Acta Neurol Belg
DOI 10.1007/s13760-013-0204-8

LETTER TO THE EDITOR

Remarkable effect of benzodiazepine in a patient with anti-NMDA receptor encephalitis

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Received: 9 April 2013 / Accepted: 1 May 2013

Here, we report a case of anti-NMDA receptor encephalitis with a history of vaccination in which peroral low dosages of benzodiazepines caused reversible episodes of wakefulness.

A 42-year-old male patient presented with a reversible attack of blurred vision, paresthesia in his right hand followed by psychiatric symptoms, visual hallucinations, and episodes of disorientation. In the end of the first month, he experienced seizures. He had a history of vaccination just 3 weeks before the symptoms started. Cranial imaging was within normal limits. EEG demonstrated persistent, repeated sharp waves localized to left parietal cortex. Cerebrospinal fluid (CSF) examination revealed an elevated protein level without any cells or microorganism. All infectious markers were negative. Antinuclear antibody profile, lupus anticoagulants were also negative. Whole body 18F-fluorodeoxyglycose positron emission tomograpghy (FDG-PET) demonstrated hyperactivity in bilateral temporoparietal cortex.

Treatment with acyclovir and meropenem was initiated. Seizures were under control with levetiracetam treatment (2,000 mg daily). The sharp waves previously observed in the left hemisphere were no longer present after treatment. In his follow-up, the patient progressively became unresponsive and the clinical picture deteriorated to a catatonic state.

With the suspicious of nonconvulsive status epilepticus, he received intravenous benzodiazepine (Bz) which caused a period of wakefulness lasting for 15 min. Phenytoin was added to the treatment, but despite an adequate free phenytoin serum level of 22 mg/ml, no beneficial clinical effect was seen, and the patient was still unresponsive. Twenty-four hour EEG monitoring demonstrated mild diffuse slowing (6–7 Hz) without any epileptic discharges.

This remarkable clinical effect was observed after diazepam injection but not with other antiepileptic drugs, and the absence of obvious EEG findings suggested a pathology rather than nonconvulsant status epilepticus. Low dosage of peroral lorazepam (1 mg) also caused a 2-h period of wakefulness which also supported another diagnosis rather than status epilepticus. Then, the dosage was increased to 4 × 1 mg daily which provided a day time wakefulness. On the other hand, he returned to his unresponsive status when the drug was delayed.

Further investigation demonstrated antibodies to NMDA receptors in CSF. No tumor was found by whole body FDG-PET, testicular ultrasound, or chest tomography.

At the end of the second month from symptom onset, all anti-infectious agents were stopped step by step and the patient was put on high dosage (1,000 mg) IV pulse corticosteroid treatment for 5 days followed by a 1-mg/kg oral dose regimen. After 2 weeks of treatment, he was awake but still experienced hallucinations and episodes of disorientation so he received seven cycles of plasma exchange (Pex) on alternate days. After Pex, oral benzodiazepine was gradually stopped, and the patient was still awake and was able to perform daily tasks.

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Published online: 14 May 2013

In his follow-up period of 6 months till now, he totally returned to his daily life and started working. Antiepileptic drugs were stopped gradually.

NMDA receptor encephalitis may present with seizures and hallucinations, resembling a psychiatric disorder [1]. The disease is related to malignancy in females, while the association with malignancy was lesser in males, and usually responds well to treatment [2].

Our patient had a history of influenza vaccination 3 weeks prior to symptom onset. Vaccination has been reported prior to anti-NMDA receptor encephalitis, after a DTP-vaccination [3] and in one case after a similar history of influenza vaccination [4]. This relation could be coincidental, but could also suggest a possible trigger by vaccination.

Another interesting finding in our patient was the remarkable effect of benzodiazepines. Benzodiazepines primarily affect GABAergic system, but they also may have direct/indirect potential effects on NMDA receptors [5].

As a result, remarkable response to oral benzodiazepines in unconscious or catatonic patients may support the diagnosis of autoimmune encephalitis. Though it may be coincidental, history of vaccination including influenza should be addressed in patients with anti-NMDA receptor encephalitis.

Conflict of interest None.

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