20	<1:20	<1:20
NMDAR antibodies: IgA (titer 1:n)	<1:20	<1:20	<1:20	<1:20
NMDAR antibodies: IgM (titer 1:n)	<1:20	<1:20	16	<1:20
NMDAR antibodies: Specific antibody index (IgG Fc)	≥7*	1	4	≥21*

Fig. 1. MR images (T2 and FLAIR) of patient 1 (A), patient 2 (B), patient 3 (C) and patient 4 (D) show hippocampal atrophy (<) in all patients. Progression is documented in patients 1–3. In the upper right-hand corners, time since viral encephalitis is given. E-G: undiluted CSF of patient 1 on cell based assays with NMDAR transfected HEK cells (Euroimmun, Lübeck, Germany). E: NMDAR antibodies detected with anti-human IgG-heavy + light chain secondary antibodies; F: NMDAR antibodies, detection anti-human-IgG Fc fragment (confirms that there are indeed IgG antibodies as opposed to a cross-reaction with IgM or IgA); G: NMDAR IgA antibodies; bar: 15 µm. H: Demographic and laboratory features of patients 1–4. *These patients have no detectable NMDAR antibodies in serum at a dilution of 1:20. Therefore, the specific antibody indices are calculated with a serum titre just below the detection threshold ("1:19") and are marked as "≥" values.

4. Discussion

On the one hand, our observations complement a growing spectrum of idiopathic, paraneoplastic and post-infectious NMDAR-associated CNS disorders. On the other hand, they offer a potential pathomechanism for the commonly observed chronic disease progression seen years after viral encephalitis. Both perspectives shall be explored.

The existing literature on post-HSVE encephalopathy and NMDAR antibodies describes patients with an acute or subacute appearance of new symptoms or symptoms reminiscent of the previous HSVE, all within three months after the first symptoms of HSVE [4,6,7]. Children usually present with choreoathetosis, whereas adults may have more heterogeneous presentations. Post-infectious autoimmunity has been suggested to evolve by autoantibodies occurring because of unmasked receptor epitopes and molecular mimicry combined with an inflammatory setting that facilitates breaking of immune tolerance [8]. The four patients presented above had NMDAR antibodies in CSF more than a decade after viral encephalitis (when NMDAR antibody tests were not available yet), and their later detection was not linked to an acute encephalitic relapse.

It is debatable whether the antibodies contributed to hippocampal atrophy. In three of the four patients (1–3), sequential MRIs prove that the hippocampal sclerosis did not result solely from the initial cerebral insult, but incrementally over many years. While longstanding epilepsy itself has been associated with hippocampal sclerosis, the presence of NMDAR antibodies suggests an alternative or complementary pathomechanism. Since hallmarks of acute autoimmune encephalitis were missing, a chronic inflammatory disorder due to postinfectious autoimmunity can be considered. In the two patients, in which the not so sensitive IgG subclass antibodies gave a result (patients 2 and 3, see Fig. 1), the NMDAR antibodies were IgG1 and thereby able to activate complement with its potential to cause tissue destruction [9]. On the other hand, NMDAR antibodies are in most instances IgG1[10] but do not cause atrophy. There has been a report of one patient who made a good recovery from severe anti-NMDAR encephalitis but still harboured NMDAR antibodies in serum and CSF [11]. This argues against the idea that the NMDAR antibodies by themselves are sufficient to cause brain atrophy. Our two patients that were treated with immunosuppression (patient 1 and 3), did not benefit. However, only patient 3 was treated with second-line immunotherapy, and other chronic autoimmune CNS disorders are known to be refractory to immunosuppression, not to mention the already established structural deficits that by themselves may underlie the chronic epilepsy. Taken together, little conclusions can be drawn from the limited immunotherapy response.

