

Anti-NMDAR encephalitis mimicking HaNDL syndrome

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Abstract

Background: Anti-NMDA receptor encephalitis typically manifests as severe multistage neuropsychiatric syndrome. However, milder or incomplete forms of the disorder have been recognised. Here, we report on a patient with anti-NMDA receptor encephalitis with a clinical phenotype mimicking the syndrome of headache with neurological deficits and cerebrospinal fluid (CSF) lymphocytosis (HaNDL).

Case: A 67-year-old man presented with recurrent stereotyped episodes of hemianopia, aphasia and right hemiparesis accompanied by throbbing headaches as well as confusion and agitation. CSF analysis showed lymphocytic pleocytosis. Additional analysis revealed NMDA receptor IgG antibodies in the patient's CSF. Following immunotherapy, no further episodes occurred and NMDAR antibodies became undetectable. No NMDAR or other neuronal antibodies were detected in archived serum and CSF samples of 12 HaNDL patients fulfilling the current diagnostic criteria.

Conclusions: While anti-NMDAR encephalitis can manifest with a HaNDL-like clinical picture, HaNDL syndrome itself does not appear to be mediated by anti-NMDAR antibodies.

Keywords

Anti-NMDA receptor encephalitis, headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL), antibodies

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Introduction

Detection of IgG antibodies directed against the NR1 subunit of the NMDAR in CSF is the hallmark of anti-NMDAR encephalitis, a severe encephalitis with a characteristic multistage neuropsychiatric syndrome (1,2). However, milder or incomplete forms, as well as atypical presentations of the disorder have been increasingly recognised (1,3,4). Here, we report on a patient with anti-NMDAR encephalitis mimicking HaNDL syndrome (5). A 67-year-old man suffered from three stereotyped episodes of transient neurological deficits that occurred over a period of two weeks. He had a history of migraine with aura (homonymous hemianopia without further symptoms; one attack every two to three years), but was otherwise well and had no vascular risk factors. Symptoms evolved slowly progressively across minutes, starting with right homonymous hemianopia followed by global aphasia and then right hemiparesis. The deficits completely resolved in inverse order within three to four hours and were followed by throbbing bilateral headaches lasting several hours. Additionally, the patient developed confusion and marked agitation,

including restlessness and aggressiveness with need for sedation, which improved slowly over the next days. The patient had retrograde amnesia for the agitation periods, but not for the preceding neurological deficits. Cerebrospinal fluid (CSF) analysis on the day after symptom onset revealed lymphocytic pleocytosis (95 cells/ μ l) with few activated lymphocytes and plasma cells and elevated protein (96 mg/dl), but no CSF-specific oligoclonal bands. Cerebral magnetic resonance imaging (MRI) scans (including gadolinium-enhanced T1, fluid-attenuation inversion recovery and diffusion-weighted sequences) performed after the first two episodes were unremarkable except for mild

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frontoparietal microangiopathic leucoencephalopathy. An electroencephalogram (EEG) on day 10 after the first episode showed moderate generalised slowing, but further follow-up EEGs were normal. Additional work-up including cerebral angiography, tumour screening with whole-body computed tomography and body fluorodeoxyglucose positron-emission tomography, and extensive virological and bacteriological studies were negative. Testing for anti-neuronal antibodies using HEK293 cells transfected with the NR1 subunit of human N-methyl-D-aspartate receptor (NMDAR) (Euroimmun, Lübeck, Germany) detected immunoglobulin (Ig)G NMDAR antibodies in the patient's CSF (titre, 1:32), but not serum. Since CSF IgG NMDAR titres at this level are indicative of anti-NMDAR encephalitis, an immunosuppressive treatment with oral corticosteroids and plasma exchange, subsequently followed by azathioprine, was started two weeks after symptom onset. Following treatment initiation, no further episodes occurred during a follow-up of currently 16 months. Azathioprine was discontinued after six months of treatment. Three weeks after symptom onset, CSF NMDAR antibodies had decreased to a titre of 1:1. Neuropsychological testing at the same time showed remaining moderate deficits of attention, working memory, and verbal long-term memory. At follow-up six weeks later, NMDAR antibodies were negative in CSF and serum, but verbal long-term memory deficit persisted.

Remarkably, the clinical and paraclinical findings of this patient fulfilled the diagnostic criteria of headache with neurological deficits and CSF lymphocytosis (HaNDL) (5), which is defined by (i) one or more episodes of moderate or severe headache that are accompanied by transient neurologic deficits, (ii) CSF pleocytosis with lymphocytic predominance and (iii) complete remission within three months (6). Furthermore, the clinical spectrum of HaNDL can include confusional states (7). Since this observation raised the possibility that patients with a clinical diagnosis of HaNDL could actually suffer from an abortive form of autoimmune encephalitis and given that auto-antibodies have recently been discussed in the pathophysiology of HaNDL (8), we searched for neuronal antibodies in archived CSF and serum samples of 12 well-characterized patients with HaNDL (four women; median (range) age, 50 (32–61) years). All patients fulfilled the current diagnostic criteria for HaNDL (6), but none of them had developed confusion or any other psychiatric symptoms. Extensive diagnostic work-up including MRI and bacteriological and virological studies had excluded alternative diagnoses. Testing for antibodies against NMDAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), gamma-aminobutyric acid-B receptor (GABABR),

leucine-rich, glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) and glutamic acid decarboxylase 65 (GAD65) (Euroimmun, Lübeck, Germany) was negative in all patients.