The interpretation of our findings is limited by its retrospective nature, the (inevitable) lack of antibody testing shortly after viral encephalitis and the limited observations on immunotreatment response. NMDAR antibody titres were at the border of detectability; however, we found them by at least two secondary antibodies (anti-human IgG heavy and light chain [anti-H+L], anti-human IgG Fragment crystallisable [anti-Fc]) making false positive results unlikely. The CSF samples with the lowest titres were negative by use of subclass specific secondary antibodies. This is not surprising as IgG1-4 antibodies are developed with the aim of higher specificity even at the price of lower sensitivity compared to anti-H+L or anti-Fc [12].

Taken together, these four cases expand the spectrum of postviral autoimmunity to a chronic course with NMDAR antibodies present decades after the viral encephalitis and step-wise development of hippocampal atrophy. This is an example of NMDAR antibody positivity that occurs with a fixed structural deficit and does not respond well to immunotherapy as opposed to "classical" acute or subacute anti-NMDAR encephalitis. Sequential long-term antibody testing on a prospective cohort of viral encephalitis survivors would be needed to complete the picture.

Conflicts of interest

Dr. Popkirov reports no disclosures.

Dr. Ismail reports no disclosures.

Dr. Grönheit has received honoraria and travel or accommodation payment or participation fee from UCB (Monheim, Germany), Eisai (Frankfurt, Germany) and Bial (Trofa, Portugal)

Dr. Kapauer reports no disclosures.

Dr. Wellmer received speaker honoraria from Eisai (Frankfurt, Germany), Desitin (Hamburg, Germany), Bial (Trofa, Portugal) and UCB (Monheim, Germany).

Dr. Bien gave scientific advice to Eisai (Frankfurt, Germany) and UCB (Monheim, Germany), undertook industry-funded travel with support of Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), and Grifols (Frankfurt, Germany), obtained honoraria for speaking engagements from Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), diamed (Köln, Germany), Fresenius Medical Care (Bad Homburg, Germany), Biogen (Ismaning, Germany) and Euroimmun (Lübeck, Germany). He received research support from diamed (Köln, Germany) and Fresenius Medical Care (Bad Homburg, Germany). He is a consultant to the Laboratory Krone, Bad Salzuflen, Germany, regarding neural antibodies and therapeutic drug monitoring for antiepileptic drugs.

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References

[1] Sellner J, Trinka E. Seizures and epilepsy in herpes simplex virus encephalitis: current concepts and future directions of pathogenesis and management. J Neurol 2012;259:2019–30.
[2] Marks DA, Kim J, Spencer DD, Spencer SS. Characteristics of intractable seizures following meningitis and encephalitis. Neurology 1992;42:1513–8.
[3] Walker MC. Hippocampal sclerosis: causes and prevention. Semin Neurol 2015;35:193–200.
[4] Armangue T, Leypoldt F, Malaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 2014;75:317–23.
[5] Schäbitz WR, Rogalewski A, Hagemeister C, Bien CG. VZV brainstem encephalitis triggers NMDA receptor immunoreaction. Neurology 2014;83:2309–11.
[6] Armangue T, Moris G, Cantarín-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 2015;85:1736–43.
[7] Hacohen Y, Deiva K, Pettingill P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord 2014;29:90–6.
[8] Venkatesan A, Benavides DR. Autoimmune encephalitis and its relation to infection. Curr Neurol Neurosci Rep 2015;15:3.
[9] Bien CG, Vincent A, Barnett MH, Becker AJ, Blumcke I, Graus F, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain 2012;135:1622–38.
[10] Tüzün E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol 2009;118:737–43.
[11] Hansen HC, Klingbeil C, Dalmau J, Li W, Weissbrich B, Wandinger KP. Persistent intrathecal antibody synthesis 15 years after recovering from anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol. 2013;70(1):117–9.
[12] Jackson ImmunoResearch, Specializing in secondary antibodies and conjugates. https://www.jacksonimmuno.com/technical/literature-download (last access: 14.07.2017).