Here, we describe a peculiar clinical manifestation of anti-NMDAR encephalitis characterised by repeated transient and stereotyped episodes of neurological deficits with a slowly progressive manifestation and resolution accompanied by headaches and CSF lymphocytosis, similar to the clinical picture of HaNDL. The diagnosis of anti-NMDAR encephalitis in this patient is supported by (i) evidence of an intrathecal production of NMDAR antibodies with a titre typically observed in anti-NMDAR encephalitis (1,9), (ii) clinical improvement in association with disappearance of NMDAR antibodies under immunotherapy, and (iii) presence of memory deficits following the acute stage of the disease as previously described in patients with anti-NMDAR encephalitis (9). Moreover, CSF IgG NMDAR antibodies are considered highly specific for anti-NMDAR encephalitis and were negative in about 8000 patients with various disorders (10) and in more than 500 healthy control subjects in previous studies (2,10,11). In line with previous observations on rare mono- or oligosymptomatic presentations of anti-NMDAR encephalitis (1,3,4), this case further suggests that incomplete and atypical manifestations of anti-NMDAR encephalitis can occur. Alternatively, early initiation of immunotherapy might have prevented the development of the complete clinical phenotype of anti-NMDAR encephalitis, which often includes seizures, catatonic features, abnormal movements and autonomic dysfunction (1,2).

Interestingly, the progressive evolution of neurological deficits and their subsequent inverse resolution may point to cortical spreading depression as a possible pathophysiological correlate of the patient's transient neurological symptoms (12). In accordance with this hypothesis, spreading depression can experimentally be induced by glutamate, and it is assumed that NMDAR antibodies cause glutamatergic hyperactivity by inactivation of GABAergic neurons (1,12).

While the patient's clinical and paraclinical findings were compatible with HaNDL, we did not detect antibodies to NMDAR and other well-characterised neuronal antigens in archived CSF and serum samples of 12 patients with a clinical diagnosis of HaNDL. We therefore conclude that anti-NMDAR encephalitis may manifest with a HaNDL-like clinical picture, but HaNDL itself is neither associated with antibodies to NMDAR nor to AMPAR, GABABR, LGI1, CASPR2, or GAD65. Thus, our findings do not support the hypothesis that HaNDL is an abortive form of an autoimmune encephalitis associated with these antibodies. This is in keeping with a recent report that did

not detect antibodies to NMDAR, P/Q-type voltage-gated calcium channels (VGCC), voltage-gated potassium channel (VGKC)-complex, LGI1, CASPR2 and GAD in four patients with HaNDL (8). Still, an antibody-mediated pathogenesis of HaNDL has previously been proposed and serum antibodies to the T-type voltage-gated calcium channel CACNA1H were recently described in two patients with HaNDL (5,8). It therefore remains possible that HaNDL is related to these or other yet unidentified neuronal antibodies.

Although HaNDL can occasionally be associated with marked confusional states (7), confusion or agitation are not typical features of HaNDL (5), and none of the 12 patients with HaNDL included in this work had such symptoms. Conversely, psychiatric symptoms including confusion, agitation and behavioural abnormalities are frequently seen in autoimmune

encephalitides (1). From a clinical practise point of view, the presence of confusion or agitation in patients with a presumptive diagnosis of HaNDL should therefore prompt a careful search for alternative diagnosis and testing for neuronal antibodies.

In summary, this report indicates that NMDAR IgG antibody-associated autoimmunity can manifest with recurrent stereotyped neurological deficits, headaches, and CSF lymphocytosis, mimicking the clinical phenotype of HaNDL. Nevertheless, HaNDL itself does not appear to be a forme fruste of anti-NMDAR encephalitis or autoimmune encephalitides associated with AMPAR, GABABR, LGI1, CASPR2, or GAD65 antibodies. This case thus highlights the challenge to disentangle well-established clinical syndromes from rare manifestations of autoimmune encephalitides mediated by antibodies to neuronal surface receptors.

Clinical implications

- Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis can manifest with a headache with neurological deficits and cerebrospinal fluid (CSF) lymphocytosis (HaNDL)-like clinical syndrome with stereotyped episodes of transient neurologic deficits and severe headache.
- Patients with suspected HaNDL syndrome should be tested for neuronal antibodies, especially when confusional states are observed.

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Conflict of interest

None declared.

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